Nutrition and Health
Series Editors: Adrianne Bendich · Connie W. Bales

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Nutritional and Medical Management of Kidney Stones

Humana Press

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The Nutrition and Health series has an overriding mission in providing health professionals with texts that are considered essential since each is edited by the leading researchers in their respective fields. Each volume includes: 1) a synthesis of the state of the science, 2) timely, in-depth reviews, 3) extensive, up-to-date fully annotated reference lists, 4) a detailed index, 5) relevant tables and figures, 6) identification of paradigm shifts and consequences, 7) virtually no overlap of information between chapters, but targeted, inter-chapter referrals, 8) suggestions of areas for future research and 9) balanced, data driven answers to patient/health professionals questions which are based upon the totality of evidence rather than the findings of a single study.
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Foreword

Kidney stones are common and, in recent years, have increased in prevalence, affecting numerous people in the United States and in many other countries. In addition, they are appearing or increasing in populations in whom stones had been relatively uncommon, including children, women, and African Americans. Because they are often recurrent, they can affect sufferers repeatedly with sudden distressing symptoms, leading to multiple visits to the emergency room or the surgical suite. We now know that they are also accompanied by less obvious problems, such as bone disease, cardiovascular disease, and chronic kidney disease. For all these reasons, prevention of recurrent kidney stones is good medicine and should engage the active interest of the multiple specialists who care for stone patients including primary care practitioners, urologist, nephrologists, and dieticians.

Our understanding of the causes of stone disease is advancing, although not as rapidly as we would hope. The genetic underpinnings of stone formation are gradually emerging, and we are beginning to appreciate the role the gut microbiome may play in oxalate degradation. Nonetheless, it is becoming increasingly clear that dietary factors play a significant role in stone formation and need to be addressed in successful prevention plans.

The book you hold in your hands fills a unique niche in the small collection of books devoted to management of kidney stones. In addition to the well-written chapters on the epidemiology, pathophysiology, and surgical treatment of stones, it includes chapters that cover the range of kidney stone types, both idiopathic and those due to systemic diseases. Most of these chapters are coauthored by a physician and a nutritionist, emphasizing the importance that diet plays in the pathogenesis and treatment of stones.

The book has six parts. The first two parts include chapters on epidemiology and pathophysiology of kidney stones and a chapter on genetic, environmental, and dietary risk factors for stone formation, which form an excellent introduction to the later chapters. Part III provides guidance on diagnostic evaluation of stone formers and an update on surgical stone removal techniques.

Parts IV, V, and VI offer the reader something not easily available in other books on stone disease – an integrated approach to the medical and dietary management of kidney stones, provided by experts in both areas. Part IV has chapters on the most common types of stones, including calcium, uric acid, cystine, and struvite, as well as a useful (and unique) chapter on management of stone formers in whom kidney stone type is unknown, an all-too-common situation. Part V takes up stones in special settings, including separate

chapters on stones in the setting of bariatric surgery, an increasingly common presentation, and in patients with other types of gastrointestinal disease. The special considerations appropriate to evaluation and treatment of kidney stones in pediatric patients are the subject of another dual-authored chapter. This part also contains a chapter about management of stones in patients with chronic kidney disease or transplant, a topic not often addressed. Finally, the part presents a much needed review of dietary myths that often crop up in the care of kidney stone patients and discusses herbal supplements.

Part VI contains valuable resources that will aid practitioners in dietary management and excellent discussions of evidence-based practice in nutritional therapy and current areas of ongoing research in this area. The appendix contains additional information that can be used to support patient care and education in the areas of stone disease and nutritional management.

This book can serve as both a reference and a guide to the comprehensive medical and nutritional care of patients with kidney stones. In most kidney stone patients, nutritional therapy is a cornerstone of their care and may be sufficient to prevent many stone recurrences. In those patients who require medication, dietary counseling is essential to assure that patients get maximal benefit from the medication they are taking. By placing nutritional evaluation and management on an even footing with medical therapy, this book provides a great service to patients with kidney stones and the practitioners who care for them.

Chicago, IL, USA Elaine Worcester, MD

Preface

The effective management of nephrolithiasis requires a coordinated effort among providers from various specialties. Starting with an emergency room visit for renal colic, patients may wind up seeing urologists for stone removal, nephrologists for recurrent kidney stone prevention, and dieticians for nutritional management.

This comprehensive book focuses on the treatment and prevention of nephrolithiasis from the perspective of nephrologists, urologists, and dieticians. For physicians, medical students, or researchers, the opening chapters on epidemiology, genetics, and physiology of kidney stones give a foundation to understand the mechanisms and risk factors for stone formation. A surgical section follows with an up-to-date review of the surgical indications and available procedures in practice. Physicians and dieticians who treat kidney stone patients will find medical chapters followed by dietary chapters on the evaluation, management of the different types of stones, and management of stones in certain populations and high-risk groups. The book continues with chapters on myth debunking in the dietary management of kidney stones, dietary supplements, and evidence-based databases that are available in the literature.

This book contains a wealth of information that would be hard to digest in one sitting, but the sections and chapters are organized in a fashion that provides easy access to practical advice and clinical pearls. The contributing authors start each chapter with key points and keywords and end them with a summary followed by references that will provide the reader with resources for further reading. The authors have supported their chapters with informative graphics and tables that are either original or adapted from previous publications. The appendix of this book is rich with relevant cases, urine test order forms, dietary education material, and frequently asked questions.

As editors, we are very excited about the publication of this book. We hope that it will solidify the reader's knowledge of nephrolithiasis, serve as a medical and nutritional reference for evaluation and management of kidney stones, and most importantly improve the cooperation of specialists in caring for their stone patients.

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We would like to thank Springer Publications and Dr. Adrianne Bendich for the opportunity to publish *Nutritional and Medical Management of Kidney Stones* as a book and Dr. Julian Seifter and Dr. Stephen Knohl for their previous mentorships that amplified our knowledge and interest on the subject. Last but not least, we express our gratitude and appreciation to all of the contributors in this book for their commitment and patience throughout the process.

Series Editor Page

The great success of the *Nutrition and Health* Series is the result of the consistent overriding mission of providing health professionals with texts that are essential because each includes (1) a synthesis of the state of the science; (2) timely, in-depth reviews by the leading researchers and clinicians in their respective fields; (3) extensive, up-to-date, fully annotated reference lists; (4) a detailed index; (5) relevant tables and figures; (6) identification of paradigm shifts and the consequences; (7) virtually no overlap of information between chapters but targeted, interchapter referrals; (8) suggestions of areas for future research; and (9) balanced, data-driven answers to patient as well as health professionals' questions which are based upon the totality of evidence rather than the findings of any single study.

The series volumes are not the outcome of a symposium. Rather, each editor has the potential to examine a chosen area with a broad perspective, both in subject matter and in the choice of chapter authors. The international perspective, especially with regard to public health initiatives, is emphasized where appropriate. The editors, whose trainings are both research and practice oriented, have the opportunity to develop a primary objective for their book, define the scope and focus, and then invite the leading authorities from around the world to be part of their initiative. The authors are encouraged to provide an overview of the field, discuss their own research, and relate the research findings to potential human health consequences. Because each book is developed de novo, the chapters are coordinated so that the resulting volume imparts greater knowledge than the sum of the information contained in the individual chapters.

Nutritional and Medical Management of Kidney Stones edited by Haewook Han, Walter Mutter, and Samer Nasser is a very welcome and timely addition to the *Nutrition and Health* Series and fully exemplifies the Series' goals. Kidney stones have afflicted individuals over the centuries as documented in the kidneys of a 5000-year-old mummy. The causes, treatment, and prevention have been studied by early Greek and Roman physicians on every continent and have been found in patients with every type of dietary intake. With the advent of more accurate diagnostic tools, identification of the site, size, and number of stones has become more routine. Yet, kidney stones remain a significant medical issue. Moreover, there has been a continuous stream of basic as well as clinical research over the last decade linking the association between increased risk of kidney stone formation and obesity, metabolic syndrome, and diabetes incidence. Additionally, the recent findings of the nutritional aspects of stone type make this volume even more relevant to medical practice.

Kidney stones, from whatever cause, are referred to as nephrolithiasis by the medical community. Thus, it is of great importance to those involved in the medical care of patients, researchers, and students that this book is edited by three of the foremost physicians in the field of kidney stone disease in the USA and thus provides the reader with objective, up-to-date data that spans the cellular to therapeutic aspects of this painful disease. Kidney stones affect about 9% of the population, and their incidence is increasing, which may be due to the increasing age of the US population, environmental factors, and other causes that are reviewed in depth in the 28 informative chapters that contain numerous tables and figures as well as up-to-date reference lists. The volume is organized into six parts that cover the major clinical and research areas associated with kidney stone diagnosis and management. The editors have also included valuable appendices that contain case studies and informative tables, sample diets for the seven most common diet programs for individuals with various types of kidney stones, informative tables listing the calcium content and oxalate content of commonly consumed foods, a targeted list of frequently asked questions, and concise responses and examples of relevant diagnostic forms.

Part I: Overview

Part I contains a single chapter, Chap. 1, that provides a broad overview that includes discussions of the demographics, dietary intake, genetic and environmental factors, and chronic medical conditions that influence the risk of nephrolithiasis occurrence and recurrence. We learn that even though calcium kidney stones are the most common form and are increasing in incidence in females, there is also an increase in the proportion of uric acid stone formation associated with elevated BMI and low urine pH. With regard to risk factors for occurrence and recurrence of kidney stones, large-scale studies indicate that patients with a family history of kidney stones tend to develop stones at younger ages and with a higher rate of recurrence. The chapter includes a review of dietary factors that are thought to play an important role in formation of kidney stones and the composition of the urine including intakes of calcium, sodium, fructose, fluids (including water and other beverages), and vitamin C. The 5 figures and tables and over 90 references add greatly to the value of this important introductory chapter.

Part II: Basics of Kidney Stones

Part II contains three chapters that prepare the reader for the more detailed discussions of specific aspects of nephrolithiasis. Chapter 2 describes the pathophysiology of kidney stone formation and potential mechanisms to reduce the risk of primary and recurrent stones. All of the major types of stones are described in detail including calcium-based, uric acid, struvite, stones resulting from genetic factors, and potential drug adverse effects. The mechanisms involved in crystal formation and supersaturation of urine with the stone-forming components are described in detail. This practice-oriented chapter includes 9 excellent figures, 4 informative tables, and 89 relevant references. Chapter 3

reviews the genetic and environmental factors linked to stone formation. There is a description of each component of the kidney and their known genetic defects that can result in stone formation. Over 20 genetic defects are reviewed including several defects that do not involve the kidney but may affect bone calcium balance. Several genetically based cancers are also described that affect endocrine gland functions. Many of the genetic defects described result in rare diseases whose effects are seen early in childhood, including kidney stones. The environmental factors described include living in US areas with increased temperature, especially in the South East, poverty, and chronic reduced intake of liquids. Chapter 4 includes concise information on dietary intakes, including fluid intake and specific recommendations that can help reduce the risk of recurrent kidney stones containing calcium and uric acid, primarily. Other nutrients reviewed include animal protein, sugars, fiber, phosphates, vitamin B6, magnesium, sodium, and potassium.

Part III: Diagnosis and Treatment

The two chapters in this part examine the importance of an accurate diagnosis and relevant treatment. Chapter 5 provides an in-depth review of the critical steps involved in the kidney stone diagnosis, acute care in the emergency room, and follow-up care; the chapter includes seven informative tables and figures. The authors indicate that almost half of first-time stone formers have a recurrent episode. Thus, a primary goal of diagnosis is to reduce recurrence. The steps involved in the evaluation of the patient for stone-forming risk factors are reviewed and include medical history (with a detailed discussion of the 20 drugs that have been implicated in increasing the risk of kidney stones), CT scan imaging, stone analysis, and metabolic work-up. Patient history focuses on medications, diseases, diet, and work habits that may increase the risk of kidney stones. Imaging with computed tomography and ultrasound helps determine the size, number of stones, and their location in the urinary tract. Chemical and/or microbial analysis can help to determine the type of stone. Metabolic work-up consists of targeted blood work and urinalysis as well as a 24-hour urine collection. The 24-hour urine collection, especially in recurrent stone formers, is a valuable tool to determine the future risk of stone formation. The 24-hour urine values guide medical management and dietary modifications for the prevention of recurrence, and follow-up collections determine the effectiveness of the therapy. Chapter 6 presents the surgical possibilities available to the patient that does not spontaneously pass the kidney stone. The numerous treatment choices are described in detail, and the author indicates that urologists have many techniques currently available to assure that patients have good prospects for minimal surgery.

Part IV: Prevention, Medical, and Nutritional Managements for Different Types of Stones

Part IV is comprised of eight chapters that review the clinical management of patients with kidney stones and also strategies to prevent recurrence. For each subject discussed, there is first a chapter on medical issues followed by a

chapter that concentrates on the nutritional aspects of stone disease. Chapter 7 emphasizes the pathophysiology, prevention, and medical management of calcium oxalate and phosphate stones. The chapter includes a detailed review of the clinical studies that examined the role of calcium and related dietary nutrients in stone formation as well as a comprehensive description of the process of stone formation within the kidney. Clinical presentation and evaluation are also reviewed. Chapter 8 describes the synergistic role of nutrition and dietary advice in the management of kidney stone formation and recurrence. The chapter contains the recommendations on dietary issues from leading medical societies and governments that emphasize increased fluid intake, reduced intake of certain foods, and increased intake of certain nutrients that are detailed in the text and tabulated for the reader.

Uric acid stones are the second most common type of kidney stones and are reviewed first in the chapter that describes their medical management followed by the chapter describing the dietary factors associated with uric acid stone formation as well as the preventive strategies currently recommended. Chapter 9 discusses the significant morbidity associated with uric acid stones and outlines the risk factors that include gout and certain cancers, low urine volume, increased uric acid production or excretion, a high purine diet, and acidic urinary pH. The chapter lists the dietary factors that can increase stone risk and recommendations to prevent uric acid stones that include increasing fluids to produce greater than 2 liters of urine a day and a reduction of animal protein and alcohol. Medications to treat uric acid stones are also reviewed. Chapter 10 reviews in detail the dietary factors that can reduce the risk of uric acid stone formation. Low urine volume, hyperuricosuria, and low urine pH are the three most important risk factors amenable to dietary intervention. Low urinary volume and low urine pH are generally viewed as the most modifiable contributing factors to stone formation. Metabolic factors that increase risk include obesity, metabolic syndrome, and diabetes, and weight reduction is recommended. Patients with chronic diarrhea or high output ostomies have an increased risk of uric acid stone formation. Excessive fructose consumption, dehydration, and reduction in animal protein intake are reviewed and tabulated.

The next chapter, Chap. 11, describes the relatively rare form of kidney stones, struvite stones, that contain the compound struvite which is composed of magnesium ammonium phosphate. The stones are associated with higher ammonia concentrations in urine and consequently a higher pH. The stones are most often associated with genitourinary infections, and as treatment for these conditions has advanced, infection-related stones have become rarer. When identified, primary treatment involves surgery and treatment of infection; no dietary recommendations are currently given.

Another rare type of kidney stone is one composed of cystine, a dimer of cysteine. Chapter 12 describes cystine stones that are associated with high morbidity. The stones occur in patients with cystinuria, a rare genetic defect in tubular reabsorption of cationic amino acids leading to high concentrations of cystine in their urine. Inheritance is autosomal and two major genetic types have been identified. Cystine nephrolithiasis and related kidney disease are usually the only clinically pertinent manifestation of this genetic disorder. The chapter stresses that dietary management is critical with the focus on increasing the urine volume and pH. Pharmacological therapy includes the use of urine-alkalizing agents and cystine-binding thiol drugs.

Chapters 13 and 14 describe the medical evaluation of patients with nephrolithiasis without knowledge of the composition of the stone. Chapter 13 describes the situations that may lead to not knowing a stone's composition and the steps taken to manage the patient's treatment. Medical history and concomitant diseases are clues to the potential stone type especially as the vast majority of stones are calcium-based. Dietary factors are considered and are covered in depth in the next chapter. Diagnostic tests of urine pH and other urinary analyses are of primary importance and can often discriminate between calcium and uric acid stones; urinary tract infection diagnosis is often seen with struvite stones. Chapter 14 describes the generally safe and reasonable dietary recommendations for reducing stone recurrence when stone composition is unknown that include adequate fluid intake of 2.5–3 liters a day, low sodium, adequate intake of dietary calcium, animal protein restriction, and weight loss, if necessary. In addition to diagnostic tests described in the above chapter, diet history and nutrient analyses that are recommended include serum calcium, phosphorus, parathyroid hormone level, vitamin D, uric acid, and 24-hour urine composition. Dietary recommendations are also reviewed.

Part V: Special Consideration

The nine chapters in this Part examine unique situations where there are links between the age of the patient, the patient's disease or surgical procedure, and particular dietary intake that increases the risk of kidney stone formation. The first topic examines the risk of kidney stone formation since this increases two- to threefolds in patients with malabsorptive bariatric surgery compared to controls. Chapter 15 looks at the medical and dietary effects of bariatric surgery that increase stone risk and includes an in-depth examination of the types of weight loss surgeries currently being used and the comorbidities often found in patients undergoing surgery. We learn that the most common type of stone in bariatric surgery patients contains calcium salts and risk is highest in patients undergoing Roux-en-Y surgery. Dietary recommendations for patients are reviewed in depth and then modified based upon stone types. Critical issues are the low intake of fluids and the potential alteration in urine pH following surgery. Chapter 16 examines the stone risk level associated with different malabsorptive gastrointestinal diseases. The malabsorptive gastrointestinal disorders reviewed include inflammatory bowel diseases, with or without bowel resection, chronic pancreatitis, and celiac disease. The malabsorption of water, sodium, oxalate, bicarbonate, and fat leads to increased urinary concentration of stone-forming factors. The most common stones contain calcium oxalate or uric acid. This technical, practice-oriented chapter provides practical recommendations for patients with ileostomy as well as the other serious conditions indicated above, and the chapter includes 70 relevant references. Chapter 17 provides an overview of the importance of the gut's microbiome and the adverse effects of gastrointestinal diseases and/or surgery on the microbiome. Additionally, the cellular and subcellular transport of oxalate is reviewed in detail, and the types of malabsorptive syndromes are discussed with regard to their mechanisms of increasing the risk of stone formation.

Chapters 18, 19, and 20 examine the interactions between nephrolithiasis and chronic kidney disease (CKD). Chapter 18 includes a review of the clinical research studies that have examined the impact of nephrolithiasis on the risk of future CKD and end-stage renal disease (ESRD) as well on those genetic diseases that most often share both as complications. The chapter includes comprehensive tables and an extensive list of almost 100 references. Chapter 19 discusses the potential for kidney stones in patients undergoing kidney transplant. We learn that there may be the presence of small stones in a donor kidney and this may increase risk of kidney stones in the transplant patient; the incidence of kidney stones following transplant is lower than found in the general public and may be the result of denervation of the transplant. Management of a kidney stone in transplanted patients is similar to management described above for patients with kidney stones; however, if the stone is in the healthy kidney, there could be further loss of kidney function. The chapter includes a helpful case study. Chapter 20 includes eight comprehensive tables that summarize the specific nutrition management necessary to prevent recurrence of stones as well as the requirements to meet adequate nutritional status for CKD patients. Nutritional assessment, drug-nutrient interactions, and nutrition recommendations are reviewed, and the chapter emphasizes that treatment should be individualized. The CKD patient that develops stones is described, and nutritional recommendations are provided based upon the stage of CKD and concurrent diseases.

Chapters 21 and 22 provide unique chapters that delve into the current uses and risks associated with dietary supplement use and kidney stone incidence. Chapter 21, entitled "Kidney Stone: Diet, Myth and Reality," highlights the common mistakes of dietary prevention of kidney stones and current recommendations included in the American Urology Guidelines. General guidelines include intake of adequate amounts of calcium, plenty of fluid intake, moderate amounts of animal protein, appropriate fruits and vegetables, and specific vitamin/mineral supplements. Myths that are clarified include "a high calcium diet causes kidney stones"; "water is the only beverage that can help prevent kidney stones"; "kidney stone formers should limit intake of vitamin C"; "eating meat causes kidney stones"; "fruits and vegetables cause kidney stones because of their high oxalate content"; "kidney stone medications for their prevention will work without any changes to diet"; "minerals and electrolytes cannot protect against kidney stones"; and "low purine diets do no good." Each myth is followed by an evidence-based review of the clinical data relevant to the myth, and the tables and references document these discussions. Chapter 22 reviews the data on the use of herbal supplements for kidney stone treatment. Currently, there are very few randomized studies using herbal supplements so that recommendations are not provided. The informative tables and references provide guidance concerning herbs and commercial products containing herbs that suggest benefits for kidney stone formers.

The final two chapters in Part V examine the medical and nutritional management of pediatric kidney stone patients. Chapter 23 looks at medical management of kidney stones in children. The impact of kidney stones presenting in the pediatric age group is lifelong, and children are at increased risk of recurrent stones. There can be genetic factors and related family history as well as metabolic risk factors in these children. We learn that children that

required neonatal intensive care and were exposed to certain drugs are also at increased risk of stones. The chapter includes a detailed case study and more than 50 important references. Chapter 24 describes the importance of diet-related factors in the prevention and management of the growing rate of childhood kidney stones. As with adults described in earlier chapters, overweight and obesity significantly increase the risk of stones in children and are thus preventable. Additionally, some of the nutritional risk factors that can be moderated by diet include excessive sodium intake, excessive animal protein intake, inadequate fluid intake, inadequate citrate and potassium intake due to lack of fruits and vegetables, excessive oxalate intake, and inadequate calcium and phytate intakes due to lack of fiber-rich foods.

Part VI: Resources

Part VI, the last section in this comprehensive volume, provides four, resource-based chapters concerning the foods that contain oxalates as well as Internet sources of information related to oxalate's role in the formation of kidney stones, an in-depth description of the development and value of evidence-based clinical studies, and a final chapter on current clinical research in nephrolithiasis. Chapters 25 and 26 provide excellent examples of the in-depth information presented on the Internet and in related sources. Chapter 25 discusses the importance of knowing the foods that are high in oxalate concentration in the clinical management of patients at risk for occurrence as well as recurrence of kidney stones. Foods with the highest concentration of oxalate are plant-based and include spinach, rhubarb, beets, chard, wheat bran, nuts, chocolate, and tea. The oxalate content of these and other foods is included in a comprehensive table. Relevant books, journals, USDA websites, and other national databases and academic resources, such as those from Harvard and academic institutions from Australia and Bangladesh, are reviewed. The different databases online provide access to food weights using the metric and US systems. We learn that the USDA maintains a database on the oxalate content of plants that also contain phytochemicals and botanical compounds. Sources of mobile apps that are available are also listed. Chapter 26 contains an extensive compilation of Internet websites relevant to physicians, dieticians/nutritionists, patients with kidney stones, and those who are at risk of nephrolithiasis. The websites are listed in order of their specialty and include many from the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK).

Chapter 27 applies the principles of evidence-based practice to medical nutrition therapy for kidney stones and reviews the best available resources including evidence-based practice guidelines, searching and evaluation of primary literature, as well as systematic outcomes tracking. The chapter reviews the steps undertaken to develop the most respected source of nutritional information on kidney stone guidelines, the American Urological Association Guideline on the Medical Management of Kidney Stones. Many other authoritative sources are reviewed and tabulated. Chapter 28, the final chapter, examines the research endeavors that are ongoing to help those with kidney stones and those at risk. The chapter reviews clinical studies published

between 2012 and 2017 and examined the outcomes. The conclusion of this analysis is that medical management research investigating patients with kidney stones focused on fluid intake and obesity as the major issues. Individual studies are compared and relevant data are presented.

Conclusions

The above description of the volume's 28 chapters attests to the depth of information provided by the 43 highly respected chapter authors and volume editors. Each chapter includes complete definitions of terms with the abbreviations fully defined and consistent use of terms between chapters. Key features of the comprehensive volume include 88 detailed tables and informative figures; an extensive, detailed index; and more than 1100 up-to-date references that provide the reader with excellent sources of worthwhile practice-oriented information that will be of great value to nephrologists and related health providers as well as graduate and medical students. Additionally, several chapters include case studies, and there are valuable appendices that also contain case studies and informative tables for each, sample diets for the seven most common diet programs for individuals with various types of kidney stones, informative tables listing the calcium content and oxalate content of commonly consumed foods, a targeted list of frequently asked questions (FAQSs), and concise responses and examples of relevant diagnostic forms.

In conclusion, *Nutritional and Medical Management of Kidney Stones* edited by Haewook Han, Walter Mutter, and Samer Nasser provides health professionals in many areas of kidney stone research and practice with the most current and well-referenced volume on nephrolithiasis and the critical need to assure the overall health of the individual with kidney stone disease and individuals who are at known risk for kidney stone formation. The in-depth reviews of the types of kidney stones and their medical treatment strategies focused on reducing the risk of adverse effects in these patients, especially those who also suffered from other chronic and/or infectious diseases. The volume serves the reader as the benchmark for integrating the complex interrelationships between nutritionally related risk factors such as obesity, genetic inherited predispositions to stone formation, and the risks and/or benefits of consumption of dietary components, including oxalate, relevant minerals and vitamins, protein, and sugars. Practice-oriented chapters examined the medical diagnosis, management, and prevention of stone recurrence. The final chapters of this valuable volume provide unique and concise data on the most relevant Internet resources on all aspects of kidney function and diseases associated with kidney stones. The recommended resources are from national research centers, academic departments, and related organizations that provide reliable, up-to-date information based upon the totality of the research on kidney stones. The broad scope as well as in-depth reviews found in each chapter makes this excellent volume a very welcome addition to the *Nutrition and Health* Series.

Adrianne Bendich, PhD, FACN, FASN

About the Series Editors

Adrianne Bendich, PhD, FASN, FACN has served as the *Nutrition and Health* Series Editor for more than 20 years and has provided leadership and guidance to more than 200 editors that have developed the 80+ well-respected and highly recommended volumes in the Series.

In addition to *Nutritional and Medical Management of Kidney Stones* edited by Haewook Han, Walter Mutter, and Samer Nasser, major new editions published in 2012–2019 include:

1. **Vitamin E in Human Health** edited by Peter Weber, Marc Birringer, Jeffrey B. Blumberg, Manfred Eggersdorfer, Jan Frank, 2019
2. **Handbook of Nutrition and Pregnancy, Second Edition,** edited by Carol J. Lammi-Keefe, Sarah C. Couch and John P. Kirwan, 2019
3. **Dietary Patterns and Whole Plant Foods in Aging and Disease**, edited as well as written by Mark L. Dreher, Ph.D, 2018
4. **Dietary Fiber in Health and Disease,** edited as well as written by Mark L. Dreher, Ph.D., 2017
5. **Clinical Aspects of Natural and Added Phosphorus in Foods**, edited by Orlando M. Gutierrez, Kamyar Kalantar-Zaden\h and Rajnish Mehrotra, 2017
6. **Nutrition and Fetal Programming** edited by Rajendram Rajkumar, Victor R. Preedy and Vinood B. Patel, 2017
7. **Nutrition and Diet in Maternal Diabetes,** edited by Rajendram Rajkumar, Victor R. Preedy and Vinood B. Patel, 2017
8. **Nitrite and Nitrate in Human Health and Disease, Second Edition**, edited by Nathan S. Bryan and Joseph Loscalzo, 2017
9. **Nutrition in Lifestyle Medicine**, edited by James M. Rippe, 2017
10. **Nutrition Guide for Physicians and Related Healthcare Professionals 2nd Edition** edited by Norman J. Temple, Ted Wilson and George A. Bray, 2016
11. **Clinical Aspects of Natural and Added Phosphorus in Foods**, edited by Orlando M. Gutiérrez, Kamyar Kalantar-Zadeh and Rajnish Mehrotra, 2016

12. **L-Arginine in Clinical Nutrition**, edited by Vinood B. Patel, Victor R. Preedy, and Rajkumar Rajendram, 2016
13. **Mediterranean Diet: Impact on Health and Disease** edited by Donato F. Romagnolo, Ph.D. and Ornella Selmin, Ph.D., 2016
14. **Nutrition Support for the Critically Ill** edited by David S. Seres, MD and Charles W. Van Way, III, MD, 2016
15. **Nutrition in Cystic Fibrosis: A Guide for Clinicians,** edited by Elizabeth H. Yen, M.D. and Amanda R. Leonard, MPH, RD, CDE, 2016
16. **Preventive Nutrition: The Comprehensive Guide For Health Professionals, Fifth Edition,** edited by Adrianne Bendich, Ph.D. and Richard J. Deckelbaum, M.D**.,** 2016
17. **Glutamine in Clinical Nutrition,** edited by Rajkumar Rajendram, Victor R. Preedy and Vinood B. Patel, 2015
18. **Nutrition and Bone Health, Second Edition,** edited by Michael F. Holick and Jeri W. Nieves, 2015
19. **Branched Chain Amino Acids in Clinical Nutrition, Volume 2,** edited by Rajkumar Rajendram, Victor R. Preedy and Vinood B. Patel, 2015
20. **Branched Chain Amino Acids in Clinical Nutrition, Volume 1,** edited by Rajkumar Rajendram, Victor R. Preedy and Vinood B. Patel, 2015
21. **Fructose, High Fructose Corn Syrup, Sucrose and Health,** edited by James M. Rippe, 2014
22. **Handbook of Clinical Nutrition and Aging, Third Edition,** edited by Connie Watkins Bales, Julie L. Locher and Edward Saltzman, 2014
23. **Nutrition and Pediatric Pulmonary Disease,** edited by Dr. Youngran Chung and Dr. Robert Dumont, 2014
24. **Integrative Weight Management** edited by Dr. Gerald E. Mullin, Dr. Lawrence J. Cheskin and Dr. Laura E. Matarese, 2014
25. **Nutrition in Kidney Disease, Second Edition** edited by Dr. Laura D. Byham-Gray, Dr. Jerrilynn D. Burrowes and Dr. Glenn M. Chertow, 2014
26. **Handbook of Food Fortification and Health, volume I** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
27. **Handbook of Food Fortification and Health, volume II** edited by Dr. Victor R. Preedy, Dr. Rajaventhan Srirajaskanthan, Dr. Vinood B. Patel, 2013
28. **Diet Quality: An Evidence-Based Approach**, **volume I** edited by Dr. Victor R. Preedy, Dr. Lan-Ahn Hunter and Dr. Vinood B. Patel, 2013
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Dr. Han has been a member of Journal of Renal Nutrition Editorial Board since 2011 and Nutrition Today. She presented multiple lectures in nutritional management of CKD and stones in the United States and international conferences. She has been serving as the RenaLink editor since 2016 as a member of National Kidney Foundation Council on Renal Nutrition (NKF-CRN) Executive Committee. She is recipient of the Outstanding Service Award from the Academy of Nutrition and Dietetics (AND), Renal Practice Group; Recognition of Outstanding Research in Nutritional Science and Practice by the Korean Nutrition Society, American Society of Nutrition; and the Recognized Renal Dietitian Award from the NKF-CRN.

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Part I
Overview

Chapter 1
Epidemiology of Kidney Stones in the United States

Jeffrey H. William

Keywords Epidemiology · Demographics · Risk factors · Dietary intake · Obesity

Key Points

- Over the last few decades, there has been a dramatic increase in the prevalence of nephrolithiasis that spans many demographic cohorts, including gender and racial/ethnic groups.
- Risk factors for stone formation include a complex interplay of genetic predisposition, dietary intake, and environmental/geographic factors.
- Fluid intake is among the most important modifiable risk factors among stone formers, and multiple observational studies have shown that increasing intake of non sugar-sweetened beverages of any kind (including coffee, tea, beer, or wine) can decrease the risk of stone formation.
- While malabsorptive surgeries for morbid obesity may increase the risk of calcium oxalate nephrolithiasis, restrictive procedures like the gastric sleeve or laparoscopic adjustable banding may reduce the risk of nephrolithiasis compared to qualified patients who do not undergo surgery.
- Systemic diseases may be under-recognized contributors to stone development, highlighting the importance of early recognition and treatment of obesity, hypertension, diabetes mellitus, and chronic kidney disease as a means to prevent nephrolithiasis.

Introduction: Why Epidemiology Matters in Kidney Stones

Our approach to kidney stone diagnosis and management has been shaped by epidemiologic studies over the last few decades. These studies have helped us quantify the burden of disease, identify changing patterns among specific populations, and delineate risk factors that predict stone development. The interaction of these key epidemiologic principles has helped us understand the pathophysiology of this complex disease process and could potentially direct us toward novel approaches that will decrease the risk of stone formation in the evolving American population as a whole [1].

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Prevalence and Incidence: Stones Are More Common Now Than Ever Before

Kidney stones are quite common among adults, with the most recent figures from the National Health and Nutrition Examination Survey (NHANES 2007–2010 sample) estimating the overall prevalence of stone disease at 8.8% (95% confidence interval, 8.1–9.5) [2]. Prior to this, the only nationally representative sample published was from a previous analysis from NHANES III in 1994, with kidney stone prevalence estimated at 5.2% [3].

Studies analyzing the data over the past few decades have attempted to characterize why this has occurred, and these aspects will be addressed individually in the sections below. Prospective data from large cohort studies show an increasing risk of stone development in those individuals with elements of the metabolic syndrome, especially obesity [4, 5]. In a 35-year longitudinal retrospective study, the authors noted an increased proportion of uric acid stone formation associated with elevated BMI and low urine pH, as well as higher numbers of female calcium stone formers [6]. Therefore, given its epidemiologic and physiologic link to nephrolithiasis, the obesity epidemic in the United States is likely related to this rise in kidney stone prevalence, though temperature-related changes have also been postulated to be contributory [7]. An increase in highly sensitive radiologic imaging techniques may also translate into increased diagnosis. Even though nephrolithiasis risk increases with age, population-adjusted estimates suggest that this only partly explains the rising prevalence [2]. Nevertheless, the dramatic increase in prevalence that cuts across many demographic cohorts including gender and racial/ethnic groups supports the hypothesis that the American population has undoubtedly changed in a variety of ways over the last two decades.

Gender

The lifetime risk of stone formation has been estimated at 12% in men and 6% in women [1]. The overall prevalence of kidney stones increased from 6.3% in the initial NHANES (1971–1974) analysis to 10.3% in the 2007–2010 sample, while prevalence in women climbed from to 5.5% to 7.1% [2]. The underlying cause of this rise in prevalence among women has not yet been elucidated, though the magnitude of the impact of obesity on increased stone risk is reported to be greater in women than men [5]. In large American populations followed over time, the peak incidence of a symptomatic first stone was between the age of 40 and 60 in white men and in the late 20s in women [1]. Researchers at the Mayo Clinic in Rochester, Minnesota, have been studying the epidemiology of stone disease since 1950. Recently updated data from 1970 to 2000 show a peak incidence in men in the seventh decade, whereas the incidence in women peaked in the fourth decade [8].

Race/Ethnicity

The change in prevalence of kidney stones from NHANES III (1988–1994) to the most recent data was quite dramatic among black, non-Hispanic individuals, rising from 1.7% to 4.5% prevalence, representing a relative increase of >150%. The relative prevalence increase among Hispanics was also notable [1–3]. Despite this increase, nephrolithiasis risk remains lower in black non-Hispanic and Mexican Americans as compared to non-Hispanic Caucasian Americans, after adjustment for age, region, and diuretic use. These data support a prior study of African Americans [9], but the observed rates of stone formation among Mexican Americans quoted in a more recent study were significantly

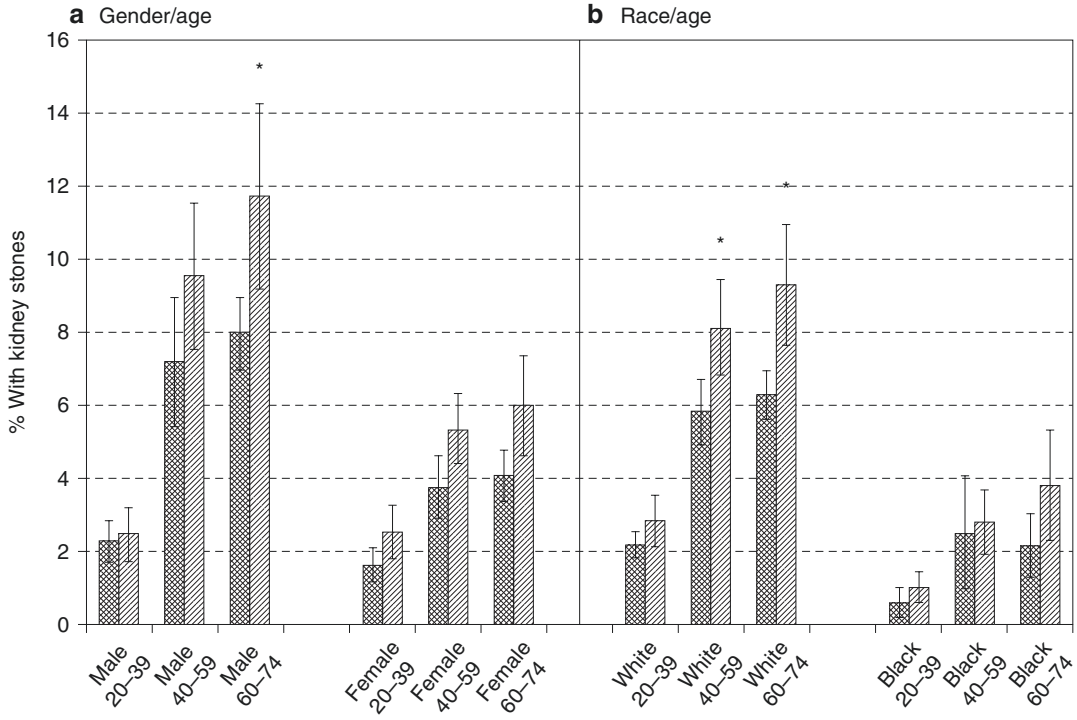

Fig. 1.1 Percent prevalence of history of nephrolithiasis for two cohorts (1976–1980 and 1988–1994) in each age group, stratified by gender (A) and race (B). Error bars indicate the 95% confidence interval. * = statistically significant time period difference. (Reprinted from Kidney International, Stamatelou et al. [3], with permission from Elsevier)

lower than those previously reported in the general Hispanic population, potentially related to population selection differences between the studies [3, 10]. Race-stratified analysis of the Atherosclerosis Risk in Communities (ARIC) cohort revealed stronger associations of kidney stones among African Americans with concurrent hypertriglyceridemia, older age, and gallstones compared to Caucasians [11] (Fig. 1.1).

Cost to Patients and Healthcare System

The costs associated with kidney stones have also increased from 1994 to 2000, including both inpatient and outpatient management, as represented by studies analyzing claims data from the Healthcare Cost and Utilization Project. From 1994 to 2000, hospitalizations decreased by 15%, but this was accompanied by many more outpatient visits for stone evaluations. Despite this shift, the total estimated cost for stone management increased from $1.37 billion in 1994 to $2.07 billion in 2000, representing a 50% increase [12]. The individual costs of nephrolithiasis are also notable. Retrospective claims-based data from 2000 were used to evaluate the incidence of stone disease in the United States. These project an average per person work-hours loss of 19 hours per year, with the total estimated costs of nephrolithiasis treatment of $3500 per person per year. Using population estimates, they proposed that $4.5 billion is spent in the treatment of the working population. However, with a projected 3.1 million lost workdays (at $250 per day), the additional indirect costs of nephrolithiasis may approach $775 million per year [13].

Stone Recurrence

Early studies in the 1980s and 1990s indicated that the symptomatic stone recurrence rate after an initial episode was 27–53% within 5–10 years [14, 15]. The recurrence rate did not appear to be influenced by gender, family history of stones, or urinary risk factors [14]. The Rochester Epidemiology Project devised a "recurrence of kidney stones" (ROKS) nomogram to predict stone recurrence, quoting the 10-year risk of recurrence of an initial episode to range from 12% to 56% between the first and fifth quintiles, depending on a set of risk factors that contradicted prior data and included gender, age, race, and family history of stones, among others (see Fig. 1.2) [16].

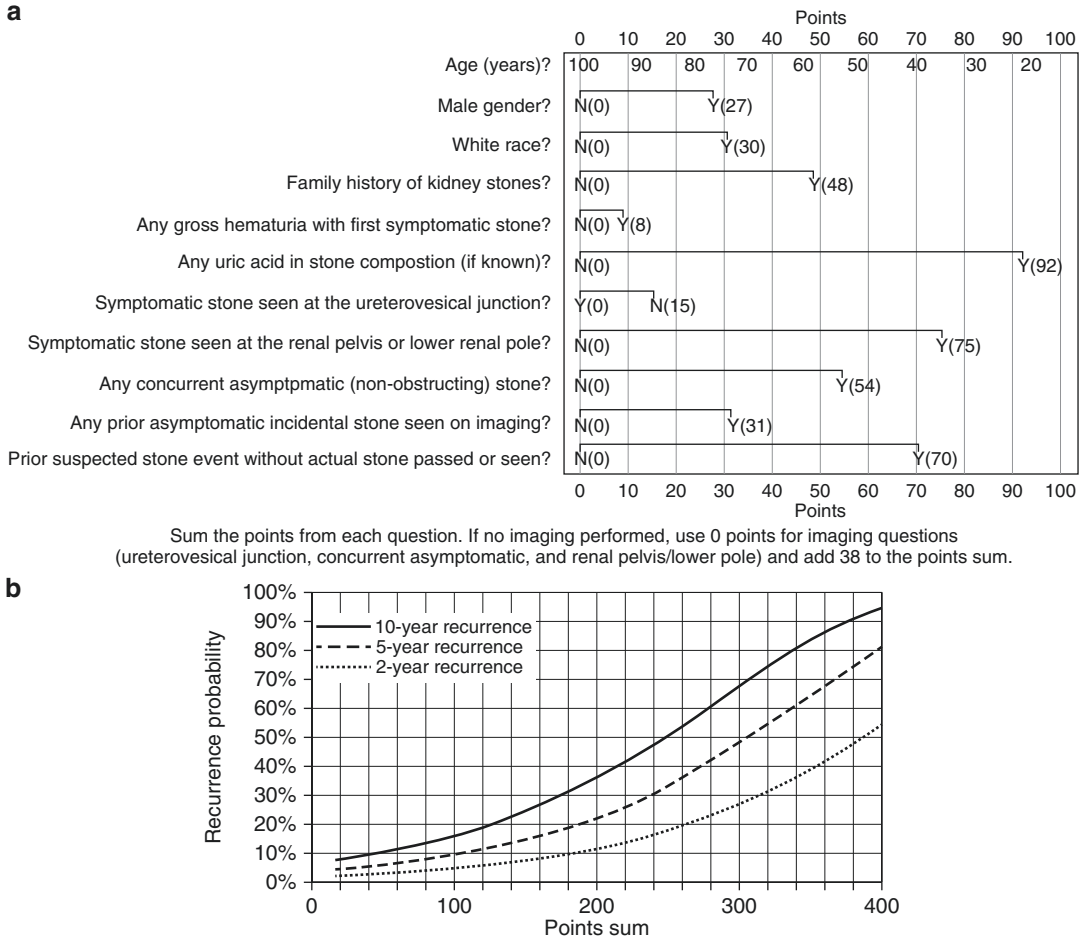

Fig. 1.2 ROKS nomogram. For an individual patient, points are totaled based on the questions in panel A. Recurrence risk estimates for 2, 5, and 10 years can then be determined based on these points' total. An electronic version of the ROKS nomogram is available on the QxMD app "Calculate." (Reprinted from Rule et al. [16], with permission from the American Society of Nephrology)

Risk Factors

Genetic: Family History

While a variety of monogenic inherited diseases, including cystinuria, distal renal tubular acidosis, variants of Bartter's syndrome, familial hypomagnesemia with hypercalciuria and nephrocalcinosis, Dent's disease, hypophosphatemic rickets with hypercalciuria, autosomal dominant hypoparathyroidism, and Lowe syndrome, can all cause nephrolithiasis [17], these rare diseases account for less than 1% of all nephrolithiasis cases [18]. A family history of nephrolithiasis is likely more complicated than simply genetics, involving a polygenic inheritance and environmental factors such as diet. In the Health Professionals Follow-Up Study cohort, family history significantly increased both age-adjusted prevalence (history of stone at baseline) and incidence (first stone found) [19]. Patients with a family history of kidney stones tend to develop stones at younger ages, with a higher rate of recurrence, and even more total symptomatic stone episodes [20, 21].

Environmental: Geography and Temperature

Temperature and geography also appear to be independent risk factors for kidney stone formation. Warm climates have long been positively associated with kidney stone formation. Across the United States, the Southeast region has a significantly higher prevalence (up to 50% in some analyses) than the Northwest [3, 7, 22]. The highest prevalence in the Second Cancer Prevention Survey (CPS II) was seen in six Southeastern states, Tennessee, Alabama, Mississippi, Georgia, North Carolina, and South Carolina, earning them the nickname "Kidney Stone Belt" [10]. Inadequate fluid intake in these hot climates may lead to higher urinary electrolyte concentrations and lower urine pH, promoting stone development [22, 23]. This phenomenon has been confirmed in a number of different populations, including American military recruits deployed to desert climates in the summer months, European immigrants to Israel, and members of Great Britain's Royal Navy serving in tropical areas [24–26]. This geographic variability may be related to differences in both sunlight indices and mean annual temperatures.

It was initially proposed in the 1970s and confirmed a decade later in an analysis of nearly 1.2 million subjects, who completed the CPS II and the National Health and Nutrition Examination Survey (NHANES II), that sunlight levels also increase the risk of kidney stones [10, 27].

In the continental United States, the mean annual temperature has increased by about 0.5 °C between the time periods of 1976–1980 and 1988–1994. As stated earlier, the prevalence of kidney stones increased from 3.6% to 5.2% between these analyses, indicating a potential correlation between this rise in temperature and the increased prevalence. With current predictions of global warming causing further increases in the mean annual temperature over the next half-century, the prevalence of kidney stones may increase markedly throughout the United States from this factor alone, with certain regions predicted to have a greater average temperature change than others (see Fig.1.3) [7].

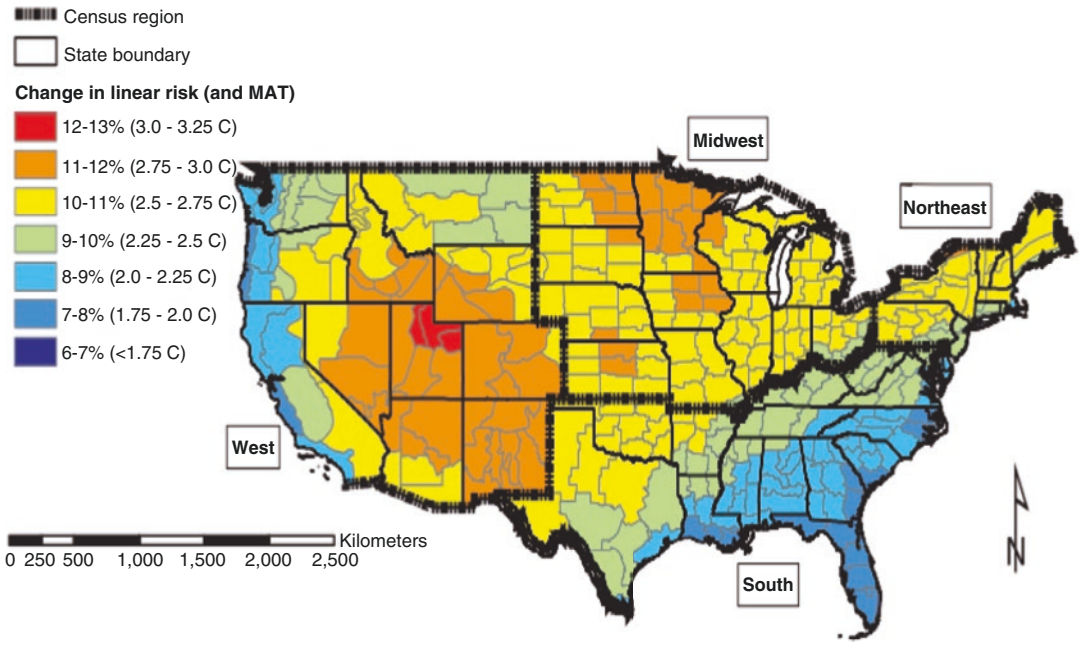

Fig. 1.3 Predicted warming and linear model nephrolithiasis risk change by 2050 for the United States. Strongest warming is in the midcontinent and upper Midwest. Heavy lines show the four US census regions, and light-gray lines show NOAA (National Oceanic and Atmospheric Administration) climate divisions. (Reprinted from Brikowski et al. [7]. Copyright (2008) National Academy of Sciences, U.S.A)

Dietary Factors

Dietary factors are thought to play an important role in the formation of kidney stones and the composition of urine. These factors include intake of calcium, sodium, fructose, fluids (including water and other beverages), and vitamin C. Since stone formers frequently change their diet prior to enrollment in studies, retrospective study data are often confounded by recall bias [1]. Additionally, studies are limited by the inability to measure concentrations of the different molecular components in food that may have multiple and contradictory effects on stone formation. Finally, changes measured in urinary chemistry do not predict the risk of nephrolithiasis, as they are intermediate endpoints for stone formation [18].

Calcium

Prospective studies of calcium intake have helped to correct misconceptions about calcium intake and stone formation. In a cohort of greater than 50,000 male health professionals aged 40–75 years, men with a higher intake of dietary calcium were found to have a lower risk of nephrolithiasis, with appropriate controlling for other risk factors [28]. This data has been confirmed in cohorts of women as well as a more recent analysis of men [29–31]. The mechanism for this apparent paradox is unclear, but low calcium intake has been shown to lead to increased oxalate absorption and urinary excretion [32]. Others have proposed that dairy products, the most common source of calcium in the United States, may have protective factors. In a randomized trial comparing two diets (normal vs. low calcium) in patients with idiopathic hypercalciuria and calcium oxalate stones, the associations in this observational studies were confirmed, with a reduction of 50% in the rate of recurrence among the

normal calcium intake cohort [33]. While it is clear that a calcium-restricted diet is not appropriate advice for calcium-based stone formers, there has not been an agreement on the recommendation of a high-calcium intake to reduce the risk of nephrolithiasis.

Oxalate

The dietary contribution of oxalate to the risk of calcium oxalate stone formation is unclear, with the proportion of urinary oxalate derived from dietary intake ranging from 10% to 50% [34]. While a portion of urinary oxalate comes from gastrointestinal absorption, there is also a significant contribution from endogenous metabolism. Dietary oxalate has variable bioavailability and may not be effectively absorbed, but it is thought that stone formers may have an increased proportion of gastrointestinal oxalate absorption than the general population. Though often recommended as a dietary modification, oxalate-restricted diets have not been studied prospectively because there is a lack of reliable information on the oxalate content of foods, though more modern measurement approaches are beginning to solve this problem [35].

Other Nutrients

A variety of other nutrients may predispose to nephrolithiasis via a variety of mechanisms. High animal protein intake increases calcium and uric acid excretion along with decreased urinary citrate [36], though an increased risk of stone formation was only seen in men with low BMIs in a prospective cohort study [31]. While increased sodium and sucrose intake increases calcium excretion [37, 38], potassium intake appears to decrease calcium excretion as well as increase urinary citrate [39]. Studies have shown gender differences among these risk factors, with sucrose intake increasing risk of stone formation in women and dietary potassium supplementation decreasing risk in men and older women [28–30]. Magnesium has also shown promising results, reducing oxalate absorption through complexing of oxalate in the gastrointestinal tract. While randomized trials examining the effect of magnesium supplementation on stone recurrence have been performed, the results have been confounded by concurrent treatment with thiazide diuretics and/or citrate supplementation [1]. Prospective studies have shown risk reduction in men but not women [29–31].

Phytate, the most abundant form of phosphate in plants, may also have an important role in stone prevention. It is found in highest quantities in cold cereal, dark bread, and beans. Phytate forms insoluble complexes with calcium in the gastrointestinal tract and prevents calcium reabsorption, subsequently decreasing urinary calcium excretion [30]. However, this mechanism may also lead to increased oxalate reabsorption from the digestive system, so a different mechanism involving inhibition of calcium oxalate crystal formation in the urine may be more applicable [40]. Urinary phytate levels have been shown to be significantly lower in calcium stone formers compared with healthy controls, but may be normalized with phytate supplementation [41]. In an analysis of the second Nurses' Health Study (NHS II), women in the highest quintile of phytate intake had a 36% lower risk of nephrolithiasis [30].

Vitamins

Vitamin C (ascorbic acid) can be metabolized to oxalate, and a metabolic study showed that 1000 mg of twice-daily vitamin C supplementation may increase urinary oxalate excretion by 20% in normal subjects and 33% in prior calcium oxalate stone formers, without a change in urinary pH [42].

Observational studies show that supplemental and dietary vitamin C intake may elevate the risk for calcium oxalate nephrolithiasis among men, after controlling for potassium intake [31, 43].

Vitamin B6 has been identified as a cofactor in oxalate metabolism, with deficiency leading to increased oxalate excretion in the urine. Supplementation of this vitamin B6 has not studied enough to support a recommendation for all calcium oxalate stone formers, but observational data has shown that higher intake of vitamin B6 may reduce the risk of stone formation in women, but not men [44, 45].

Vitamin D has become increasingly popular, and its influence on calcium and phosphorus metabolism has raised concern about the effect on kidney stone formation. While a small study of vitamin D repletion in healthy women did not increase urine calcium excretion [46], vitamin D metabolism in those with hypercalciuria may be disordered and have a greater effect on active dihydroxyvitamin D [18].

Beverages

Fluid intake is among the most important modifiable risk factors among stone formers, with multiple observational and randomized controlled trials supporting this [28–30, 47]. Though there are many myths about the ill effects of a variety of beverages in stone formers, observational studies have found that tea, coffee, beer, wine, soda, and orange juice are not associated with any increased risk of nephrolithiasis [48, 49]. A more recent study of high caffeine intake, which has previously been shown to increase urinary calcium excretion, concluded that there is actually a decreased risk of kidney stone formation [50]. The mechanisms underlying this paradox remain unclear but is likely related to protective properties of other unmeasured components of the caffeine-containing beverage (Table 1.1).

Table 1.1 Dietary risk factors for kidney stones examined in epidemiologic studies

Parameter	Risk of stone formation
Fluid intake	↓ Risk in men and women
Calcium (dairy and nondairy)	↓ Risk in men
Calcium (dietary)	↓ Risk in women
Magnesium	↓ Risk in men
Potassium	↓ Risk in men
Phytate	↓ Risk in women
Fruits, fiber, vegetables	↓ Risk in women
Coffee, tea, wine, beer, orange juice	↓ Risk in men and women
Sugar-sweetened beverages	↑ Risk in men and women
High fructose intake	↑ Risk in men and women
Animal protein consumption	↑ Risk in men with BMI <25 kg/m^2
Vitamin C	↑ Risk in men consuming >1000 mg/d
Spinach	↑ Risk in men and older women
Sodium	No change in risk
Sucrose	No change in risk
Vitamin B6	No change in risk
Vitamin D	No change in risk
Supplemental calcium	No change in risk

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Systemic Disease

The Metabolic Syndrome

A proposed mechanism of the metabolic syndrome leading to nephrolithiasis is increased acid load to the kidney coupled with a sustained increased delivery of fat to the kidneys that occurs with a high-fat Western diet. This may lead to renal proximal tubular injury (lipotoxicity) and consequently defective renal ammoniagenesis. Compensatory hyperinsulinemia seen in the insulin resistance of type 2 diabetes mellitus may also lead to impaired renal acid excretion [52] as well as increased urinary calcium excretion [53]. While a low urinary pH clearly contributes to the formation of uric acid stones [54, 55], this defect in renal acid excretion may also lead to hypocitraturia, leading to calcium-based stone development [56]. The etiology of these two major stone types are inextricably linked as well, since calcium oxalate stones can also develop from uric acid-induced crystallization of calcium salts [57].

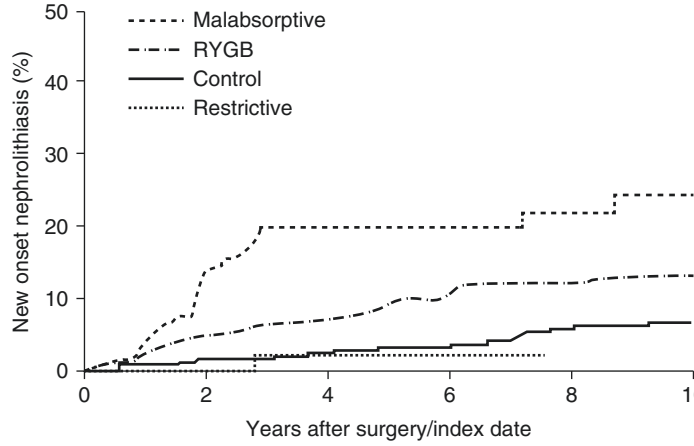
Obesity and Bariatric Surgery

Among the largest cohort studies with long-term follow-up analyzed for kidney stone history, prevalence and incidence of nephrolithiasis were highly associated with increased BMI and obesity [58].This prevalence seems to be a bit higher in women, potentially attributable to a higher degree of adiposity at a given BMI. The elevated risk in obesity is abrogated once a BMI of 30 is reached and does not increase further with very elevated BMI [59]. Obesity also seems to favor uric acid nephrolithiasis, though indirectly through insulin resistance and subsequent impairment of ammoniagenesis with persistently acidic urine [60].Such an association has not been consistently seen in urinary calcium or citrate excretion, raising the possibility that the association of increased nephrolithiasis among obese individuals may be driven primarily by uric acid stone formation [61, 62].

Bariatric surgery has evolved over the last 50 years, improving from the highly malabsorptive jejunoileal bypass eventually banned by the FDA in the 1970s due to severe complications to the immensely popular Roux-en-Y gastric bypass (RYGB) and gastric sleeve procedures [18]. Malabsorptive surgeries lead to hyperoxaluria and hypocitraturia, increasing the risk for calcium oxalate nephrolithiasis [63–65]. Restrictive procedures like the gastric sleeve or laparoscopic adjustable banding may reduce the risk of nephrolithiasis in obese controls who do not undergo surgery (see Fig.1.4) [65].

Diabetes Mellitus

A large cross-sectional analysis of three cohorts totaling greater than 200,000 subjects (Nurses' Health Study [NHS I and II] and the Health Professionals Follow-Up Study [HPFS]) revealed a relative risk of prevalent kidney stone formation ranging from 1.31 in men to 1.60 in younger women. Conversely, the relative risk of incident diabetes mellitus in subjects with a prior history of nephrolithiasis was also higher among the entire study population [4]. In a study confirming the defective renal acid excretion contributing to uric acid nephrolithiasis, investigators also noted that there is a high incidence of glucose intolerance and type 2 diabetes mellitus in pure uric acid stone formers as compared to calcium oxalate [67, 68]. Among patients with uric acid nephrolithiasis, two studies concluded that 28.5–33% of the diabetics reported stone formation versus 6.2–13% of the nondiabetics, with a greater difference detected in the female cohort [69, 70]. Postprandial insulinemia in normal subjects is associated with increased calcium and phosphorus excretion, implying that hyperinsulinemia



No. at risk						
Malabsorptive	101	77	58	47	36	27
RYGB	563	502	408	293	208	94
Control	729	673	572	416	282	135
Restrictive	55	54	36	18	0	0

Fig. 1.4 The risk of incident stones was greater after RYGB or malabsorptive bariatric procedures, compared with that in matched obese controls ($P < 0.001$ overall). Patients with restrictive procedures were not at increased risk. (Reprinted from Lieske et al. [66], with permission from Elsevier)

occurring postprandially may play an important physiologic role in the regulation of renal tubular calcium reabsorption [71]. However, given the predominance of calcium-based stones in the general population, the prevalence of calcium oxalate stones still remain higher in nondiabetics vs. diabetics who form stones [70].

Hypertension

A cross-sectional study of greater than 1 million men and women demonstrated a higher prevalence of nephrolithiasis in hypertensive versus normotensive subjects [22]. This association was confirmed in a large prospective cohort study of 51,529 men, where among subjects who reported a diagnosis of both nephrolithiasis and hypertension, 79.5% reported that nephrolithiasis occurred either prior to or concomitant with the diagnosis of hypertension. These data would seem to support the hypothesis that the occurrence of nephrolithiasis may increase the risk of future hypertension [72]. Some believe that the pathophysiologic explanation underpinning this association is the disruption in normal calcium metabolism, as hypercalciuria appears more frequently in those with essential hypertension [73–75]. As an additional physiologic link, evaluation of 24-hour urine collections among the three large cohorts described above (NHS I, NHS II, and HPFS) showed an independent association of hypertension and hypocitraturia [76]. These data support those of salt-sensitive hypertensive rat models [77–79]. Hypertensive patients may also be at risk for uric acid nephrolithiasis, as childhood serum uric acid elevations have been associated with both childhood and adult hypertension [80].

Atherosclerosis/Cardiovascular Disease

The link between cardiovascular disease and nephrolithiasis was first reported in a longitudinal study with a 20-year follow-up, where a significant association was found between kidney stones and subclinical carotid atherosclerosis [81]. The CARDIA study, a population-based observational

study of >5000 white and African American young men and women aged 18 to 30, used ultrasound to determine carotid thickness and stenosis, showing an association between increased carotid thickness, particularly in the internal carotid artery, and symptomatic kidney stone formation. A case-control study of calcium oxalate stone formers and normal controls reported that significantly more stone formers had a history of coronary artery disease (CAD) versus controls, who had no CAD history [82]. Further data from the Rochester Epidemiology Project revealed a 31% increased risk of myocardial infarction in stone formers, after adjustment for chronic kidney disease and other comorbidities associated with myocardial infarction [83]. Gender discrepancies were revealed in analysis of the HPFS and NHS I and II, where a history of kidney stones was associated with an increase in the risk of coronary heart disease in women, but was not significant in men.

Chronic Kidney Disease

Studies have shown an association between the development of chronic kidney disease (CKD) and nephrolithiasis. In case-control studies, kidney stone formation was found to be an independent risk factor for CKD and ESRD, after adjusting for the most common etiologies including diabetes mellitus, hypertension, and cardiovascular disease [84, 85]. In the NHANES III cohort, subjects with higher BMI (> = 27 kg/m^2) who formed stones were more likely to have lower GFR than lower-BMI subjects. Additionally, the investigators calculated that the probability of a GFR in the stage 3 CKD range (30–59 mL/min/1.73m^2) in an overweight stone former was almost twice that of a similarly overweight non-stone former (relative risk ratio 1.87) [86]. With similar gender-based differences reported in the HPFS and NHS I and II cohorts above, analysis of a more recent NHANES cohort from 2007 to 2010 uncovered an increased risk of CKD and ESRD among women with a history of kidney stones, but not men [87].

Pediatric Population

Numerous studies have noted the increasing incidence and prevalence of nephrolithiasis in the pediatric population [88–90]. Using the Kids' Inpatient Database (KID), authors have analyzed national data that captures the use of hospital services in pediatric kidney stone disease [91]. Kidney stones appear to be more prevalent among males in the first decade of life, but this transitions to females in the second decade. Between 1997 and 2003, there was a dramatic increase in stone diseases treated in the inpatient setting across both sexes (up to 365%). As the prevalence of adult obesity doubled between 1980 and 2002, it nearly tripled in children aged 6–19 years [92]. Some implicate these coincidental findings to explain this rise, though there is no data to support this in the pediatric population at present. Analyses indicate that hypertension and diabetes mellitus in children younger than the age of 6 may predispose to stone formation, but these associations did not retain significance at older ages. Stone disease among the very young may also be associated with greater systemic effects, a marker for overall poor health. Given the small numbers of children with kidney stones, interpreting these findings can be challenging.

To provide further clarification, investigators completed a population-based study in Olmsted County, Minnesota, over a 25-year period (1984–2008). They found that the incidence of kidney stones increased threefold in adolescents (12–17 years old), though the overall incidence in the pediatric population was still ten-fold less than adults in the same county. The authors suggest that increased use of computed tomography technology among children may be contributing to the increased incidence, rather than a true increase in stone disease, though the exact reasons remain unclear [93].

Summary

Decades of observational cohort studies and randomized controlled trials have revealed important trends in the epidemiology of stone disease in the United States. As the overall prevalence and incidence of nephrolithiasis rise across the population, the identification of important unmodifiable (e.g., genetic) and modifiable (e.g., dietary) risk factors may help us target ways to decrease the overall burden of stone disease and stem the costs to the healthcare system and the economy. Systemic disease is being increasingly recognized as a contributor to stone development, and early recognition and treatment of obesity, hypertension, diabetes mellitus, and chronic kidney disease may prove to be key interventions in the prevention of nephrolithiasis.

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Part II
Basics of Kidney Stone

Chapter 2
Pathophysiology of Kidney Stone Formation

Elaine M. Worcester

Keywords Calcium oxalate · Calcium phosphate · Supersaturation · Citrate · Idiopathic hypercalciuria Hyperoxaluria · Randall's plaque

Introduction

Kidney stones are common, and in the United States, the prevalence of kidney stones has been rising steadily over the past 50 years in both men and women, and in all ethnic groups [1]. The prevalence in children is rising as well [2]. The reasons for this are unclear, but epidemiology suggests links to other diseases increasing in prevalence, such as diabetes and obesity, which are known to have genetic risk factors, and strong environmental drivers – particularly diet. The main pathway by which these factors lead to stones is by increasing renal excretion and urinary supersaturation of stone components, allowing crystals to form and grow in the urinary tract and become clinically apparent stones. Although some stone formers have monogenic diseases such as cystinuria, or acquired conditions such as bowel resection, which create the conditions for stone formation, most stone formers have no systemic disease that explains their stones. These so-called idiopathic stone formers account for the large majority of patients and may make either calcium or uric acid stones.

The majority of stones – about 80% – are composed of calcium salts, and most are made primarily of calcium oxalate (CaOx), often with a small admixture of calcium phosphate (CaP) as apatite [3]. Stones composed mainly (>50%) of CaP are less common, although they are relatively more common among female stone formers below the age of 50 [4]. Uric acid stones are most common in stone formers above the age of 50 and comprise about 10% of stones overall. In rare cases stones are the result of infection (struvite stones), inborn errors of metabolism (cystine or 2,8-dihydroxyadenine stones), or insoluble drug metabolites [5].

Although each stone type has unique pathophysiologic features, in one sense the final cause of stones is similar for all – urine supersaturation (SS) with respect to stone components has reached levels that permit crystal formation and retention in the urinary tract. The corollary is that treatment modalities for all stones share the common goal of lowering SS. Specifics of treatment will be dealt with in other chapters.

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Driving Forces for Crystallization

Nucleation and growth of crystals require urine contain the crystal-forming substances at concentrations above their solubility, termed SS [6]. SS is driven by daily excretions of water and stone-forming material, which determine the concentration of the stone solutes. For uric acid and CaP, urine pH is also a factor (Fig.2.1) [7]. Median urine pH is about 6 in normal subjects. Uric acid solubility falls markedly as urine pH drops below 6, while CaP solubility falls as urine pH rises above 6. Most uric acid stone formers are notable for their low urine pH, while CaP stone formers generally have higher urine pH (persistently > 6.2), although they do not usually have any defects of urine acidification.

SS for calcium and urate salts is calculated using 24 hour urinary pH, volume, and concentrations of calcium, oxalate, phosphate, uric acid, and other urine molecules that form complexes with them. Computer algorithms can solve for the concentrations of all available salts, and, correcting for the ionic strength of the urine [8], one obtains a useful measure of SS for a given salt, often expressed as a multiple of solubility: 1 means that the salt is present in a concentration equal to its solubility, <1 means undersaturated, and >1 is SS. Urine SS for calcium oxalate is >1 in almost everyone but is higher in stone formers than in normal subjects. By contrast, urine SS for CaP (actually brushite, the precursor phase) and uric acid is often <1 in non-stone formers.

The risk for SS with respect to CaOx rises directly with urine calcium (also true for CaP stones) and oxalate concentration (Fig. 2.2) [9], while increased urine volume will lower SS. Not surprisingly, the same relationships are found between excretion and the risk of stone formation in large cohort studies (Fig. 2.3).

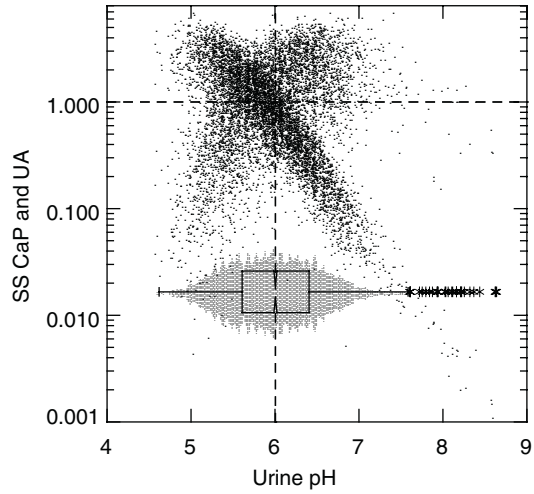

Fig. 2.1 Relationship between urine pH and relative supersaturation (SS) for uric acid (UA) and calcium phosphate (CaP). The horizontal dashed line at 1 represents the thermodynamic solubility point; above the line represent urines that are supersaturated, and below the line urines are undersaturated. Each point represents a single 24 hour urine from a stone former or normal subject from a single lab. The figure illustrates the rise in CaP SS (points rising to the right) and the fall in UA SS (points falling to the right) with increasing urine pH. The horizontally distributed points represent the distribution of urine pH values in the population; the notched box is a nonparametric representation of the median and one quartile above and below. The median is at approximately pH 6 (dashed vertical line), which also represents the dual minimum for SS. (Used by permission from Ref. [7])

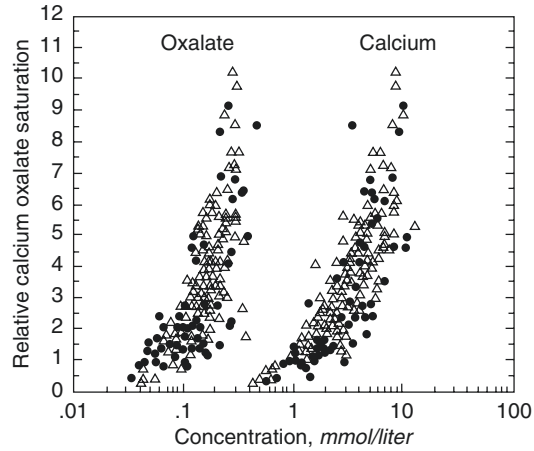

Fig. 2.2 Relationship between the concentration of oxalate and calcium in urine and relative SS for calcium oxalate. Each point represents a 24 hour urine collected by a healthy adult man (triangle) or woman (circle). Note log scale on X-axis. (Used by permission from Ref. [9])

It is common to assess stone risk by using 24 hour urines that quantitate daily excretions of stone salts. However, it is important to remember that excretion of water and solutes, and therefore SS, vary over the course of the day (Fig. 2.4) and that the 24 hour urine is therefore an average [10]. In a clinical research center, calcium stone formers (gray bars) and normal subjects (hatched bars) were fed identical diets at fixed intervals, with timed urine and blood collections done fasting (Fast),between breakfast (B), lunch (L), and supper (S) and overnight (ON) (Fig. 2.4). Urinary calcium concentrations are higher in the stone formers after meals and tend to be highest ON, when urine volume falls. SS for CaOx and CaP reflects that the integrated effect of solute excretion, fluid intake, and urine pH is higher in stone formers much of the day and highest ON. Given that the ON period is a significant fraction of the day, it is important to remember that SS may be significantly above the average at that time. Note that urine pH falls ON, so that uric acid SS will also be higher during that time period (not shown).

Crystal Inhibitors

That a 24 hour urine can possess SS > 1 means crystallization must be retarded; otherwise crystals would form, grow, and dissipate the SS. A number of urinary substances, including small molecules such as citrate and pyrophosphate, proteins such as osteopontin and uromodulin, and glycosaminoglycans, have been found to inhibit nucleation, aggregation, and growth of CaP and CaOx in vitro [11, 12], and differences in the inhibitory activity of urine toward calcium crystallization have been found between idiopathic calcium stone formers and normal individuals [13, 14], suggesting that defects in inhibitors may play a role in stone formation in some patients. Many of the same molecules are also found as part of the organic matrix of stones [15], suggesting that their role in stone formation may be complex. However, the only inhibitor with current clinical significance is citrate, which can be measured in the urine and administered as a medication. Citrate binds calcium, thus reducing its availability to form CaOx or CaP crystals, and also inhibits the growth of both crystals. Inhibitory molecules probably play a role in non-calcium stone formation as well [16].

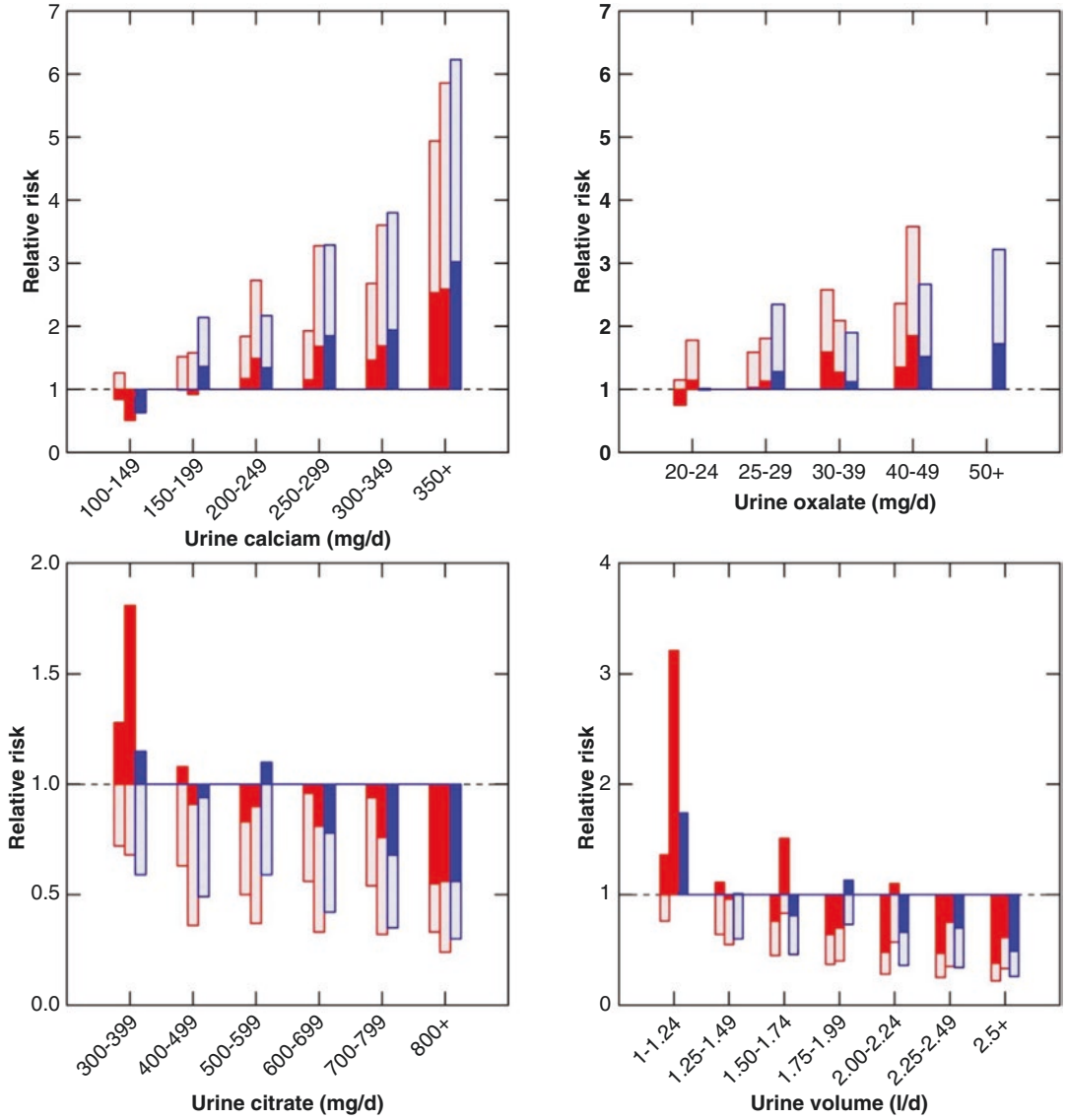

Fig. 2.3 Association between daily urine excretion of calcium (upper left), oxalate (upper right), and citrate (lower left) and volume (lower right) and relative risk of incident stone formation in three large cohorts. Data from women (open red bars) and men (open blue bars) shown separately. Horizontal lines in each panel indicate a relative risk of 1. For calcium and oxalate, the top of the bar indicates the relative risk, while the bottom of the bar marks the lower 95th percentile of that risk. When the bottom of the bar is above 1, the risk of stone formation is significantly increased. For citrate and volume, the relationship is inverse: the bottom of the bar marks relative risk, and when the top of the bar is below 1, risk is significantly decreased. (Used by permission from https://kidneystones.uchicago.edu/chapter-five-idiopathic-calcium-stones, redrawn from Ref. [48])

Site of Stone Formation in the Kidney

Current evidence suggests that there are at least three pathways to stone formation [17], which may coexist in a given patient. Stones may form (1) in free solution in the renal pelvis, (2) as overgrowths on suburothelial papillary mineral deposits called Randall's plaque (RP), or (3) as extensions of

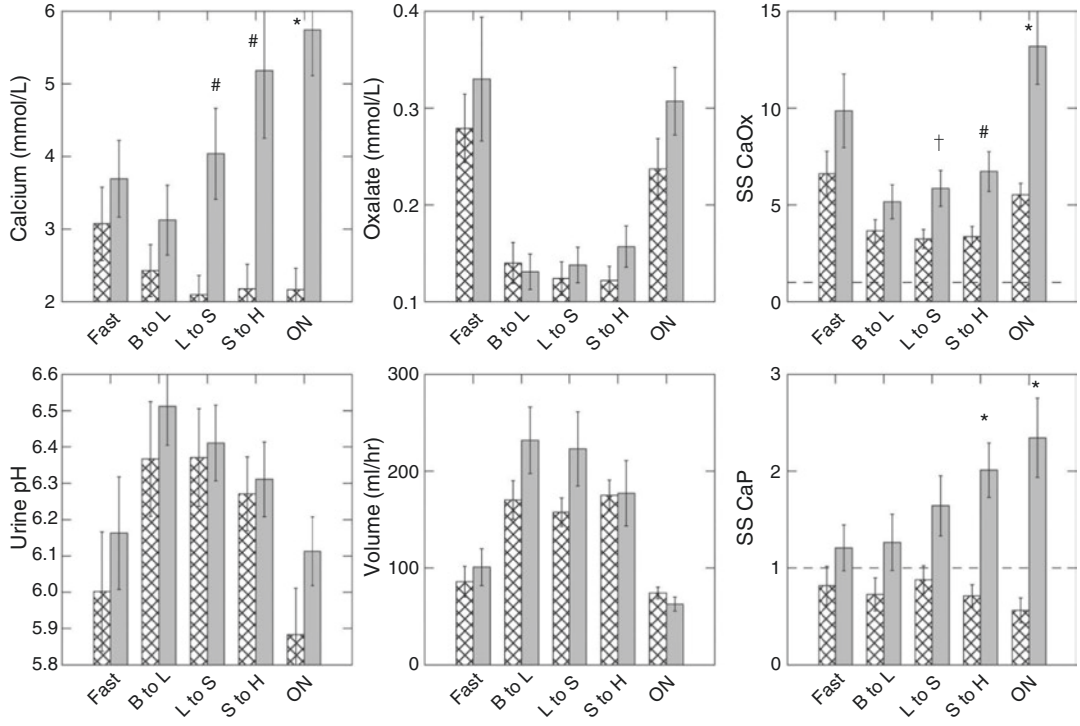

Fig. 2.4 Urinary solute concentrations, pH, volume, and supersaturation for calcium oxalate and calcium phosphate throughout the day. Normal subjects (hatched bars) and calcium stone formers with idiopathic hypercalciuria (gray bars) were studied on fixed metabolic diets during the fasting period (Fast), between breakfast (B) and lunch (L), lunch to supper (S), supper to home (H), and overnight (ON). Horizontal lines in the upper and lower right panels indicate SS of 1. Calcium oxalate supersaturation is above 1 at all time points in all subjects, while supersaturation for CaP is above 1 only in stone formers. Values are mean ± SEM. Differences between stone formers and normal within time period:*, $p < 0.001$; #, $p < 0.01$; †, $p < 0.05$. (Used by permission from Ref. [10])

intratubular mineral plugs. In the second and third pathways, mineral deposits within the renal parenchyma provide nucleating sites for stone growth and attachment, while the nucleating site in the first pathway is often unclear. Certain pathways appear to be characteristic of specific types of stone formers; in particular, growth on RP seems to be the way many idiopathic CaOx stones form [18].

RP initiates in the basement membranes of the thin limbs of Henle's loops as micro-particles containing CaP and macromolecules [19], which enlarge and extend into the interstitium and eventually reach the underside of the urothelium, where they are visible as white plaque (Fig. 2.5). Plaque formation appears to be fostered by low urine volume and pH, and hypercalciuria [20].

Idiopathic CaOx stones (Fig. 2.5, *panel a*) often form as overgrowths on RP on otherwise normal appearing renal papillae [21, 22]. Stone growth appears to start with loss of urothelial integrity over a plaque deposit which allows urine molecules such as Tamm-Horsfall protein and osteopontin to adhere to the exposed plaque. This surface permits nucleation of apatite crystals, and eventually CaOx crystals, intermingled with urine macromolecules, gradually forming the bulk of the stone, which remains attached to the papillae in most cases. When the stone is detached, some of the interstitial plaque often pulls away with it (Fig. 2.5, *panel b, inset*).

Idiopathic stones composed primarily of CaP (as either apatite or brushite (CaHPO4)) do not generally form in this way, although RP may be present. Papillae often exhibit plugging of inner medullary collecting ducts (IMCD) and Bellini ducts (BD) with apatite crystals (Fig. 2.6, *panel a*), which damage the tubular lining cells and promote peritubular scarring (Fig. 2.6, *panel b*) [23]. Apatite plugs may extend out into the urinary space from the mouth of dilated BD (Fig. 2.6, *panels*

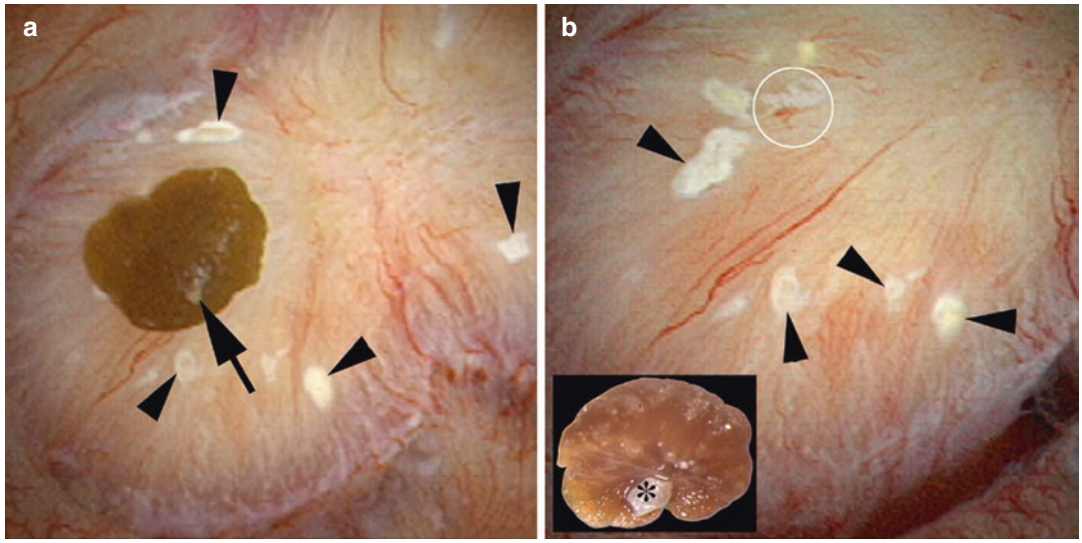

Fig. 2.5 Calcium oxalate stone attached to papillum, before and after removal during endoscopic stone surgery. A 3 mm stone (arrow, panel **a**) is seen lying on the papillary surface; panel **b** shows the same papillum after stone removal. Sites of Randall's plaque can be seen on the papillary surface (arrows, panel **b**), including at the site of prior stone attachment (upper arrow, panel **b**).The removed stone (panel **b**, inset) has a white patch on its undersurface (arrow) representing plaque which came off with the stone when it was detached. (Used by permission from Ref. [7])

a and b, asterisk) and tiny stones can grow over them. Plugged IMCD filled with apatite can also be seen beneath the papillary urothelium (Fig. 2.6, *panels c and d*). Perhaps because of papillary injury, or because as a group they have more episodes of shock wave lithotripsy, the renal cortex of patients with idiopathic CaP stones may exhibit scarring, which is rare in idiopathic CaOx stone formers.

All patients studied thus far with stones in the setting of systemic diseases, such as cystinuria [24], primary hyperparathyroidism [25], distal renal tubular acidosis [26], bowel resection [27, 28], or primary hyperoxaluria [29], have been found to have plugging of their BD and IMCD, usually with apatite but sometimes with other crystals as well, and plugging is always associated with papillary scarring and often cortical damage [30]. If tubule plugging is extensive, it may appear as nephrocalcinosis on radiographs; this can be seen in patients with idiopathic CaP stones as well as in patients with distal renal tubular acidosis or primary hyperparathyroidism.

Patients with medullary sponge kidney may also have nephrocalcinosis on X-ray, but differ from all other groups of stone formers in the site of stone formation [31]. In this developmental disease, papillae contain numerous dilated IMCD, and multiple small stones composed of CaOx or CaP may form in these ducts, without adhering to or damaging the epithelium. Due to their anatomical abnormalities, stone formation can be difficult to control in this group of patients.

Genetic Factors in Stone Formation

An increasing number of monogenic causes of calcium stone formation have been identified in the past few years (Table 2.1), and it is likely that more will be uncovered as genetic medicine matures. It is notable that most of the identified genes appear to cause hypercalciuria, through various mechanisms,

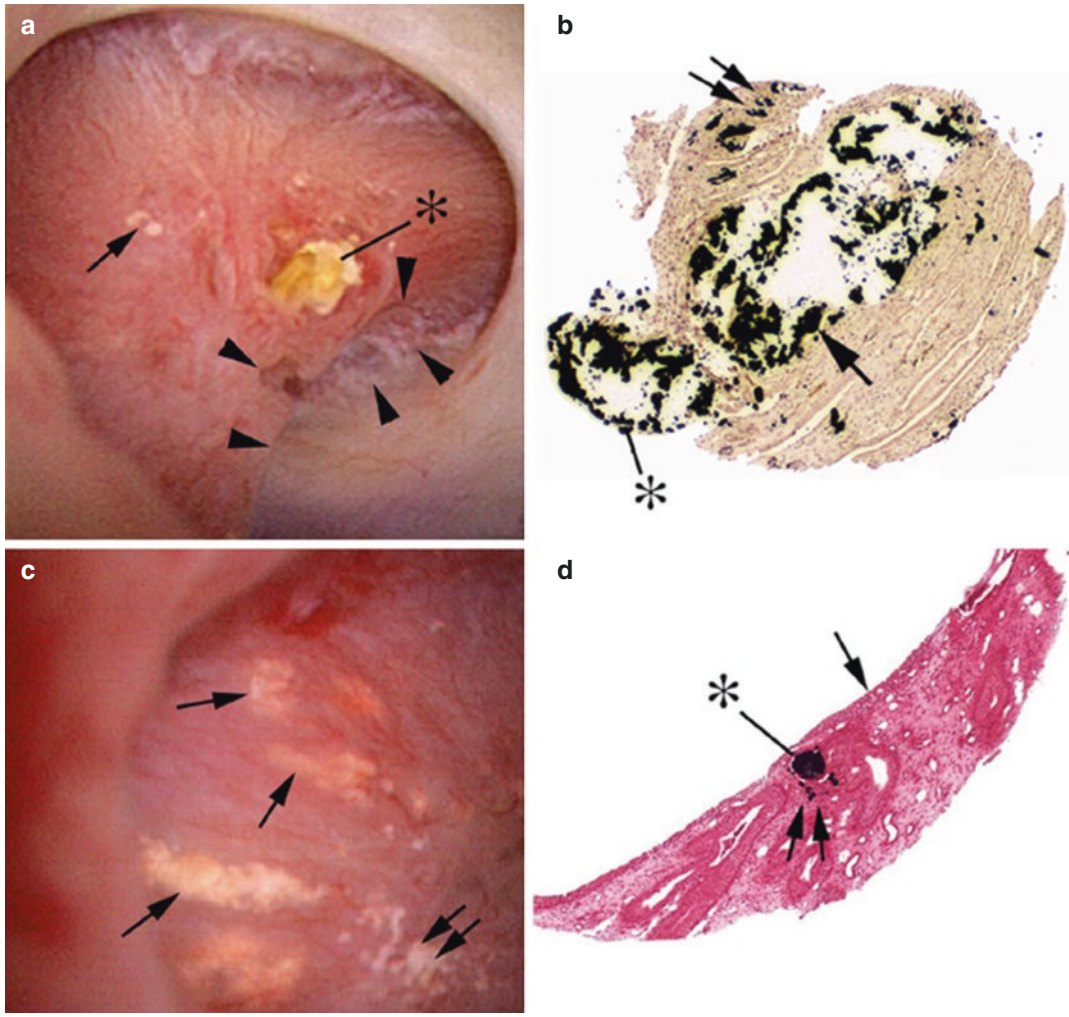

Fig. 2.6 Endoscopic and histologic images from brushite stone former. Panel **a**, a papillum with crystal deposits protruding from the mouth of an enlarged duct of Bellini (asterisk). A site of Randall's plaque is seen (arrow) and evidence of papillary damage including pitting (arrowheads). Panel **b**, a light microscopic image shows crystal deposition in a papillary biopsy stained with the Yasue method, which detects calcium deposits. Crystals protrude from the mouth of the duct of Bellini (asterisk) and fill the associated inner medullary collecting duct (arrow) which is greatly dilated; the lining epithelium is absent, and peritubular fibrosis is present. The double arrows show an area of Randall's plaque in the interstitium. Panel **c** shows yellowish mineral deposition in the lumens of inner medullary collecting ducts visible on the papillary surface (arrows). Double arrows show plaque. Panel **d** confirms that the site of the deposits seen in panel **c** is the collecting duct lumen (asterisk), just below the urothelium (arrow). (Used by permission from Ref. [7])

with the remainder causing hyperoxaluria. Although these diseases cause a small percent of stone disease, they are important to identify because they are often associated with chronic kidney disease as well. In addition to these genes, some additional genetic risk factors have been identified by their association with stone formation, such as claudin 14 [32], although they have not yet been linked with specific syndromes.

Table 2.1 Monogenic causes of calcium stones

Disease	Mode	Gene/gene product	Function	Stones	NC	Phenotype
Dent's disease type 1	XR	CLCN5/ClC-5	Endosomal Cl channel	+	+	Hypercalciuria, LMW proteinuria, CKD
Dent's disease type 2	XR	OCRL/inositolpoly-phosphate-5-phosphatase	Located in Golgi	+	+/−	Hypercalciuria, LMW proteinuria, CKD
Bartter syndrome type I	AR	SLC12A1/NKCC2	Na-K-2Cl co-transporter		+	Hypercalciuria, hypokalemic alkalosis
Bartter syndrome type II	AR	KCNJ1/ROMK	K channel		+	Hypercalciuria, hypokalemic alkalosis
Bartter syndrome type III	AR	CLCNKB/ClC-Kb	Basolateral Cl channel	+	+	Hypercalciuria, hypokalemic alkalosis
Bartter syndrome type V	AD	CASR/CaSR (severe gain of function)	Calcium-sensing receptor	+	+	Hypercalciuria, hypokalemic alkalosis, CKD, hypocalcemia
Hypocalcemic hypercalciuria	AD	CASR/CaSR (gain of function)	Calcium-sensing receptor		+	Hypercalciuria, CKD, hypocalcemia
Familial hypomagnesemia with hypercalciuria	AR	CLDN16/claudin 16	Tight junction protein	+	+	Hypercalciuria, hypermagnesuria, CKD, hypomagnesemia
Familial hypomagnesemia with hypercalciuria	AR	CLDN19/claudin 19	Tight junction protein	+	+	Hypercalciuria, hypermagnesuria, CKD, hypomagnesemia, ocular abnormalities
Hypophosphatemic nephrolithiasis/ osteoporosis	AR	SLC34A1/NaPi-IIa	Sodium-phosphate co-transporter	+	+	Hypercalcemia, hypercalciuria, hypophosphatemia
Hereditary hypophosphatemic rickets with hypercalciuria[a]	AR	SLC34A3/NaPi-IIc	Sodium-phosphate co-transporter	rare	rare	Hypercalciuria, hypophosphatemia, rickets
Distal renal tubular acidosis	AD	SLC4A1/AE1	Cl-bicarbonate exchanger	+	+	Hypercalciuria, hypokalemia, osteomalacia,
Distal RTA with hearing loss	AR	ATP6V1B1/B1 subunit of vacuolar H-ATPase	Proton secretion	+	+	Hypercalciuria, hypokalemia, rickets
Distal RTA	AR	ATP6V0A4/A4 subunit of vacuolar H-ATPase	Proton secretion	+	+	Hypercalciuria, hypokalemia, rickets
Primary hyperoxaluria type I	AR	AGXT/alanine glyoxylate aminotransferase	Converts glyoxalate to glycine	+	+	Hyperoxaluria, CKD
Primary hyperoxaluria type II	AR	GRHPR/glyoxylate reductase	Converts glyoxylate to glycolate	+		Hyperoxaluria, CKD
Primary hyperoxaluria type III	AR	HOGA1/4-hydroxy-2-oxoglutarate aldolase 1	Converts HOG to glyoxylate and pyruvate	+		Hyperoxaluria, CKD
CYP24A1 deficiency/ idiopathic infantile hypercalcemia	AR	CYP24A1	Degrades 1,25 vitamin D	+	+	Hypercalcemia, hypercalciuria

NC nephrocalcinosis, *LMW* low molecular weight, *CKD* chronic kidney disease, *XR* X-linked recessive, *AR* autosomal recessive, *AD* autosomal dominant, *RTA* renal tubular acidosis, *aa* amino acid

[a]Also associated with idiopathic infantile hypercalcemia

Idiopathic Calcium Stones

Calcium stones may form as a result of a number of acquired and some inherited diseases; however, idiopathic stone formers are the most commonly encountered patients in clinical practice. Most have metabolic abnormalities that foster high urine SS, and more than one abnormality may coexist in the same patient (Table 2.2).

Idiopathic Hypercalciuria (IH)

The hypercalciuria found in about 50% of idiopathic calcium stone formers is a familial trait, affecting about half of the first-degree relatives of affected patients [33]. The exact cut-off separating normal and elevated urine calcium excretions has never been precisely defined, but the upper 95th percentiles (250 and 300 mg daily, women and men, respectively) are commonly used for research on pathogenesis. However, in large prospective cohorts, the risk for stones is significantly increased in both men and women at excretions above 200 mg/day (Fig. 2.3, *upper left panel*). IH is an important risk factor for kidney stones in childhood as well [34].

The extra urine calcium arises in part from high gut calcium absorption, driven by high serum levels of calcitriol [35]; the cause of high calcitriol levels in these patients is unclear. Balance studies show that gut calcium absorption in normal men and women averages 21% of intake at most levels of dietary calcium [36], while median absorption of dietary calcium in patients with IH was 37.5%. However, renal tubular calcium reabsorption is reduced in IH compared to normal subjects [37] (Fig. 2.7). In men and women with IH, urine calcium is significantly higher for a given filtered load of calcium, fasting, but particularly after eating, compared to normal subjects. Thus, tubular reabsorption of calcium is lower in IH, especially in the fed period when excretion rises markedly, although all subjects were fed identical diets.

Urine calcium excretion in IH can often exceed gut calcium absorption, meaning bone mineral balance is negative (Fig. 2.8). While most normal subjects can reach neutral calcium balances at intakes of calcium of 1000 mg daily, many patients with IH remain in negative calcium balance at this level of intake, despite higher gut calcium absorption [36]. In concordance with this physiology, low bone mineral density has been repeatedly found in patients with IH, and fracture risk is increased [38].

Studies using endogenous lithium clearance show that patients with IH have lower reabsorption of calcium and sodium in the proximal tubule than normal subjects fed the same food, which is most evident in the post-prandial period [39, 40]. The increased sodium delivered to the distal nephron can be reabsorbed quantitatively, but the additional calcium cannot be completely reclaimed. However, when the sexes are examined separately, women with IH do not differ from normal women with respect to proximal tubule calcium handling, and the distal nephron appears to be the most important site of diminished calcium reabsorption [41]. The mechanism for this altered calcium reabsorption is unclear but may involve increased sensitivity to serum calcium levels at the level of the kidney and the parathyroid gland [42].

Calcium excretion in IH may be especially sensitive to dietary intakes of sodium. Multiple observational and experimental studies have demonstrated that calcium excretion rises more steeply in IH than in normal subjects for a given increase in sodium excretion [36]. It may be that lower sodium diets can improve calcium balance in IH, but this has not yet been tested. Thiazide diuretics have been used to prevent stone recurrence, as they increase proximal tubule sodium and calcium reabsorption, decrease urinary calcium excretion, and can improve the negative calcium balance that is often present [43, 44].

Table 2.2 Major causes of calcium stone formation with associated metabolic findings

Disease	High urine calcium	High serum calcium	Low serum phosphate	Low urine citrate	High urine oxalate	Low urine volume	Urine pH >6.2	High plasma PTH	Comments
Idiopathic									
Calcium oxalate	++	−	+	+	+	++	−	−	Multiple metabolic causes can coexist
Calcium phosphate	++	−	+	+	+	−	++	−	Multiple metabolic causes can coexist
Granulomatous disease	++	+/−	−	+/−	+/−	+/−	+/−	−	Sarcoid most common
Primary hyperparathyroidism	++	++	++	+/−	+/−	+/−	+	++	Adenoma or hyperplasia; can make CaOx or CaP stones
Ileostomy or chronic diarrhea	+/−	−	−	++	−	++	−	NA	CaOx stones, also uric acid stones
Enteric hyperoxaluria	+/−	−	−	++	++	++	−	NA	CaOx stones
Primary hyperoxaluria	+/−	−	−	+/−	++	+/−	−	NA	Genetic (three variants), CaOx stones
Distal RTA	+	−	−	++	−	−	++	NA	Genetic or acquired; CaP stones. Low serum CO2, often have low serum K
Carbonic anhydrase inhibitor	+	−	−	++	+/−	+/−	++	−	Drug causes mild hyperchloremic RTA

− Rare or not seen,+/− occasional,+ common,++ very common, *NA* not an applicable diagnostic variable, *RTA* renal tubular acidosis

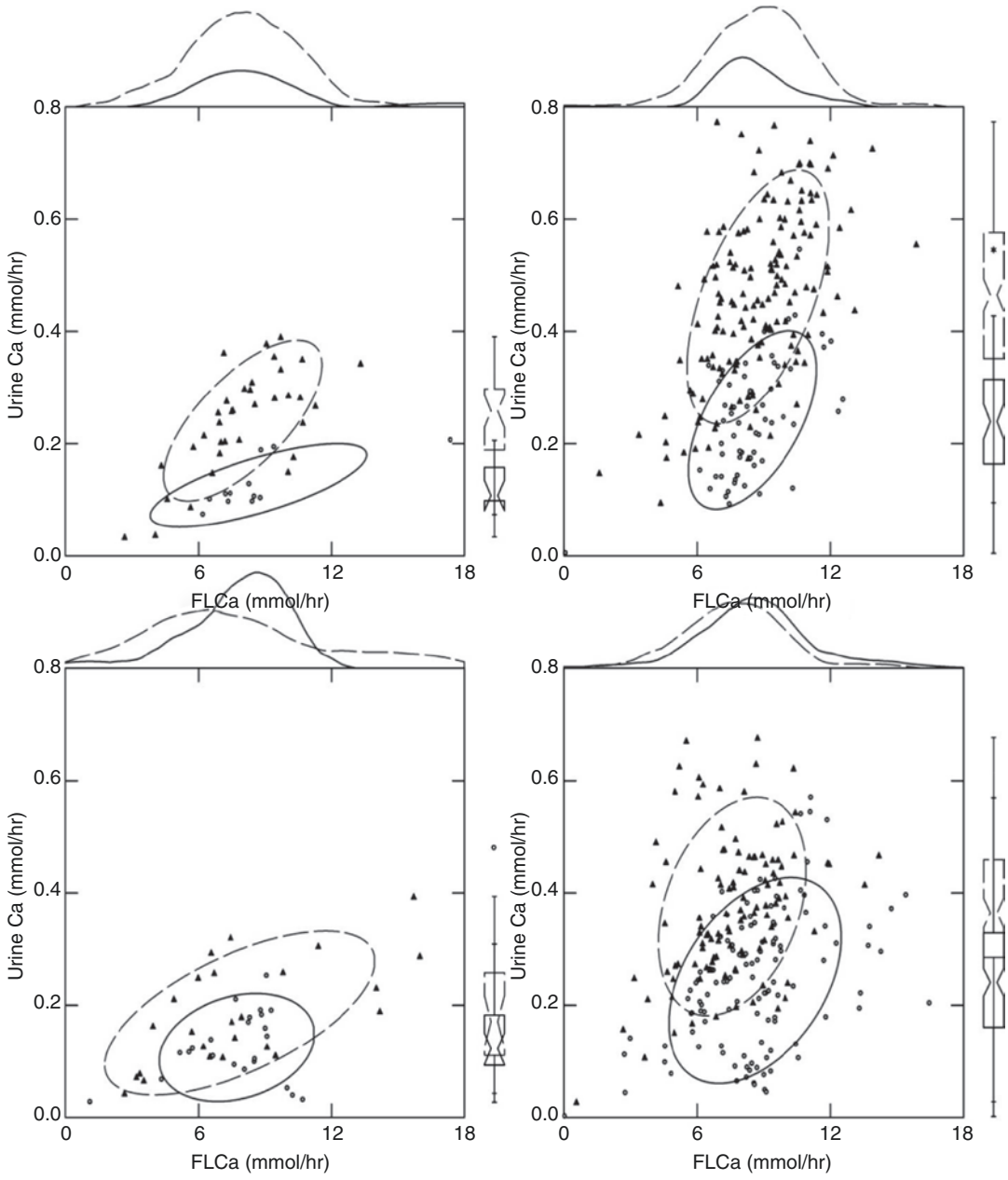

Fig. 2.7 Urine calcium excretion as a function of filtered load of calcium (FLCa). Subjects were studied while on fixed metabolic diets. Men are shown in the top two panels, women in the bottom two panels. Data from the fasting period is in the left panels, fed period in the right panels. Normal subjects, open circles and solid lines; stone formers, closed triangles and dotted lines. Urine calcium excretion is higher in stone formers, particularly the men, at similar levels of FLCa (as shown by the lines above each panel), indicating that fractional reabsorption of calcium was lower in the stone formers. This is particularly striking during the fed period. The notched bars at the right border of each panel do not overlap, indicating that urine calcium excretions differ significantly. (Used by permission from: https://kidneystones.uchicago.edu/idiopathic-hypercalciuria-ih-general-facts/, redrawn from Ref. [41])

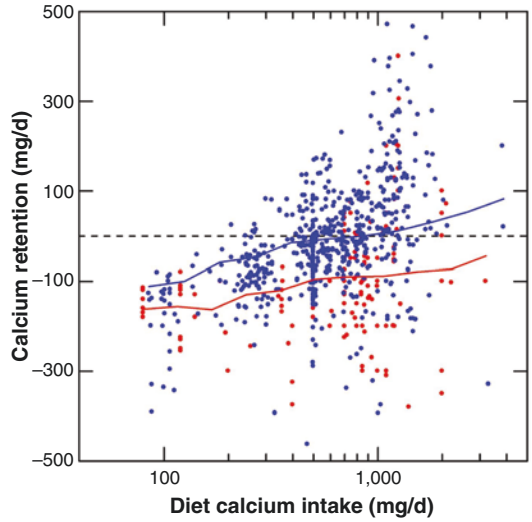

Fig. 2.8 Calcium balance in normal subjects (blue) and patients with IH (red).The horizontal dotted line indicates neutral calcium balance. Each point represents an individual balance study. Points above the line indicate net calcium retention, those below the line, net calcium loss. The lines indicate the mean level of retention in normal subjects or IH. As dietary calcium increases, retention increases, and normal subjects come into neutral balance at average diet calcium intakes above 500 mg/day. Mean retention for IH patients remains negative even at much higher calcium intakes, indicating loss of bone mineral. (Used by permission from: https://kidneystones.uchicago.edu/idiopathic-hypercalciuria-ih-general-facts/)

Glucose intake has also been shown to alter renal tubule calcium reabsorption, and the effect is more dramatic in patients with IH [45]. The mechanism for the reduced calcium reabsorption and increased calcium excretion when IH patients are fed glucose without calcium is unclear, but cannot be attributed solely to insulin [46].

Hypocitraturia

Citrate binds Ca in urine, lowering SS with respect to CaOx and CaP, and is also an inhibitor of the formation and growth of both crystals. Citrate is filtered at the glomerulus and reabsorbed in the proximal tubule by the transporter NaDC1 [47]. Reabsorption of filtered citrate is increased by acidosis and hypokalemia, and what escapes reabsorption in the proximal tubule will be excreted in the urine. Therefore potassium depletion (e.g., from thiazide treatment), alkali losses from the intestine from diarrhea, and the acid-ash diet common in industrialized society, which is high in potential acid, may all reduce urine citrate. Low excretion rates of citrate are associated with increased risk of stone in both men and women (Fig. 2.3, *lower left panel*) [48], and correcting urine citrate levels is associated with decreased stone recurrence in clinical trials.

Potassium alkali can also lower urine calcium excretion in stone formers and non-stone formers [49, 50], which may improve markers of bone health [51]. The mechanism of this effect may involve decreased net acid excretion [52] which occurs because the alkali neutralizes acid production from the diet. In stone formers, the decrease in urine calcium can lead to a drop in urine SS with respect to calcium oxalate; however, the rise in urine pH that accompanies administration of alkali may prevent a fall in calcium phosphate SS [50].

Hyperoxaluria

Mild hyperoxaluria is common in idiopathic calcium stone formers, and may be dietary, due to either increased intake of oxalate in food, or low calcium diet, which permits augmented gut oxalate absorption. In large prospective cohorts, increased risk for stone formation begins when urine oxalate excretion is higher than about 25 mg/day, in both men and women (Fig. 2.3,*upper right panel*)[48].

In studies of normal subjects, eating a diet with no oxalate and generous calcium, urine oxalate excretion averaged 10 mg/gm creatinine/day, which came from endogenous production [53]. As the oxalate content of the diet was increased, urine oxalate rose, and the percent of oxalate absorbed from the diet was about 10–15%. Overall, on a high-calcium diet (1000–1200 mg/2500 calories), the percent of urine oxalate that came from the diet ranged from 24% on a very low-oxalate diet (10 mg/2500 calories) to 42% on a high-oxalate diet (250 mg/2500 calories). However, when dietary calcium is decreased, oxalate absorption from the diet rises, as does urinary oxalate excretion [53, 54]. Some stone formers may have higher basal rates of oxalate absorption from diet. Absorption will thus be determined by dietary oxalate and calcium and the baseline rate of gut absorption.

In the gut, oxalate may be absorbed actively (transcellulary) or passively (paracellularly). Anion exchangers such as SLC26A6 which transport oxalate are found in the apical membranes of both the proximal tubule and the intestinal epithelium. At both sites they are capable of absorbing or secreting oxalate [55, 56], and gut secretion is thought to be particularly important for regulating net oxalate uptake, although the mechanisms are still under investigation. Mice in whom SLC26A6 was knocked out became hyperoxaluric due to decreased gut oxalate secretion.

Higher lean body mass is associated with increased oxalate excretion [9], thought to be due to increased production of oxalate by the liver. Severe obesity has been associated with mild-moderate hyperoxaluria, which is not due only to increased lean body mass, and which may be due to both increased dietary intake and increased net gut absorption of oxalate [57], which may be linked to pro-inflammatory cytokines which decrease gut oxalate secretion [58].

Restricting foods high in oxalate may be helpful in patients with dietary hyperoxaluria, but no trials have been done to assess the effect of such diets on stone recurrence. Equally as important is to ensure that dietary calcium is adequate to prevent excess absorption [59]. Oxalate production can be increased by excessive intake of ascorbic acid, which can raise stone risk in men, though not in women [60].

The presence of gut bacteria that can metabolize oxalate, such as Oxalobacter, may affect net absorption of oxalate, but their role in stone disease is still unclear [59]. Enteric and primary hyperoxaluria, specific diseases of stone formation, are discussed below.

Hyperuricosuria

High urine uric acid excretion may increase the risk of CaOx stones by reducing CaOx solubility [61]. In CaOx stone formers with hyperuricosuria and without other metabolic abnormalities, allopurinol, which lowers urine uric acid, reduced calcium stone recurrence [62]. High diet purine raises urine uric acid in almost all cases, so decreasing dietary purine intake may be effective, but has not been tested in this setting.

Urine Volume

Increased fluid intake leads to higher urine volume and decreased urinary supersaturation with stone-forming salts [63]. In large prospective cohorts (Fig. 2.3, *lower right panel*), higher urine volume (over 2.25 liters/day) was associated with decreased risk for stone formation in men and women [48], and low urine volume was the most significant modifiable risk factor found to contribute to incident stone events [64]. The effect of increased fluid intake was tested in a prospective trial of first-time calcium stone formers and shown to decrease recurrence of stones over 5 years [65]. The amount of fluid needed will vary according to the level of existing SS in a given patient, but the type of fluid appears to matter less than the amount.

Alkaline Urine pH

CaP stone formers are characterized by having urine pH that is persistently above 6.2; the higher urine pH leads to more marked SS with respect to CaP (Fig. 2.9) [66]. These patients seldom have evident abnormalities of proton excretion, although some cannot maximally acidify their urine after an acid challenge [67]. A few may be heterozygotes for genes that cause distal RTA [68]. Patients may convert from making primarily CaOx stones to making CaP stones, but seldom if ever the reverse; those who convert have higher urine pH at baseline [69]. CaP and CaOx stone formers share most other risk factors, and there is no clear difference in stone risk factors between patients who form apatite and those with brushite stones [66].

We have recently shown that urine pH is more alkaline in normal women (mean age 35 ± 5) than in normal men (mean age 43 ± 4) fed identical diets in the CRC, because the women absorb more alkali from the diet, lowering net acid excretion [70]. This may be related to the increased prevalence of calcium phosphate stones in younger women [4]. The mechanism for this difference in acid handling in women is still unclear.

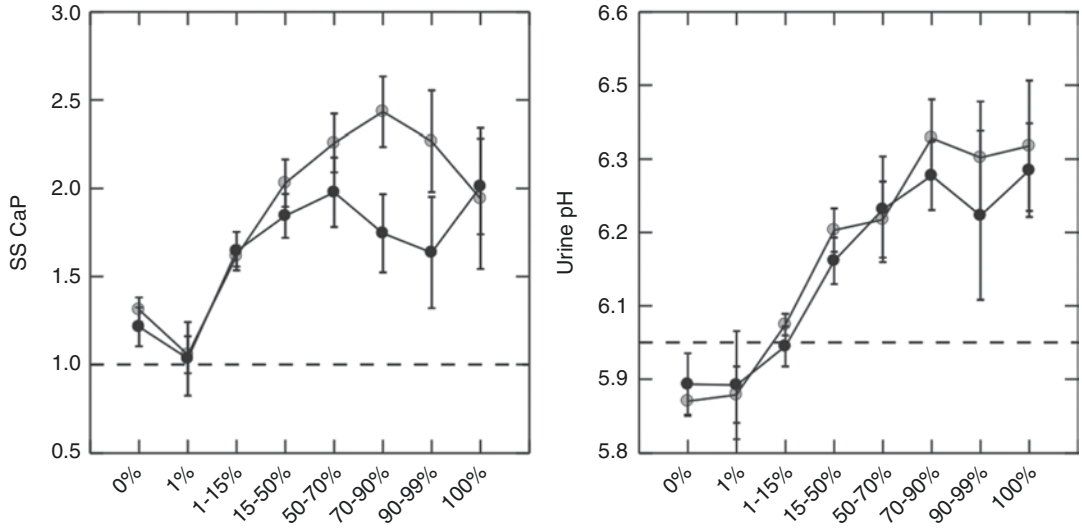

Fig. 2.9 Urine SS for CaP (left panel) and urine pH (right panel) with increasing amount of CaP in analyzed stones. Both SS CaP and urine pH rise as the amount of CaP in stones increases, in both sexes. Men, gray circles; women, black circles. The horizontal line in the left panel indicates SS of 1, and the horizontal line in the right panel indicates a urine pH of 6. Values are means ± SEM. Used by permission from Ref. [66]

Calcium Stones from Systemic Diseases

In general the factors that promote calcium stone formation in systemic diseases (Table 2.2) are similar to but often more severe than the abnormalities found in idiopathic stone formers.

Primary Hyperparathyroidism (PHPT)

PHPT is found in less than 5% of Ca stone formers, with a somewhat higher incidence in women [71]; conversely about 50% of patients with PHPT have stones [72]. Parathyroid hormone (PTH) increases bone turnover, increases GI calcium reabsorption via an increased renal production of calcitriol, and increases renal calcium reabsorption by a direct action on the distal convoluted tubule and thick ascending limbs [73]. All three effects raise blood calcium concentration, so hypercalcemia, often of mild degree (10–11.5 mg/dl), is a prime diagnostic finding; hypophosphatemia is also present [71]. PTH secretion is downregulated by blood calcium ion acting through the cell surface calcium receptor (CaSR), so serum PTH levels need not be elevated in PHPT; it is enough for diagnosis that serum calcium be high and PTH not suppressed, as it is in other hypercalcemic states such as vitamin D excess, sarcoidosis, and malignancy [71]. Although the entity of normocalcemic PHPT exists, it is important to exclude all other causes of elevated PTH, such as vitamin D deficiency [73].

The cause of high PTH in PHPT is one or more adenomas (80% of cases) and multi-gland hyperplasia in the remainder [73]. Parathyroid cell malignancy is very rare. The multiple endocrine neoplasia syndromes can include hyperparathyroidism. Treatment is surgical removal of the abnormal gland tissue. After surgery, normocalcemic hypercalciuria may persist; it appears clinically identical to IH and appears to promote continued stones in some cases [71]. When this occurs, treatment is as already discussed.

Because PTH raises both GI calcium absorption and bone turnover, urine calcium is high; when urine calcium is low or even low normal, one must suspect familial hypocalciuric hypercalcemia, an autosomal dominant genetic downregulation of CaSR sensitivity which does not cause stones and does not require treatment [74].

Stones Due to Bowel Disease: Ileostomy

Because of often copious and alkaline fluid losses, urine is scanty and acidic [75, 76]. CaOx, uric acid, or ammonium acid urate stones may form. The former are caused by very high CaOx SS from low urine volume and hypocitraturia; oxalate excretion is normal and calcium excretion may be below normal. Uric acid is poorly soluble at low pH. The pKa for the dissociation of the N-9 proton is about 5.35 in urine, so at that pH 5, when 50% of total urate species are fully protonated, no more than 200 mg/liter can be dissolved. Given common urine excretion for total urate of 600–800 mg daily, high SS is common.

Very high ammonia production from metabolic acidosis and potassium depletion could create sufficient SS for ammonium acid urate crystals [76]. These may also be seen in states of laxative abuse or other forms of chronic diarrhea.

Stones Due to Bowel Disease: Enteric Hyperoxaluria

Small bowel malabsorption with at least some colon to receive its effluent commonly leads to increased gut oxalate absorption and urine oxalate excretion, and increased risk for CaOx stones [77]. Causes include inflammatory bowel disease, particularly with small bowel resection, pancreatic insufficiency,

and any other cause of steatorrhea. Bariatric surgery of the malabsorptive type (e.g., Roux-en-Y) can also lead to hyperoxaluria and increased risk of stone [78]. Urine is often scanty and acidic because of chronic diarrhea, raising urine SS; hypokalemia is common [75].

Increased gut oxalate absorption is dependent on the level of fecal fat, which increases oxalate availability for absorption as well as colonic permeability to oxalate. Steatorrhea appears to largely affect passive paracellular oxalate absorption [79], and urine oxalate rises with fecal fat. A weight loss drug, orlistat, which produces fat malabsorption, has been associated with hyperoxaluria in case reports, as well as acute oxalate nephropathy [80].

Primary Hyperoxaluria (PH)

The three types of PH identified so far are rare autosomal recessive genetic defects leading to hepatic overproduction of oxalate (Table 2.1) [81]. As oxalate has no known physiological role in the body, all produced oxalate is excreted in the urine. Hyperoxaluria causes urinary SS with respect to CaOx, promoting stone formation which may start in early childhood. CaOx plugging fills the IMCD and BD, with massive subsequent cell damage and fibrosis. Stones appear to form in free solution and as overgrowths on plugs.

Oxalate is secreted into the proximal tubules as well as filtered and poses the threat of cortical crystal formation with cell loss and acute and chronic renal failure [29]. Volume depletion or falling glomerular filtration rate may promote sudden loss of renal function, perhaps because of cortical crystallizations.

Distal Renal Tubular Acidosis (RTA)

Distal RTA, which may be genetic (Table 2.1) or acquired (such as in Sjogren's syndrome), is a defect in proton secretion in the distal nephron, which leads to hyperchloremic metabolic acidosis with alkaline urine, potassium wasting with mild hypokalemia, and perhaps acid-mediated hypercalciuria (Table 2.2). Persistently alkaline urine and hypercalciuria produce SS with respect to CaP, and CaP stones. IMCD and BD plugging is very severe with near replacement of papillary tissue [26]. Cortex shows significant tubule loss and scarring, and progression to renal failure is well described. Bone disease is also a feature of this disorder. Carbonic anhydrase inhibitors such as topiramate, used for the treatment of epilepsy and migraines, have been associated with a picture similar to distal RTA with alkaline urine pH and increased risk of CaP stones [82].

Uric Acid Stones

Major non-genetic causes of uric acid stones, and other less common purine stones, are shown in *Panel 1*, and genetic diseases that foster purine stones are shown in Table 2.3. In the United States, about 8–10% of stones are made of uric acid, but the prevalence is higher in diabetics and obese stone formers [83], and in stone formers over the age of 60 [4]. Patients with gout are also at increased risk of stones, and approximately half their stones are composed mainly of uric acid [84]. Stones may also contain mixtures of uric acid and calcium oxalate.

The main cause of urine uric acid SS – and uric acid stones – is low urine pH, which is present throughout the day [85]. As noted above, the low pH may be due to loss of fluid and alkali from the GI

Table 2.3 Monogenic causes of non-calcium stones

Disease	Mode	Gene/gene product	Function	Stones	NC	Phenotype
Cystinuria type A	AR	SLC3A1/rBAT	Heavy chain of dibasic aa transporter	+	–	Cystinuria, cystine stones, CKD
Cystinuria type B	Incomplete AR	SLC7A9/ $b^{0,+}$AT	Light chain of dibasic aa transporter	+	–	Cystinuria, cystine stones, CKD
Adenine phosphoribosyltransferase deficiency	AR	APRT/Aprt	Purine salvage enzyme	+	+	2,8-dihydroxyadenine stones, CKD
Xanthinuria type 1	AR	XDH/xanthine dehydrogenase		+	–	Xanthine stones
Hypoxanthine-guanine phosphoribosyl transferase deficiency	XR	HGPRT	Purine salvage enzyme	+	–	Severe deficiency, Lesch-Nyhan syndrome; partial deficiency, Kelley-Seegmiller syndrome – hyperuricemia, hyperuricosuria, gout, CKD. Both, uric acid stones
Phosphoribosyl pyrophosphate synthetase superactivity	XR	PRPS1	Purine synthetic pathway	+	–	Hyperuricemia, hyperurocosuria, gout, uric acid stones; may have neurological deficits

AR autosomal recessive, *XR* X-linked recessive, *aa* amino acid, *CKD* chronic kidney disease

tract in patients with ileostomy or other chronic diarrheal diseases, but the majority of uric acid stones are idiopathic. Most patients with uric acid stone do not have hyperuricosuria [86].

The cause of low urine pH is not completely understood, but uric acid stone formers demonstrated increased endogenous net acid production, with decreased excretion of ammonium in the urine, compared to normal subjects when both groups were fed fixed diets [87]. The defective ammonium excretion appears to be linked to steatosis in the proximal tubule cells leading to the use of fatty acids for energy in preference to glutamine, with subsequent decreased ammonia synthesis [87]. In a large study of stone formers, urine pH was inversely related to body weight [88]. The implications for treatment are a focus on raising urine pH by alkali administration in order to increase uric acid solubility.

Cystine Stones

Cystine is the homodimer of the amino acid cysteine. Due to one of two possible transporter defects (Table 2.3), reabsorption of filtered cystine (as well as ornithine, lysine, and arginine) in the proximal tubule is defective, and urine cystine excretion may rise from the normal value of <50 mg daily to values of 200–1200 mg or more. These high excretion rates lead to cystine SS above 1 unless urine volume is very high, and cystine stones form mainly in free solution. IMCD and BD plugging is mild [24], but patients often lose renal function and progression to dialysis is known [89]. The solubility of cystine increases at alkaline urine pH, so treatment includes raising urine pH. Fluid intake to lower SS

is critically important for stone prevention in these patients. Medications that can form more soluble dimers with cysteine, such as tiopronin, are also used. Dietary maneuvers may be modestly effective at lowering cystine excretion.

Struvite Stones

Always the result of infection, these form when microorganisms in the urinary tract possess urease which hydrolyzes urea to ammonia and carbonate ion (*Panel 1*). The ammonia raises local pH as high as to 9, and at this pH the triple salt of phosphate, magnesium, and ammonium forms spontaneously. Calcium carbonates also form in the high-pH, carbonate-rich locale and admix with the struvite. The usual settings include abnormal urinary drainage from chronic obstruction, spinal cord injury with bladder catheterization, and super-infection of stones that arose metabolically. Being infected foreign bodies, struvite stones are treated surgically. They are often diagnosed from their gnarled laminated morphology, and suspected when urine pH reaches values of 9 which the kidneys cannot achieve, when the coffin lid struvite crystals are seen on urinalysis, or when cultures reveal urease possessing bacteria in abundance and stones are present in the kidneys or bladder.

Summary

Stone formation is the end result of crystal formation and retention in the kidney, driven by excess supersaturation with respect to the substance of which the stone is formed. Most stones are not due to monogenic disease but to environmental factors superimposed on genetic risk factors that are currently unknown. In the commonest case, idiopathic calcium oxalate stones, one or more metabolic abnormalities such as hypercalciuria, hyperoxaluria, or hypocitraturia, are usually present, often in combination. These abnormalities are linked to derangements of renal or gut transport which are not yet fully explained. An understanding of the metabolic causes of stone disease can improve prevention by focusing dietary counseling on the key factors driving stone disease.

Panel 1. Non-genetic Causes of Organic and Infection Stones
Purine Stones

- *Uric acid stones*
  - Low urine pH
    - Gouty diathesis
    - Idiopathic (metabolic syndrome)
    - Diabetes
    - Obesity
    - Bowel disease (especially colon resection)
  - Persistent low urine volume (volume depletion states)
  - Hyperuricosuria
    - High-protein diet
    - Overproduction

    - Myeloproliferative disorders
  - Uricosuric drugs
- *Ammonium acid urate stones*
  - Volume depletion with hypokalemia
    - Bowel disease, laxative abuse

Struvite Stones

- *Urinary tract infection with urea-splitting organisms*
  - Usually Proteus mirabilis
  - Other urease-producing bacteria include Proteus sp., Providencia, Enterobacter, Bordetella, Bacteroides, Staphylococcus aureus, Corynebacterium, and Ureaplasma
  - Occasionally urease-producing bacteria: Serratia, Pseudomonas, Klebsiella, Aeromonas, and Pasteurella
  - May also have metabolic or anatomic abnormality predisposing to stone formation

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Chapter 3
Genetic and Environmental Risk Factors for Kidney Stones

Hala Yamout and Seth Goldberg

Keywords Genetics · Environmental factors · Adenine phosphoribosyltransferase (APRT) deficiency Cystinuria · Hypercalciuria · Hyperoxaluria

Key Points

- Genetic factors may result in the overproduction of lithogenic solutes, their over-excretion, or alterations in urinary pH to increase the risk of nephrolithiasis.
- Genetic causes of hypercalciuria can be divided along the nephron segment classically affected.
- With a central role in the fine regulation of calcium reabsorption and excretion, the loop of Henle is the target of several known mutations resulting in hypercalciuria, including those of the calcium-sensing receptor and its downstream targets of the claudins.
- Primary hyperoxaluria has three known distinct forms resulting in marked elevations of urinary oxalate, with an increased risk of nephrolithiasis and loss of kidney function.
- Cystinuria is a genetic disease involving an amino acid transporter in the proximal nephron that results in a distinct nephrolithiasis phenotype.
- Environmental factors including warmer temperatures and professions associated with restricted access to fluids have been linked to an increased risk of kidney stone formation.

Introduction

Kidney stones affect approximately 9% of the US population [1]. When specific risk factors for kidney stones can be identified, dietary habits are most frequently implicated. However, an underlying genetic cause for nephrolithiasis may occasionally be encountered, including several well-described syndromes. Genetic causes should be suspected in patients diagnosed at a young age, with recurrent or bilateral disease or with concurrent renal failure. Genetic disorders may result in loss of enzyme or transporter function or alteration of metabolic pathways. Known genetic diseases typically result in overproduction or over-excretion of lithogenic components or more rarely alteration of the urine

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pH to favor crystal precipitation. Although the total number of genes involved is not clear, one study showed at least 15% of stones can be related to 14 monogenic genes [2]. Despite this, a single identifiable genetic cause for increased stone risk is not identified in the majority of patients with kidney stones, even those with a strong family history, suggesting that most cases of nephrolithiasis may ultimately be polygenic in nature. Additionally, environmental factors may contribute to an increased risk of stone formation, and these are addressed at the end of the chapter.

Genetic Causes

Genetic Causes of Hypercalciuria

Hypercalciuria may result from any process that leads to increased renal filtration of calcium or decreased calcium reabsorption by the kidney. The defect may be in the kidneys themselves or from increased calcium liberation from the bone or absorption from the gastrointestinal tract.

Renal Causes

Each segment of the nephron has a role in the handling of calcium. Genetic defects affecting a variety of these pathways have been identified and are known to lead to hypercalciuria and thereby an increased risk of calcium-based nephrolithiasis [3, 4]. Although a detailed description of these individual mutations and polymorphisms is beyond the scope of this chapter, it is helpful to approach these diseases with representative examples of defects at each segment, with a focus on the more commonly encountered disorders (Fig. 3.1).

Proximal Convoluted Tubule

Most of the filtered calcium is reclaimed by the proximal nephron. Therefore, it is not surprising that genetic defects at this location may result in hypercalciuria. Dent's disease is a rare X-linked recessive mutation of the ClC5 chloride channel, with 250 affected families reported. This channel colocalizes with albumin-containing endocytic vesicles of the proximal tubule, and its absence is believed to result in a generalized trafficking dysfunction and impaired sodium-coupled transport that normally occurs at this site [5]. This leads to diminished calcium reabsorption, and when distal calcium reclamation is unable to fully compensate, hypercalciuria may result. Studies in ClC5 knockout mice showed that other sodium-coupled transporters are also affected, resulting in the Fanconi syndrome with glycosuria, amino aciduria, bicarbonaturia, and phosphaturia [6]. As this cell type is also the location of 1-alpha hydroxylation of 25-OH vitamin D, diminished calcitriol production is seen and may result in bone mineral disease and rickets. Patients may present with kidney stones in childhood or early adulthood and may show progression to renal failure over time. Treatment of the hypercalciuria is centered on thiazide diuretics, and preclinical research has shown that a high citrate diet may delay the progression of renal disease.

Loop of Henle

In the kidney, the calcium-sensing receptor (CaSR) is primarily located on the basolateral membrane of the cell of the thick ascending limb of the loop of Henle. In states of calcium surfeit, the receptor is activated, triggering a signaling cascade that inactivates potassium flux on the luminal membrane,

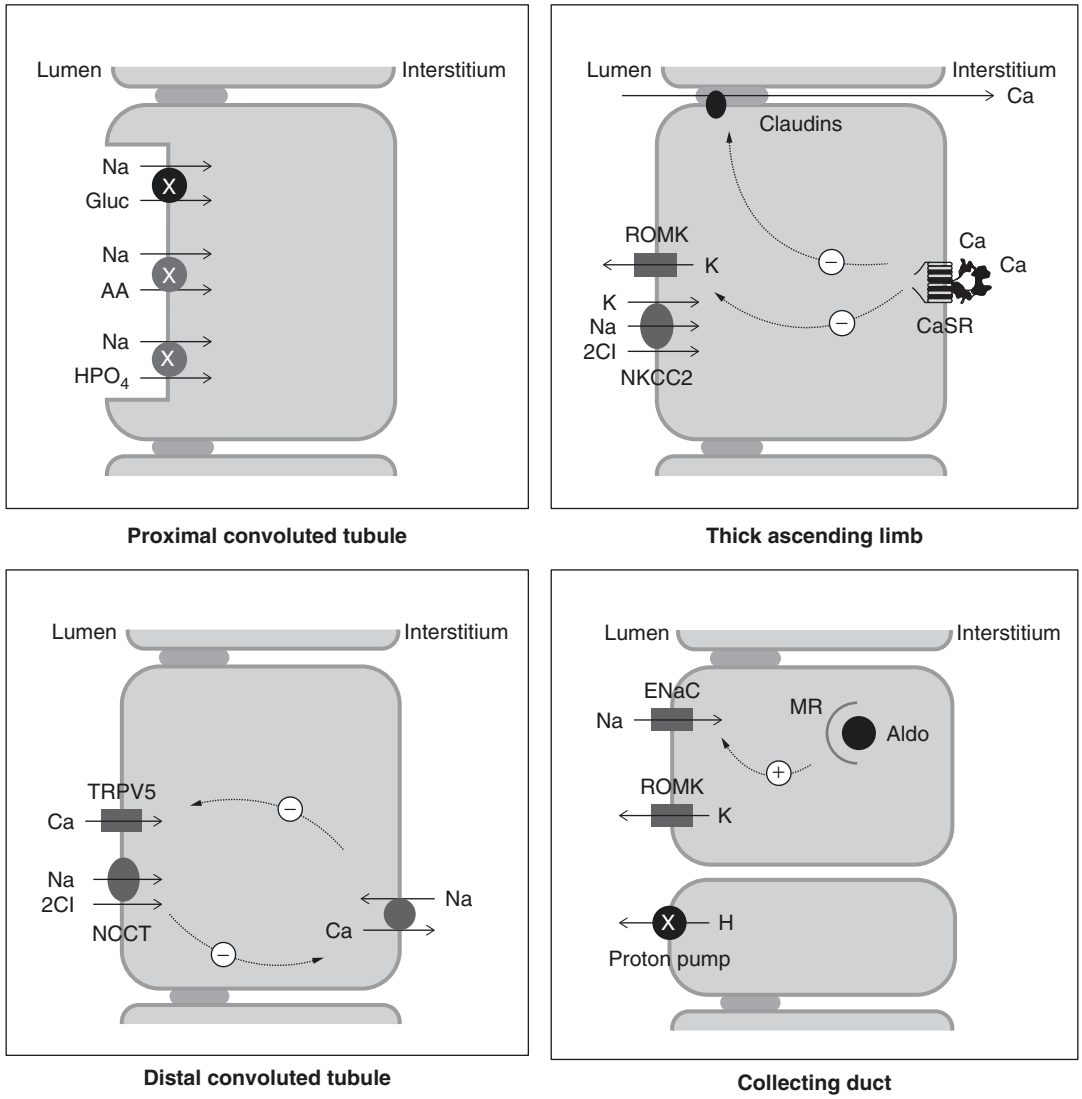

Fig. 3.1 Hypercalciuria

effectively shutting down the activity of the Na-K-2Cl transporter (loop diuretic-like effect). Loss of the luminal positive charge results in less paracellular reclamation of divalent cations (Ca^{++} and Mg^{++}), which appear in the urine [7].

Therefore, an activating mutation of the CaSR would likely result in constitutive renal calcium loss, increasing the risk of calcium-based stones. Such a situation is present in the disease autosomal dominant hypocalcemia, whose name indicates its mode of inheritance as well as its major clinical feature of low serum calcium. In the parathyroid gland, the mutated receptor behaves as it would in states of calcium excess, and the gland is unable to sense the prevailing hypocalcemia; parathyroid hormone (PTH) levels remain low [8]. A mutation in the CaSR has also been implicated in type 5 Bartter's syndrome, with a similar clinical presentation [9]. In fact, any variant of Bartter's syndrome may result in hypercalciuria, given that a reduction in Na-K-2Cl transporter activity ultimately results in the same loss of the luminal positive charge and diminished calcium reabsorption.

The mechanism of this paracellular calcium transport has also been implicated in another family of mutations that may lead to hypercalciuria and increased nephrolithiasis risk. Calcium (and magnesium) transport occurs through the tight junctions via Claudin-16 and Claudin-19 channels. A disorder called familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) has been associated with a mutation in Claudin-16 [10]. Claudin-14, another member of the family, may serve as a link between the CaSR and Claudin-16/Claudin-19 activity. Claudin-14 is inhibitory of Claudin-16 activity and is itself stimulated by excess calcium through the CaSR. Polymorphisms of Claudin-14 with increased activity have been described in families in the Netherlands and Iceland with known susceptibility to calcium-based kidney stones [11].

Distal Convoluted Tubule

The Na-Cl cotransporter (NCCT) is found at the distal convoluted tubule segment of the nephron. Blockade of this transporter with a thiazide diuretic results in an increased activity of the basolateral Na^+/Ca^{++} exchanger and a calcium sink facilitating luminal entry of calcium through the TRPV5 channel [12]. This is one of the suspected mechanisms by which thiazide diuretics assist with calcium reabsorption making them useful in the treatment of patients with hypercalciuria.
Conversely, overactivity of the NCCT may be expected to result in the opposite effect, with excess calcium in the urine. Indeed, this has been variably observed in patients with Gordon's syndrome (pseudohypoaldosteronism type 2) where mutations in WNK1 and WNK4 result in a diminished ability to suppress the NCCT. These patients also present with hypertension, hyperkalemia, and a non-anion gap metabolic acidosis [13]. Treatment is typically centered on the administration of thiazide diuretics.

Collecting Duct

The collecting duct does not play a major direct role in calcium handling by the kidney. However, as a site of urinary acidification, it may indirectly be implicated in a sequence of events that increases the risk of calcium-based kidney stone formation. Decreased hydrogen ion secretion leads to an inability to maximally acidify the urine (distal renal tubular acidosis) with the development of metabolic acidosis. Genetic mutations in α-intercalated cell transporters including those encoding H+ ATPase, anion exchange (AE1), and carbonic anhydrase II have been found to decrease distal acidification [14]. Mutations in H+ ATPase, where ability to secrete H+ is impaired, have an autosomal recessive pattern as do carbonic anhydrase II mutations, where the enzyme catalyzing CO_2 to HCO_3– is affected. AE1 proteins have a role in bicarbonate exchange with mutations tending to follow an autosomal dominant pattern [15].

The resulting systemic acidosis triggers bone resorption releasing calcium and phosphorus which are eventually filtered by the kidneys. Additionally, the systemic acidosis leads to increased citrate reabsorption at the proximal nephron, which, while helpful from an acid-base standpoint, may increase the risk of nephrolithiasis due to the resultant hypocitraturia. Thus, patients would present with hypercalciuria, hypocitraturia, and an alkaline urine pH, all contributing to calcium phosphate stone formation [16].

Specific genetic mutations of the proton pump have been identified, but these are rare. A more common disorder is medullary sponge kidney. It is considered a developmental disorder, rather than a genetic disease, with no identified mode of inheritance. Dilation of the distal nephron gives it the

classic sponge-like appearance when cut in cross section, and urinary stasis in these cyst-like segments increases the risk of urinary tract infections and stone disease [17].

Other Genetic Causes

Other genetic mutations have also been described that can cause hypercalciuria. These include mutations in the diacylglycerol kinase gene, which is important in transplasmalemmal calcium regulation and was found to be associated with hypercalciuria [15]. Those with mutations in the genes encoding NPT2a, which is responsible for most of the phosphate reabsorption in the proximal kidney, develop hypophosphatemia with increased 1,25-$(OH)_2$ vitamin D production and hypercalciuria [4]. The transient receptor potential vanilloid member protein (TRPV5) is found in the distal convoluted tubule, and its mutation has also been found to be associated with hypercalciuria [15].

Non-renal Causes

Genetic diseases can result in hypercalciuria without involving the kidneys themselves, either through excessive bone turnover or gastrointestinal absorption of calcium. Multiple endocrine neoplasia type 1 (MEN1) occurs in 1 in 30,000 people and is associated with overactivity of the parathyroids, pancreas, and pituitary gland. The hyperparathyroidism leads to increased bone turnover, a loss of the well-knit bone matrix, and in increased risk of fracture [18]. Although PTH typically has a calcium-reabsorptive effect on the kidneys, the ensuing hypercalcemia ultimately results in calcium spillage into the urine and an increased stone risk.

Osteogenesis imperfecta type 1 is the most common and the mildest form of osteogenesis imperfecta affecting approximately 1 in 15,000 people in an autosomal dominant fashion. Patients exhibit a deficiency in type 1 collagen that results in abnormal bone formation and calcium homeostasis [19]. Approximately 20% of patients develop kidney stones. Treatment should be centered on avoiding excessive calcium supplements and maintaining a balanced dietary calcium intake.

Genetic disorders resulting in increased gastrointestinal calcium absorption are rare and not well-defined. An animal model has been identified where increased intestinal vitamin D receptor activity results in hyperabsorptive hypercalciuria despite normal active vitamin D levels, but whether human correlates exist is unknown. It should be noted that moderate amounts of dietary calcium (700–800 mg elemental calcium per day) are not generally associated with hypercalciuria, and may actually decrease the risk of stone formation.

Genetic Causes of Hyperoxaluria

Excessive excretion of oxalate in the urine can result from a number of processes. Most commonly, hyperoxaluria is related to dietary intake or gastrointestinal absorption. However, genetic conditions may result in increased oxalate production and urinary excretion. There are several distinct forms of primary hyperoxaluria, characterized by the conversion of endogenous metabolic precursors to oxalate, resulting in massive elevations in urinary oxalate, tissue deposition, stone formation at an early age, and loss of renal function [20].

Primary Hyperoxaluria Type 1

A rare autosomal recessive disorder, primary hyperoxaluria type 1 (PH1) occurs in 1–3 per 1,000,000 live births. The defect is in the AGXT gene that encodes for the hepatic alanine glyoxylate aminotransferase, an enzyme that converts glyoxylate to glycine. The reduced ability to metabolize the glyoxylate results in its accumulation and ultimate conversion to oxalate.

The fate of the oxalate determines the clinical manifestations. Urinary excretion of the oxalate results in profound hyperoxaluria (>135 mg/d, normal <40 mg/d) with an increased risk of calcium oxalate nephrolithiasis in over 80% of affected individuals. The oxalate which is not excreted can also complex with calcium and lead to tissue deposition in the heart, bone, eyes, and kidneys [21]. Renal oxalosis with nephrocalcinosis results in diminished kidney function often in late childhood and leads to end-stage renal disease, with 50% requiring renal replacement therapy by the age of 25.

Diagnostic testing typically begins with the finding of severely elevated urinary oxalate levels. The additional finding of an elevated urine glycolate is suggestive of the disease. As kidney function declines, urinary levels of oxalate and glycolate may become less reliable, and blood levels of oxalate can be measured instead. In the past, liver biopsy showing decreased alanine glyoxylate aminotransferase enzyme activity has been used for confirmation, though this is being replaced by genetic testing of the AGXT gene.

Treatment is centered on dietary oxalate restriction, avoidance of vitamin C, administration of calcium-based binders with meals, and increased fluid intake. Traditional stone risks should be addressed and managed. Additionally, pyridoxine (vitamin B6) has been used in the treatment of PH1 but is only effective in lowering the oxalate excretion in approximately one-third of patients with the disease. The mechanism of action may be related to the improved peroxisomal targeting of a specific mutant form (Gly170Arg) and thus may explain why not all patients show a benefit with therapy [22]. All patients should be offered treatment with pyridoxine 5 mg/kg/d increasing to 20 mg/kg/d over 3 months.

As many patients with PH1 progress to end-stage kidney disease, renal transplantation is frequently considered. However, isolated kidney transplant would be ineffective long term given that deposition will recur in the allograft. Instead, combined liver-kidney or sequential liver-kidney transplantation is recommended, as the liver allograft would provide the missing enzyme and normalize glyoxylate metabolism [23]. For patients on hemodialysis, intensive daily dialysis may help reduce the risk of systemic manifestations of oxalate accumulation.

Primary Hyperoxaluria Type 2

Primary hyperoxaluria type 2 (PH2) is also an autosomal recessive genetic disorder with a frequency much lower than that of PH1 accounting for approximately 10% of cases of primary hyperoxaluria. It is caused by a defect in the enzyme glyoxylate reductase/hydroxypyruvate reductase (GRHPR) that normally metabolizes glyoxylate. As with PH1 this excess glyoxylate is converted to oxalate which can be deposited in tissues and increase the risk of kidney stone formation.

While nephrolithiasis and nephrocalcinosis are seen in over 80% of individuals with PH2, progression to end-stage kidney disease is less common than in PH1 in less than one-third of patients [24]. Diagnosis may rely on measuring increased urinary oxalate and L-glycerate (as the D-isomer is deficient); confirmation can be through reduced glyoxylate reductase activity on liver biopsy or by molecular testing of the GRHPR gene [25].

Dietary treatment measures are similar as with PH1. Given the rarity of this disease, pyridoxine has not been studied specifically in PH2, although multivitamins may allow for better glyoxylate

metabolism. Isolated kidney transplantation has been performed in patients with PH2 with varying success, which may be accounted for by the milder phenotype as compared with PH1.

Primary Hyperoxaluria Type 3

Most recently, a third form of primary hyperoxaluria (PH3) has been described, with an activating mutation in the HOGA1 gene that encodes for the mitochondrial 4-hydroxy-2-oxoglutarate aldolase enzyme [26]. This results in an overproduction of glyoxylate and eventual conversion to oxalate. Less is known about the natural history of PH3, although it is believed to follow a more benign course, with no known reports of progression to end-stage kidney disease yet available. Patients present with calcium oxalate nephrolithiasis early in life and may also show concomitant hypercalciuria, with treatment focused on managing traditional stone risk factors.

Cystinuria

Cystinuria is a genetic disease that causes 1% of adult and 6–8% of pediatric stone disease [27, 28]. It results from a mutation in the genes encoding the amino acid transporter in the proximal nephron responsible for reabsorption of cystine, ornithine, lysine, and arginine. Cystine, however, is the only one of these amino acids insoluble enough in urinary pH to cause kidney stones [29].

Two major genes are responsible for the development of this disease, SLC3A1 and SLC7A9, which are responsible for the heavy subunit rBAT and light subunit b0,+AT, respectively, composing the amino acid transporter [29]. Disease severity is not related to genotype [28, 30]. The traditional classification of this disease was based on the quantification of urinary cystine, however, a more recent classification was developed that is based on genotype. Type A is associated with a mutation of SLCA1 and type B involves a mutation of SLC7A9 [30]. The disease is generally thought to have an autosomal recessive inheritance pattern, however, heterozygotes may have a variable degree of penetrance, with type B mutations more commonly expressing a hyperexcretor phenotype [31]. Type AB includes mutations of each gene; further evidence shows that digenic inheritance is rare and that compound heterozygotes are unlikely to form cystine stones [31, 32].

Diagnosis should be suspected in those with recurrent or bilateral disease, those with young age at onset, or those with a family history [27]. Those with the disease are at significant risk for developing chronic kidney disease, with approximately 70% developing a measurable decrement in renal function [27]. Historically, patients with cystinuria had an increased serum creatinine as compared to patients with calcium oxalate nephrolithiasis, although part of this risk may have been driven by the increased performance of open surgical stone removal and nephrectomy [33]. Progression to end-stage renal disease is not common in cystinuria.

Adenine Phosphoribosyltransferase Deficiency

Adenine phosphoribosyltransferase (APRT) deficiency is an autosomal recessive disease that is a rare cause of uric acid kidney stones and chronic kidney disease.

APRT is important in the metabolism of adenine. When deficient, adenine is catabolized to 2,8-dihydroxyadenine (DHA) by xanthine oxidase [34]. DHA is insoluble in urine and can lead to

kidney stones with a significant number of patients developing chronic kidney disease and end-stage kidney disease [35] even if no stones are detected [34, 36]. Given similarity to standard uric acid stone disease, this disorder may remain undiagnosed or only diagnosed in adulthood [34, 35]. The use of allopurinol is thought to reduce the risk of renal disease progression [36].

Environmental Factors

The prevalence of kidney stone disease is significantly increasing with time [1, 37]. This may be due to a combination of genetic, behavioral, and environmental factors. Climate, profession, socioeconomic class, and geography have all been found to be associated with the development of kidney stones.

Many studies have shown a positive association between higher temperature and the development of kidney stones [38, 39]. With increasing temperature, insensible losses increase with subsequent development of intravascular depletion and lower urinary output [38]. This will lead to precipitation of salts into crystals and the creation of stones [38]. Urine studies have shown higher urine calcium, supersaturation of calcium oxalate and phosphate, and decreasing urine sodium [40] in higher ambient temperature environments.

For each 1° increase in temperature, there is an approximate 10% increase in stone incidence [41]. In spinal cord injury patients, average temperature explained variability of stones by 21% within the first year of injury and up to 71% in those after year one [41]. With global temperatures expected to continue to rise due to climate change, the annual cost of treating kidney stones is projected to rise by $0.9–1.3 billion [42].

There has also been geographic variation in the incidence of stone formation. In the United States, rates tend to increase from north to south and west to east, with prevalence almost twice as high in the Southeast as compared to the Northwest [37, 41, 43]. This is thought to be secondary to differences in temperature and sunlight; it could also be due to an enriched gene pool [43]. In men, sunlight index was responsible for more variation than beverage intake or temperature, although they equally contributed to the geographic effect in women [43].

Profession may also affect the risk of kidney stone formation, especially as it pertains to access to fluid. Studies have shown that those exposed to higher temperatures, such as steel workers, and those with restricted access to fluid, such as physicians working in the operating room, have a significantly higher prevalence of stone formation as compared to others in the same institution [44, 45].

Lower socioeconomic status has also been associated with the formation of kidney stones [1], with worsening poverty associated with higher urine calcium and supersaturation of calcium oxalate and phosphate [46].

Summary

Kidney stones affect about 9% of the US population with prevalence increasing over time. There are several genetic and environmental factors that are thought to contribute to this risk. Genetic factors can increase the risk by increasing the production of specific lithogenic solutions or their secretion. They are also responsible for changing the pH to favor precipitation of crystals that form the stones. The formation of calcium stones, the most commonly encountered, can develop from hypercalciuria. There are several diseases that are associated with this form of kidney stones depending on the location of the nephron. Hyperoxaluria has three distinct entities as well where there is development of increased urinary oxalate depending on specific genetic defects.

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Chapter 4
Basics of Kidney Stones: Dietary Risk Factors of Kidney Stones

Rania El Tawil and Zeina Bachir

Keywords Nephrolithiasis · Calcium oxalate · Uric acid stone · Fluid intake · Animal protein

Abbreviations

BMI	Body mass index
CaOx	Calcium oxalate
DASH	Dietary Approach to Stop Hypertension
SSCaOx	Supersaturation calcium oxalate
UA	Uric acid

Introduction

Kidney stones occur when the urine has higher concentration of crystal-forming substances (such as calcium, oxalate, and uric acid) or when the urine lacks substances that prevent crystallization, such as citrate, thus creating an ideal environment for the formation of kidney stones [1]. Diet composition can promote or inhibit kidney stone formation in people who have a history of kidney stones [2].

Calcium stones are most prevalent and account for 70–80% of all stones. The majority of the calcium stones consist of calcium oxalate and calcium phosphate [1, 3–5]. Uric acid and struvite stones each make up about 10% of all kidney stones, while 1–2% are composed of cystine or other rare stones [1]. There was a 4% increase, from the National Health and Nutrition Examination Survey (NHANES) II (1976–1980) to the NHANES III (1988–1994), in the prevalence of stone formation that was reported among adults in the United States [1, 6, 7].

Dietary changes can reduce the formation of kidney stones especially if there is a suspected nutritional component; however, there is no standard diet that is commonly accepted. Screening and assessment of nutritional contributing factors to kidney stone formation is crucial for the success of the treatment [2].

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Types of Kidney Stones

Calcium Stones

Calcium oxalate (CaOx) is the most common stone. Oxalate is a naturally occurring substance found in foods such as spinach, rhubarb, beets, and some berries. Consumption of these foods may increase the excretion of urinary oxalate [1]. High-protein diets that consist of more than 2.0 g/kg/d as well as a high consumption of sodium in the diet increase the excretion of urinary calcium, which will lead to a higher risk of kidney stone formation. Moreover, a diet that is high in oxalate content as well as consuming supplements of vitamin C at more than 1000 mg/d will increase urinary oxalate levels and may increase the risk of kidney stone formation in some patients [1, 8, 9].

Calcium phosphate stones form when calcium combines with phosphoric acid instead of oxalic acid in alkaline urine [8].

Uric Acid Stones

Uric acids stones form in individuals with high uric acid in the urine, and are associated with low urine pH. Foods that have a high purine content, such as animal protein, may increase the risk of uric acid stone formation as uric acid is produced during catabolism. Patients who have a history of untreated gout are more prone to uric acid stones [1, 10–13].

Struvite Stones

Struvite stones are called triple phosphate stones or infectious stones that are usually associated with upper urinary tract infections and more common in women [1]. This kind of stone is caused by the action of bacterial urease causing high ammonium carbonate and urinary pH. Generally, these stones are not amenable to dietary therapy and require surgical and medical treatment.

Cystine Stones

Cystine stones are those that appear in patients with cystinuria, an autosomal recessive disorder found equally in both men and women, affecting men more severely. Urinary infections and obstruction are common [1]. A high urine pH is favorable to prevent crystallization. General dietary recommendations include high fluid intake and avoiding animal protein which may lower urine pH.

Dietary Risk Factors and Prevention

Several dietary components, such as calcium, animal protein, oxalate, sodium, sucrose, magnesium, citrate, and potassium, are important with regard to kidney stone formation and prevention [1, 14].

Calcium

Prospective studies done on men [2, 15] and women [2, 16, 17] show an inverse relation between calcium intake and kidney stone formation. One mechanism may be that low calcium intake increases oxalate absorption and urinary excretion, resulting in higher 24-hour urine oxalate excretion [14, 18]. A randomized trial done by Borghi and colleagues showed a 50% reduction in the recurrence rate among a group of men with hypercalciuria and calcium oxalate stones who consumed a diet high in calcium (1200 mg/d) as compared to a 400 mg/d calcium diet along with low sodium and a low animal protein intake [14, 19].

Supplemental calcium intake however may have a different effect than dietary calcium. An observational study done on older women showed that there was a 20% increased chance in forming a stone among the calcium supplement users [14].

Calcium binds to oxalate in the gastrointestinal tract and is excreted as CaOx in stool. Certain malabsorptive gastric conditions such as inflammatory bowel disease, celiac sprue, and gastric bypass surgery lead to calcium binding to malabsorbed fat which leaves more free oxalate available for absorption. Thus this may lead to hyperoxaluria. Adequate dietary calcium is important to prevent excess oxalate absorption [14, 18, 19].

Oxalate

Dietary intake of oxalate is not the only contributor to urinary oxalate excretion because urinary oxalate is not only derived from dietary intake of oxalate but also from the endogenous metabolism of glycine, glycolate, hydroxyproline, and vitamin C.

High intake of vitamin C supplementation could increase the risk of kidney stone formation. This is confirmed in an observational study in men but not women [15]. Nevertheless, some guidelines recommend against intake of vitamin C supplements.

Table 4.1 shows oxalate content of foods that should be limited in consumption.

Other Nutrients

Protein (Animal Protein)

High animal protein intake among men has been shown to increase the risk of kidney stone formation [14, 20]. Animal protein unlike vegetable protein contains more sulfur-containing amino acids which increases acid load promoting urinary acidity. The very-high-protein diet, which is popular in the Middle East population, also leads to an increased uric acid concentration in the urine, a decrease in the pH levels, increased oxalate excretion, and a decrease in citrate excretion leading to an increased risk of stone formation [18].

Moderate (as opposed to high) animal protein intake of 0.8–1.4 g/kg/day is recommended as it may lower uric acid generation [1].

Potassium

High dietary potassium intake is associated with a decreased risk of kidney stone formation in both men and older women [14, 20]. Potassium supplementation may decrease calcium excretion. In addition, many potassium-rich foods increase urinary citrate, which may reduce kidney stone formation. This has been shown in studies including men and older women [1–3, 15].

Table 4.1 Oxalate content of foods [1]

Foods (100 mg)	Oxalate (mg)	Foods (100 g)	Oxalate (mg)
Flour		*Leafy vegetables*	
Buckwheat flour	269	Amaranth leaves, raw	1090
Wheat germ	269	Beet leaves, raw	610
Fruits		Brussels sprouts, raw	360
Lime peel	110	Chicory, raw	210
Rhubarb	800	Chives, raw	1480
Nuts		Collards, raw	450
Almonds, roasted	469	Parsley, raw	1700
Cashews, roasted	262	Lettuce, raw	330
Hazelnuts, roasted	222	Spinach, raw	970
Peanuts, raw	142	Watercress, raw	310
Pine nuts, raw	198	*Root vegetables*	
Soy nuts	392	Boiled beetroot	675
Vegetables		Raw carrot	500
Raw eggplant	190	Cassava root, raw	1260
Raw snap beans	360	Radish, raw	480
Raw asparagus	130	Sweet potato, raw	240
Raw broccoli	190	Turnip, raw	210
Raw cauliflower	150	*Other foods*	
Raw celery	190	Black pepper	419
Garlic, raw	360	Cocoa powder	623
		Soy protein	496
		Tofu	275

One potential mechanism is that potassium inhibits the tubular reabsorption of citrate increasing urinary citrate and protecting against calcium stone formation [18].

Sodium

Consuming a high-sodium diet increases the excretion of calcium and potassium [1]. High sodium intake can inhibit calcium reabsorption in the distal tubule and lead to hypercalciuria [18, 21]. A low-sodium diet 2000–3000 mg/d can decrease urinary calcium excretion and lead to lower risk of calcium stones [1].

Table4.2 shows low-sodium diet recommendation.

Magnesium

In prospective observational studies, higher dietary magnesium was associated with a 30% lower risk of stone formation in men [2, 15] but not in women [2, 16, 17]. Magnesium supplementation may reduce the intestinal absorption of oxalate as well as the urinary oxalate excretion and prevent recurrence of calcium stones [18, 20].

The DASH diet, which is high in magnesium, showed a decreased risk of kidney stone formation by increasing the urinary pH and lowering SSCaOx [1, 9, 22, 23, 24] although the DASH diet has a number of potential benefits beyond magnesium.

Table 4.2 Low salt guidelines: www.diabetes.org

Low-salt diet guidelines	
Instead of	Choose
Cold cuts, corned/chipped beef, herring, sardines, smoked meats, bacon, salt pork	Fresh/frozen beef, chicken, fish, veal, or other meats
Regular, hard, and processed cheese	Low-sodium cheese
Regular peanut butter	Low-sodium peanut butter
Regular canned soup, soup mixes, broth, bouillon	Reduced sodium canned soup, broth, bouillon
Canned vegetables, vegetable juice	Fresh/frozen vegetables or "no salt added" canned vegetables, lower sodium vegetable juice
Potato chips, pretzels, salted nuts, party dip and spread, crackers with salted tops	Unsalted chips, pretzels, nuts, popcorn, crackers, mini rice cakes
Regular salad dressing	Oil and vinegar, low-sodium salad dressings
Salt, soy sauce, steak sauce, Worcestershire sauce	Herbs, spices, black pepper

Sugars

An increased consumption of refined sugars may result in obesity, the metabolic syndrome, and an increase in the risk of type 2 diabetes. These metabolic changes are associated with a reduced urinary ammonium excretion and a more acidic urine causing an increase in uric acid and CaOx stone formation [18].

Fiber and Phytate

Phytates, present in whole grain and legumes, were also found to reduce substantially the likelihood of stone formation in younger women [1, 2, 17, 25].

Dietary fiber has been shown to have an inverse relation to kidney stone formation thought mainly due to the phytate content. A high fiber diet can lead to diarrhea, thus decrease urine volume, and increase stone risk [18].

Vitamin B6

Vitamin B6 is a cofactor in oxalate metabolism. Vitamin B6 deficiency increases endogenous oxalate production and urinary oxalate excretion. However, there is no substantial evidence for B6 supplementation and reduction of CaOx stones [14].

Fluid

Consuming more than 3 L of fluids per day will help prevent all types of kidney stones. Cystine stones may require even more hydration. Other types of fluids such as citrus drinks may help prevent calcium and uric acid kidney stones by increasing the pH of urine. Observational studies have shown that consumption of coffee, tea, beer, and wine is associated with a reduced risk of kidney stone formation [14]. This effect may be simply because of increased fluid consumption rather than factors specific to each beverage. Milk intake, skimmed or whole, generally reduces kidney stone formation [2]. However, some fluid may increase stone risks such as sugar drink (regular soda) which may decrease urine pH [14].

Table 4.3 Summary of dietary risk factors for kidney stones [8]

Common dietary factors implicated in calcium or uric acid stone formation	
Dietary factor	Potential stone risk caused by dietary factor
Fluid intake insufficient to promote at least 2.5 L of urine daily	Lower urine volume, higher urine supersaturation
Intake of calcium insufficient to bind dietary oxalate	Higher urinary oxalate excretion
Excessive intake of dietary oxalate despite adequate calcium intake	Higher urinary oxalate excretion
Excessive alcohol intake	Higher urinary acid excretion
Insufficient intake of magnesium	Lower magnesium urinary excretion
Excessive sodium intake	Higher urinary calcium excretion
Fiber intake insufficient to normalize calcium absorption from the gastrointestinal tract	Higher urinary calcium excretion
Excessive intake of carbohydrates, caffeine, and/or alcohol	Higher urinary calcium excretion
Excessive vitamin D intake	Higher urinary calcium excretion
Excessive calcium supplementation	Higher urinary calcium excretion

Low urine volume increases SSCaOx and uric acid. People living in hot climate tend to have higher risk of kidney stone due to higher perspiration and dehydration [18]. A general recommendation is to drink enough water and other fluids especially citrus drinks (lemonade and orange juice) to produce at least 2.5 L urine per day [26].

Table 4.3 summarizes dietary risk factors for kidney stones.

Summary of Key Recommendations

- Nutrition therapy should be tailored to each patient based on history and stone type.
- Patients should drink at least 3 L of fluids per day except sugar drinks in order to decrease the risk of stone formation [26].
- Limit sodium intake to less than 2300 mg/d for patients with a history of calcium oxalate stones [26].
- Moderate protein intake of total 0.8–1.4 g/kg/d is advised. The patient should favor vegetable over animal protein [1].
- Eliminate the consumption of high oxalate foods for those patients with pre-existing hyperoxaluria as well as patients with gastric bypass surgery.
- Consume dietary calcium as opposed to calcium supplements. Recommendation is 1000–1200 mg per day [26].
- High doses of vitamin C should not be recommended to patients who have a history of kidney stone formation, especially men.

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Part III
Diagnosis and Treatment

Chapter 5
Evaluation of Patients with Nephrolithiasis (Diagnosis of Nephrolithiasis)

Matthew Lynch and Samer Nasser

Keywords Nephrolithiasis · Kidney stones/calculi · 24-hour urine collection · Ultrasound · Uric acid Ultrasound CT scan · Supersaturation · Renal colic

Key Points

- Renal colics may be debilitating in symptoms. Their management is usually conservative with pain control unless there is obstruction where urological intervention is required. The benefit of medical expulsion therapy is controversial but is commonly used.
- Evaluation of stone formers is important for the prevention of stone recurrence, and it primarily consists of focused history and physical, imaging, basic metabolic analysis, stone analysis when available, and most importantly 24-hour urine collection for stone formation markers.
- 24-hour urine analysis is recommended for recurrent stone former and certain group of first-time stone formers. The results may suggest the risk factors and certain systemic disease implicated in stone formation, and may help guide dietary and medical management of stone prevention.

Introduction

Nephrolithiasis is a prevalent disorder of the urinary tract affecting millions of individuals around the world. The incidence is on the rise, possibly related to an increase in risk factors such as diabetes and obesity, migration to warmer climates, and change in dietary habits. In addition to pain and suffering, nephrolithiasis is costly medically and socially, causing hospitalization and emergency room visits and missed days at work for patients. Almost 50% of stone formers have a recurrent renal colic in the next 10 years [1, 2]. Thus, evaluation and eventually treatment for prevention of recurrence is of paramount importance and is preferred by most patients who have experienced a renal colic. Evaluation of kidney stones provides both patients and physician guidance toward preventing recurrence whether

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through medical or dietary therapy. Evaluation to prevent stone recurrence occurs in the outpatient setting and involves focused history taking, stone analysis, urinalysis imaging, and metabolic workup. First stone formers require a basic metabolic workup, while recurrent stone formers and pediatric first stone formers require a comprehensive metabolic workup including a 24-hour urine collection which helps determine risk factors for stone formation [1].

Signs and Symptoms of Kidney Stones

Patients with kidney stones are often asymptomatic, and the stones are sometimes discovered incidentally on imaging done for other purposes. Patients who develop renal colic are usually experiencing stone passage from the renal parenchyma into the ureter. The symptoms include ipsilateral flank pain, hematuria, nausea, vomiting, or urinary tract infection [3]. The pain is usually severe enough to lead to an emergency room visit where they are evaluated and treated by the emergency room physician. Initial treatment usually includes pain control and intravenous fluids. Often the stone will pass to the bladder with conservative management, and symptoms will abate. A urologist is urgently consulted for consideration of surgical intervention when there is evidence that the stone is not passing spontaneously and causing persistent obstruction of urine flow or if there is concurrent infection resulting in a systemic inflammatory response syndrome. In such situations, there may be a need for surgical intervention to relieve the obstruction (See Chap. 5). The nephrologist has little role in the emergent renal colic setting unless the patient has concurrent acute kidney injury related to underlying chronic kidney disease (CKD), obstruction of a solitary kidney, or rarely bilateral ureteral obstruction where the patient may develop uremia and electrolyte disturbances [3].

Nonobstructing stones in the kidney parenchyma usually do not cause pain. The pain happens with the passage of the stone through the highly innervated ureter. The pain usually waxes and wanes, and those paroxysms last around 60 minutes. The pain may be excruciating, but this is not universal. Because the ureters share innervation with many adjacent organs, the pain maybe perceived as coming from the intestine or groin or external genitalia [3, 4]. The pain from stone passage may change based on the stone location as it moves from the kidney to the bladder with the pain moving from the flank to abdomen to groin, but symptoms are nonspecific. Rarely patients may be found to have an obstructing ureteral stone but are asymptomatic [5].

The hematuria can be microscopic or gross, and the absence of it does not exclude a stone. Other common findings include urgency, frequency, dysuria, and pain at the urethral meatus. When the stone is in the bladder, it is asymptomatic. The urethral diameter is larger than that of the ureter, and thus the passage of the stone through the urethra is less painful or painless [6]. Stones may sometimes fail to exit the bladder and may become quite large. Sometimes these may cause intermittent bladder obstruction and require surgical intervention [7].

On exam, most patients present with tachycardia and hypertension because of the pain, and they may have costovertebral tenderness at the site of the stone.

Emergency ward (EW) treatment includes pain control with either Nonsteroidal Anti-inflammatory Drugs (NSAIDs) or opioids or both; success has been reported more with NSAIDs while opioids are associated with more vomiting [8]. Intravenous fluids are routinely administered to help augment urine output and facilitate stone passage and are especially useful if there is vomiting. Nausea is a common symptom and antiemetics are also routinely used. Basic metabolic workup and urinalysis are done to assess for the renal function and the presence of a urinary tract infection (UTI). Imaging is done either with an ultrasound or a non-contrast computed tomography (CT) scan to determine the location and size of the stone and whether it is obstructing or not. Imaging modalities are discussed in detail below. CT scan is still the gold standard, especially to determine the size of the stone and to rule out other causes on the differential diagnosis of an acute abdomen [9].

Patients in the EW are treated with attention to the size and location of the stone. Factors that predict stone passage include smaller size and a more distal location in the ureter. Medical expulsion therapy (MET) with alpha-antagonists such as tamsulosin or calcium channel blockers is often used. They inhibit smooth muscle contraction and peristalsis to decrease basal tone. There is debate about the clinical benefit of MET. Some studies cite success of MET increases passage and decreases the pain and frequency of the colic by the same stone [3]. However, other studies do not reveal any clinical benefit of MET or calcium channel blockers for expulsion therapy [10].

After discharge, the patient is asked to strain the urine to collect the stone if it has not passed yet. If the patient had more than one episode of renal colic, referral to a urologist or nephrologist for evaluation of kidney stone formation, as discussed below, is advised.

History and Physical

Evaluation of patients for kidney stone formation is usually done by the primary care physician, nephrologist or urologist. The purpose of the evaluation is to assess for risk factors of stone formation and to formulate dietary and medical plan to alleviate these risk factors and thus decrease recurrence. Patients are evaluated or referred for evaluation after a first or second renal colic or after a urological procedure. Stone formers require evaluation with focused history including past medical, past surgical, social, and family history looking for environmental factors, dietary habits, or systemic disease that may predispose to kidney stones.

Past Medical History

History taking should start with the stone-forming history. The number of stones a patient has passed may determine the treatment pattern. Patients who pass stones more frequently require more aggressive treatment. Patients should be asked about their last imaging and the number of surgical procedures to determine a baseline of the stone burden [1].

Kidney stones can accompany many systemic and comorbid diseases. Patients with inflammatory bowel disease, short bowel syndrome, ileostomy, or chronic diarrhea have increased absorption of oxalate and can develop calcium oxalate kidney stones. They can also develop hypocitraturia because the bicarbonate losses through the gastrointestinal tract are compensated by reduced urinary citrate excretion [11]. Hypocitraturia increases the risk of calcium oxalate and uric acid stones. Metabolic syndrome, which is a combination of elevated body mass index, hypertension, and insulin resistance, is associated with hyperuricemia and can be a clue for uric acid stone formation [11]. While most uric acid stone formers have at least one criterion of metabolic syndrome, most people with metabolic syndrome do not have uric acid stones. Although disorders of uric acid metabolism may result in gout, only 10% of patients with gout develop uric acid stones [12]. Sjögren syndrome is a cause of type 1 renal tubular acidosis and can be associated with hypercalciuria and leads to calcium stone formation. Patients may present with arthritic symptoms, dryness in the eyes and mouth, and gingival disease. Recurrent urinary tract infections especially with Proteus and Klebsiella, which contain the urease enzyme, suggest a risk of forming struvite stones [1].

Kidney stones can sometimes lead to the diagnosis of other diseases. Sarcoidosis and primary hyperparathyroidism are associated with hypercalcemia and hypercalciuria; any may present with kidney stones. Wheezing and rash may be associated with sarcoidosis [13]. Medullary sponge kidney can put the patient at risk of kidney stones, urinary tract infection, and nephrocalcinosis [14]. Osteoporosis may accompany stones in people with primary hyperparathyroidism [15].

Past Surgical History

Bariatric surgery may alter stone risk. Roux-en-Y gastric bypass is most strongly associated with nephrolithiasis. This procedure causes short bowel syndrome resulting in increased oxalate absorption and hyperoxaluria (see Chap.12) [1]. Other forms of bariatric surgery may alter stone forming risk factors as well since most require a significant change in diet and fluid intake.

Environmental History

The work environment can create a risk factor for renal stone formation by mainly decreasing the urine volume. Lack of access to fluids at work may increase the risk for stone formers. Working in a hot environment in factories may also increase risk by increasing insensible losses and concentrating the urine. Some people have specific jobs (truckers, primary school teachers, bus drivers) that require long stretches without access to toilets, so they may avoid drinking fluids [1]. Patients living in hotter climates have higher risk of stone formation. People involved in vigorous exercise especially in summertime are at higher risk for stone formation [16]. This information may guide therapy and encourage the clinician to help the patient come up with strategies to increase fluid intake.

Medication History

Around 20 medications are implicated in stone formation. Medications can either crystallize in concentrated urine to form stones, or they can alter the urinary components such as oxalate and urinary pH that increase the risk of stones (Table 5.1)**.** Some HIV- positive patients are on indinavir and atazanavir, which may crystallize and cause stones [17]. Triamterene and sulfadiazine are other examples of medications that have low solubility and can cause stones [18]. Over the counter medications and supplements are commonly used and can crystallize when used in excess. For example, guaifenesin, a common anti-tussant, has low solubility and can form stones if taken chronically in high doses as can ephedrine, which is found in formulations of many cold medicines [1]. Vitamin C taken at more

Table 5.1 Medication that may cause nephrolithiasis

Active compounds crystallizing in urine	Substances impairing urine composition
Allopurinol/oxypurinol	Acetazolamide
Amoxicillin/ampicillin	Allopurinol
Ceftriaxone	Aluminum magnesium hydroxide
Quinolones	Ascorbic acid
Guanefesin	Calcium
Ephedrine	Furosemide
Indinavir/atazanavir/nelfinavir	Laxatives
Magnesium trisilicate	Methoxyflurane
Sulfonamides	Vitamin D
Triamterene	Topiramate
Zonisamide	SGLT2 inhibitors

References: [1, 17, 18]

than 1000 mg per day can increase the risk of calcium oxalate kidney stones due to the metabolism of ascorbic acid into oxalate in men but not in women [19]. Vitamin D toxicity can lead to hypercalcemia and hypercalciuria. Calcium supplements have been shown to increase risk of kidney stone formation, especially if they are not taken with meals [18]. Carbonic anhydrase inhibitors can increase the urinary pH and increase precipitation of calcium phosphate. Topiramate, when used chronically, has carbonic anhydrase inhibitor action that will lead to metabolic acidosis which results in alkaline urine pH that can precipitate calcium phosphate stones [1]. Detailed history of anti-hypertensives is important as that will dictate therapy, and some diuretics also may affect interpretation of the 24-hour urine collection and should be taken into consideration. Diuretics have variable effects on stone-forming risk factors. Generally, they increase sodium excretion and alter calcium, potassium, and uric acid excretion and may change the pH of the urine.

Family History

Genetics play a role alongside environmental and dietary factors in determining the risk of kidney stones. Notably, half of the patients with calcium stones have a first-degree relative with a kidney stone [20]. While the inheritance seems autosomal dominant, it is more likely polygenic. There are however monogenic disorders that manifest as kidney stones or nephrocalcinosis. Primary hyperoxaluria is an autosomal recessive disorder that leads to endogenous production of oxalate and nephrocalcinosis. Cystinuria is usually an autosomal recessive disorder but can also be autosomal dominant that leads to stone formation at a young age. There are forms of inherited distal renal tubular acidosis that may lead to kidney stone formation [21]. Family history of kidney stones, proteinuria, and CKD should raise questions about Dent's disease, an X-linked disorder [1].

Diet History

A dietary history will inform the clinician of the dietary habits and components that are increasing the risk of kidney stone formation.

Fluid intake directly correlates with the urine volume and the concentration of its lithogenic components. Most types of fluids even the ones with high oxalate content are found to decrease the risk of stones due to the dilution effect they have by increasing the volume. However, sweetened soda has been specifically associated with higher rate of kidney stone formation and should be avoided [19].

Dietary calcium intake history is important. Contrary to intuition and to many patients' surprise, patients on low-calcium diets have higher incidence of calcium stones as compared to people who consume over 1200 mg dietary calcium daily [22].

Sodium intake must be assessed in all calcium stone formers as increased urinary sodium leads to hypercalciuria. Patients should be asked about their addition of salt to food and to their consumption of prepared foods such as canned soups, microwave dinners, pickles, and processed meats[1].

A high animal protein diet can lead to an increase in the acid load and reabsorption of citrate from the renal tubules which in turn lead to low urinary citrate, a known inhibitor of kidney stone formation. This increases the risk of calcium and uric acid stones. Animal protein is also high in purines, which are metabolized into uric acid and can cause hyperuricosuria [1].

Physical Exam

No pertinent signs on physical exam can predict the type or the burden of kidney stones, but a full physical exam is important for ruling out other conditions. Blood pressure measurement is important. Detecting low blood pressure is important as it may hinder hypercalciuria therapy with antihypertensives such as thiazide diuretics.

Imaging

Imaging not only allows assessment of symptomatic stone disease and related complications, but it also gives important information regarding stone burden and can be used to follow the success of stone reduction interventions. As with all imaging tests, the appropriate test may vary for each patient. This decision should be guided by the patient's age, weight, medical history, acuity of presentation, renal function, and findings on physical exam. As summarized in Table 5.2, each imaging study has strengths and weaknesses, and there are some types of stones that are radiolucent with certain modalities.

Current Society Recommendations

The American Urological Association (AUA), the American College of Radiography (ACR), and the European Urological Association (EUA) have published guidelines for obtaining imaging studies during the evaluation of a patient with suspected nephrolithiasis and for follow-up visits. The AUA and ACR suggest patients presenting acutely have a low-dose CT to rapidly diagnose the likely stone disease while examining stone burden and any complications of the stone and ruling out any other intra-abdominal pathology which may be causing the patient's acute presentation [23, 24]. The EUA differs from the AUA and ACR somewhat, suggesting ultrasound be the first test used, with CT performed if the ultrasound is equivocal, in effort to minimize exposure to radiation [25].

Table 5.2 The strengths and weaknesses and types of stones that can and cannot be imaged for each imaging modality

Modality	Advantages	Disadvantages
Computed tomography (CT)	Rapid High sensitivity and specificity Can identify other abnormal pathologies, stone burden, and stone complications	Exposure to ionizing radiation Can only use "low-dose" CT in patients with BMI less than 30 Relatively expensive Radiolucent stones: protease inhibitor stones, cystine
Ultrasound	Rapid and portable assessment of kidney No ionizing radiation exposure Good specificity Relatively inexpensive	Decreased utility in patients with BMD over 30 or overlying bowel gas Low sensitivity Inter-user variability Difficult to fully assess stone complication
MRI	High sensitivity No ionizing radiation exposure	Extremely expensive Longer to acquire image
Plain film radiographs	Less ionizing radiation than CT Good for follow-up to assess stone burden in those with calcium stones	Low specificity Non-calcium-containing stones are radiolucent

Resources: [23–25, 35]

Computed Tomography (CT)

CT is a modality where images are created by measuring the degree to which tissues, or stones, absorb radiation in "slices" along the area being imaged [26]. Thus, the final images obtained are constructed by compiling these "slices," providing excellent structural information. The degree of radiation absorbed by stones may help identify stone composition [27]. However, as CT is a compilation of slices, stones under 3 mm in size may fall between these slices, and go undetected [28].

CT is the most sensitive and specific modality available for imaging nephrolithiasis patients, with reported values of >95% and 95%, respectively [29]. The rapid identification of a stone, stone burden, and potential complications of hydronephrosis or hydroureter, as well as possibly identifying other potential intra-abdominal pathologies mimicking the presentation of acute nephrolithiasis, make CT the preferred modality of the AUA and ACR in those presenting acutely with suspected nephrolithiasis [23, 24]. Furthermore, it is the only modality that provides the imaging needed for full pre-procedure planning.

The use of CT does not come without some drawbacks. The largest drawback is exposure to ionizing radiation. A standard abdominal CT exposes a patient to approximately 10 mSv of radiation [24], or 10% of the minimum level of cumulative lifetime radiation exposure reported to cause malignancy [30]. In effort to reduce radiation exposure, protocols for "low-dose" CT have been developed which require less than 3 mSv of radiation [29]. These scans are now the preferred variation of CT for those patients with a BMI less than 30, where this lower dose of radiation can still lead to high-quality CT imaging [31]. Compounding the risk posed by radiation is the relatively high cost of CT compared to some of the other modalities described below. Thus, while CT is very useful in the acute setting, follow-up imaging recommendations from the AUA and EUA only suggest CT as a first-line option if either recurrent acute events occur or a procedure is planned [24, 25].

CT modality using dual energy capabilities can differentiate types of stone in vivo and ex vivo based on the energy threshold ratio. The ratio can differentiate between uric acid stones, cystine stones, and calcium-based stones with 90% sensitivity. However, the differentiation between calcium phosphate and calcium oxalate was more difficult [32, 33]. Although CT scans are reliable for most stone detection, they cannot detect stones caused by protease inhibitors such as indinavir [34].

Ultrasound

Ultrasound works by transmitting acoustic energy into the area under an ultrasound probe then measuring the degree of reflection of these energy waves by tissues and stones back to the probe, creating an image [26]. Ultrasound is a very specific (88–94%) but poorly sensitive (45%) test for the detection of renal stones [35]. Notably, one large trial, found ultrasound to have similar sensitivity and specificity to CT in patients with suspected nephrolithiasis; however, several patients in the ultrasound arm also had a CT, complicating the interpretation of conclusions derived from the trial [36].

Ultrasound is the EUA's preferred first option in the acutely presenting patient, owing to its lower cost as compared to CT and absence of radiation [25]. The absence of radiation also makes it the first choice for any pregnant stone patient or patients under the age of 14 [37]. Additionally, the ultrasound can be brought to the patient's bedside, minimizing potentially painful patient transfers in the setting of an acute presentation. Although the usefulness of the ultrasound can be limited by patient's body habitus, overlaying bowel gas, or sonographer ability, it can readily identify a stone or stone shadow, hydronephrosis, and proximal hydroureter[26]. Furthermore, stone size may be overestimated due to the way ultrasound waves bounce off the stone [35]. Despite these shortcomings, ongoing research may enhance the sensitivity of this test [26, 38]. One recent advancement is the observation of the "twinkling artifact," which takes advantage of bubbles on the stone surface to provide better contrast with ultrasound [26].

Plain Film

Although once considered the gold standard radiologic exam for nephrolithiasis, with a sensitivity of 57% and specificity of 76%, intravenous pyelogram, where IV contrast is visualized in the renal collecting system by abdominal plain film, has been surpassed by the other modalities noted above [26]. Moreover, many kinds of stones are radiolucent on plain film, such as struvite or cystine or uric acid, owing to the lack of calcium in the stone. Even typically radiopaque, or visible, calcium-containing stones may be obscured if they overlay bone. Despite these drawbacks, those with known calcium-containing stones can benefit from abdominal plain film, as it is a rapid and low-cost method to assess stone burden and treatment response with relatively low (0.3 mSv per film) radiation exposure [26]. These benefits, along with its good sensitivity, have prompted the AUA to recommend combining plain films with the more sensitive ultrasound to monitor the progression of small stones traversing the ureter during active passage of the stone [24].

MRI

MRI works by measuring the energy released by water when exposed to a magnetic field; thus no radiation is used. In the setting of nephrolithiasis, the ACR, AUA, and EAU all recommend MRI as a second-line choice for imaging in pregnant patients where the ultrasound is equivocal [23–25]. The sensitivity of MRI for detection of a renal stone is 82% (AUA) with a specificity of 98% [37]. However, the test is very expensive, costing up to three times as much as a CT, and takes much longer to acquire [26].

Nephrocalcinosis

Nephrocalcinosis is a relatively common finding and can be detected on Kidney Ureter and Bladder (KUB), CT, or ultrasound. It frequently refers to deposition of calcium salts – calcium oxalate and/or calcium phosphate – in the renal medulla. Radiographically, it may appear as radiopaque pyramids on plain film or CT or echogenic pyramids on ultrasound [39]. When found, investigation for the cause of the nephrocalcinosis must be done. Family history and past medical history are important as several genetic diseases, shown in Table 5.3, can lead to nephrocalcinosis. Furthermore, distal renal tubule acidosis can be both a cause for, and caused by, nephrocalcinosis, intertwining the finding of nephrocalcinosis with an increased risk of stone formation.

Table 5.3 Common genetic causes of nephrocalcinosis with associated findings on a metabolic workup

Disease name	Gene mutations	Phenotype
Dent's disease	CLCN5	Hypercalciuria associated with Fanconi-like phenotype
Lowe syndrome	OCRL1	Hypercalciuria with cataracts and mental impairment
Bartter syndrome (types 1–4)	SLC2A2 SCL12A1 KCNJ1 CLCNKB, BSND	Hypercalciuria, hypokalemia, metabolic alkalosis
Bartter syndrome (type 5)	CASR	Hypercalciuria, hypokalemia Hypomagnesemia, metabolic alkalosis
Medullary sponge kidney	RET, GDNF	Hypercalciuria and hypercitraturia

Resource: [60–63]

Summary

Imaging is an important component to the initial and ongoing evaluation of a patient with nephrolithiasis. Ultimately, the choice of initial and follow-up imaging will depend on the patient's clinical course, comorbidities, and stone composition. While a non-contrast low-dose CT scan is the preferred modality for many patients, those with a body mass index (BMI) greater than 30, those who are pregnant or under age 14, and those with previous extensive ionizing radiation exposure may benefit from initial evaluation with ultrasound instead. Radiation exposure limits the use of CT scanning and is the reason it is not the preferred modality for routine follow-up imaging. Rather, ultrasound, with or without KUB, presents a better option for continued assessment of stone burden and response to treatment.

Metabolic Evaluation

Metabolic evaluation is aimed at identifying kidney stone risk factors with the goal of preventing future stone formation and symptomatic stone passage. Metabolic evaluation may be limited to history and physical, blood tests, urinalysis, and stone analysis when available for uncomplicated patients with a single episode of symptomatic nephrolithiasis. A comprehensive or complete analysis includes a 24-hour urine collection in addition to the tests above and is often recommended for recurrent stone formers, pediatric patients, patients with multiple stones, or patients with complicating factors such as a solitary kidney. Patients who are at high risk of recurrence of kidney stones, with a strong family history, chronic diarrhea, or a history of calcium phosphate, uric acid, or cystine stones, should probably have comprehensive analysis including a 24-hour urine collection. [40].

There is no consensus as to the exact components of an initial evaluation after the first episode of nephrolithiasis. Some question the utility of a complete metabolic workup after the first episode of nephrolithiasis, citing cost concerns [41] and others worry through their experience about the noncompliance of younger first stone formers with dietary modifications and medical therapy [14]. Some literature supports that comprehensive metabolic workup, as would be done for all patients with recurrent stone disease, is indicated for first-time stone formers given the high risk of recurrence [42]; there is evidence that urinary metabolic abnormalities found in first-time and recurrent stone formers are similar [43] and that more pre-treatment stones predict a high rate of relapse during treatment for stone disease [44].

Laboratory Evaluation of Kidney Stones

Urinalysis

A dipstick urinalysis and sediment microscopy should be performed. The components of the dipstick urinalysis pertinent for a kidney stone evaluation are shown in Table5.4. This simple test can be quite helpful in identifying risk factors for stone formation. For example, a patient found to have a pH above 7.0, positive leukocyte esterase, and positive nitrites may have a urease-producing bacterial urinary tract infection, predisposing them to struvite stone formation; this patient should also have a urine culture obtained to help with treatment.

Microscopic evaluation of the urine sediment is another in-office test that may provide further details as to the patient's risk factors for stone formation. Seeing leukocytes or erythrocytes may suggest either a urinary tract infection or epithelial irritation from additional stone disease. Furthermore, plain and polarized light may reveal crystalluria as seen in Fig. 5.1, which not only

Table 5.4 Components of the urine dipstick and their meaning as part of the workup in a patient with nephrolithiasis

Dipstick component	Importance
pH	Helps determine if a renal tubular acidosis or urease-producing bacterial infection may be present
Specific gravity	May suggest high saturated urine or volume depletion as contributing factor
Blood	If positive, could suggest either residual urinary tract irritation from stone passage or urinary tract infection
Leukocyte esterase	If positive, could suggest either residual urinary tract irritation from stone passage or urinary tract infection
Nitrite	If positive, a urinary tract infection is likely present

Resource: [1, 2]

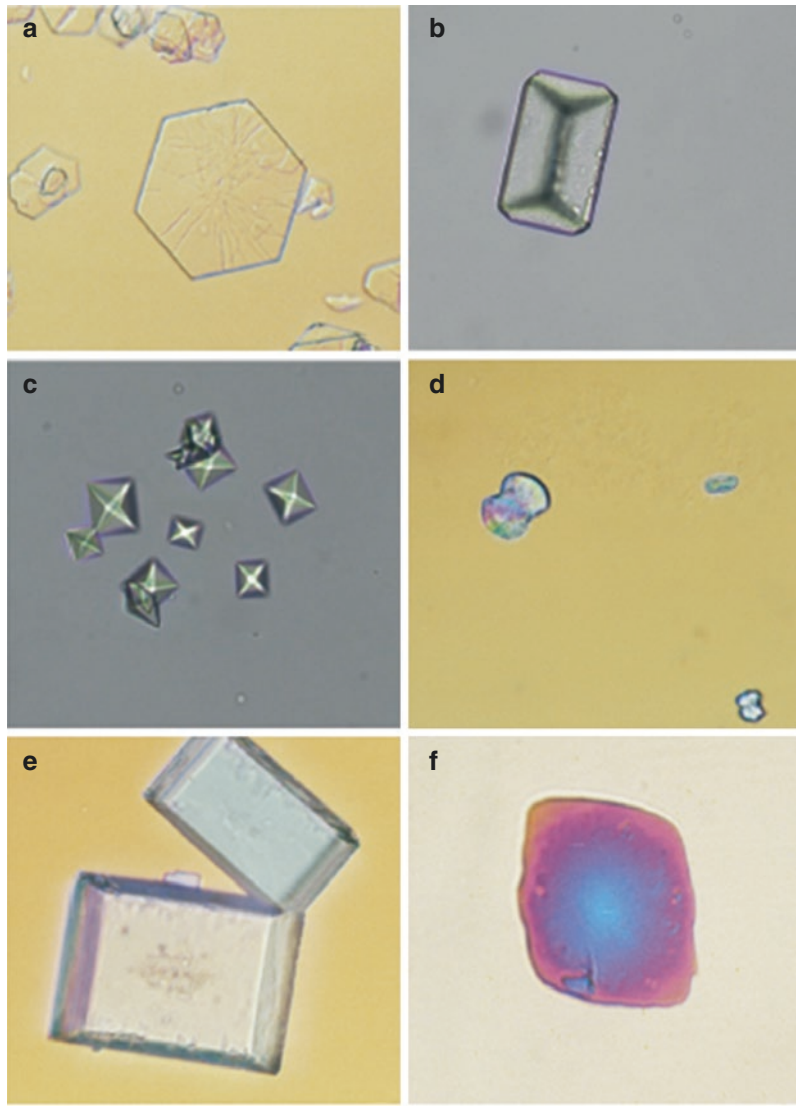

Fig. 5.1 Crystals which may be seen on sediment microscopy from Asplin [1]. (**a**) Hexagonal cystine crystals (200×), (**b**) coffin-lid triple phosphate (struvite) crystal (200×), (**c**) pyramidal calcium oxalate crystals (200×), (**d**) dumbbell calcium oxalate monohydrate crystals (400×), (**e**) rectangular uric acid crystals (400×), (**f**) polarized, rhomboidal uric acid crystal (400×). (Reprint permission)

suggests the content of any recently passed stone, but may also hint at a patient's ongoing risk for additional stone formation [14]. While spotting calcium oxalate and calcium phosphate crystals on the sediment does not provide any diagnostic significance on whether the patient has those stones, the presence of cystine crystals and struvite crystals may be pathognomic [1].

Stone Analysis

Stone analysis is an important factor in evaluation, but one that is not always available. Each stone type has somewhat different risk factors; therefore, the data provided by stone analysis can greatly impact the subsequent medical management of a patient. For patients who have known additional stones that have not been passed, supplying them with a strainer through which they can pass their urine will aid in recovering a stone for analysis. Stone analysis is done through crystallography in most laboratories. Other methods such as optical microscopy, infrared spectroscopy, and radiograph crystallography are acceptable methods to analyze stones, but crystallography is the best method to also detect rare stones and drug-induced stones [41].

The stone analysis may give clues about the etiology of the lithogenesis. In some cases, metabolic workup may be unrevealing for the type of stone, such as in adenine phosphoribosyltransferase deficiency where the analyzed stone dihydroxyadenine could be the only indicator of the disorder. 1-Methyluric acid stones can be seen only in patients with aluminum toxicity. In another example, predominance of calcium oxalate monohydrate (COM) is seen more with hyperoxaluria conditions, while calcium oxalate dihydrate (COD) is more common with hypercalciuria. Many stones contain the combination of both COM and COD indicating both etiologies, hyperoxaluria and hypercalciuria, for the stone formation [45].

24-Hour Urine Collection

This type of urine collection was once reserved for recurrent stone formers or any pediatric stone former to evaluate the risk factors leading to stone formation and to evaluate supersaturations, pH, and urine volumes. As mentioned above there are data that support doing 24-hour urine collection for first-time stone patients especially if they have a high risk of recurrence. Spot urine sample for calcium and phosphate to creatinine ratios is not reliable as the excretion differs for all components at different times of the day.

The number of 24-hour urine collections performed in the initial evaluation is also a matter of debate. Given the importance of the 24-hour urine collection in identifying potential treatment targets, a collection accurately reflecting the metabolic conditions present is essential. For many years, the standard has been two 24-hour collections to ensure consistency between the collections, with a third collection performed if the results of the first two are markedly different. However, there is some thought that a well-collected first sample with patients on their standard diet can suffice [46]. Given the noted intra-patient variability in urine composition [47], missing a clinically significant metabolic abnormality outweighs the inconvenience of multiple urine collections and the recommendation would be two collections for initial evaluation. On the other hand, for follow-up of dietary and medical therapy, one 24-hour urine collection suffices.

Improper preservation of the urine can result in inaccuracies. For example, if the sample is overly acidic and processing is delayed, uric acid can precipitate, falsely lowering the uric acid measurement [48]. Given the nature of the test there are opportunities for human error to alter the results; over or

under collection, patient diet modification, supplement intake, and poor sample handling can all skew the metabolic profile. Patients may be instructed to stop vitamin C before the collection as this is converted to oxalate altering the urinary oxalate concentration. [49]. One way to ensure proper collection is to provide clear instructions to the patient regarding how to collect the sample, which may be provided by the laboratory doing the analysis.

Note that the urine collection should be done while a patient is performing their routine activities and eating their usual diet, while the blood tests should be drawn at the same time as at least one of the 24-hour urine collections to ensure proper interpretation of the urine studies. This is mainly to ensure that the patient has a normal renal function. The collection should be at least 1–3 months after passing stone or a urological procedure to ensure recovery from obstruction and going back on their regular diet.

To learn more about the laboratories that carry the instructions, handling, and analysis of the urine collections, please refer to the Appendix section in the book.

Table 5.5 provides the tests that should be ordered on a standard 24-hour urine collection. In addition to these tests, if cystinuria is suspected, a collection for cystine must also be done.

Interpretation of 24-Hour Urine Collection

The components of the 24-hour urine collection are discussed in the following section. While measured substances have normal ranges as determined by the laboratory, those values may not be optimum for stone prevention [50] and the values can be trended with follow-up collection to determine the success of therapy.

Table 5.5 List of tests that should be performed on a 24-hour urine collection. See related text for further details

Test name	Why it is ordered
Volume	Assessment of daily urine flow
Creatinine	Assessment of sample adequacy
pH	Assessment of risk for certain stones. Values less than 5.5 increase uric acid stone risk. Values over 6.5 increase calcium phosphate risk
Sodium	Assessment of sodium intake
Potassium	Assess risk of hypocitraturia and to follow medication compliance, if started on a diuretic
Calcium	Assessment of risk. High values can be from diet, high sodium intake, or primary hyperparathyroidism
Oxalate	Assessment of calcium oxalate stone risk. High values can be seen with excess intake or malabsorptive states
Citrate	Hypocitraturia increases calcium stone risk
Phosphorus	Hyperphosphaturia can be seen in primary hyperparathyroidism Hypophosphaturia is seen with malnutrition or malabsorption
Magnesium	Magnesium binds oxalate. Hypomagnesuria increases risk for calcium stones as more oxalate will be available
Uric acid	High levels of purine intake, diabetes, and the use of SGLT2 inhibitors are risk factors for uricosuria
Sulfate	High values are indicative of a diet high in animal protein
Urea nitrogen	Assessment of total protein metabolism
Supersaturation	Determines the risk of crystal formation in the urine

Resources: [1, 51]

Adequacy of Sample

Examining the total creatinine collected can assess the adequacy of the sample by comparing it to the amount of creatinine a patient is expected to excrete in 24 hours. As most laboratories will report the creatinine in mg/dl, to calculate the total creatinine excreted, you will need to multiply the creatinine by the volume (in deciliters). Next, calculate the expected creatinine excretion for your patient; male patients excrete 20–25 mg/kg/day and females excrete 15–20 mg/kg/day [51]. If the value obtained is greater than expected, either an over-collection or over-excretion of creatinine (as in a muscular patient) is present. If the value obtained is less than expected, under-collection, malnourishment, or low muscle mass may be present. Note that 24-hour urine collections should be obtained with stable kidney function.

Volume

A common risk factor of stone formation is low urine volume. Low volume is associated with low urine flow and leads to a relatively high concentration of salts in the tubule, increasing the likelihood of intratubular precipitation and stone formation. A trial conducted by Borghi et al. demonstrated a urine volume of at least 2.5 liters daily reduced recurrence of calcium stones, with even greater risk reduction at larger urine volumes [52].

pH

The pH of the urine impacts the solubility of crystals. Low pH (less than 5.5) can increase the risk for uric acid stones. High pH (over 6.5) increases the risk of calcium phosphate stones [49]. As noted earlier, alkaline pH is suggestive of a urease-producing bacterial infection and enhanced struvite stone risk.

Sodium

High urine sodium, suggestive of high dietary sodium intake, enhances urine calcium concentration by decreasing passive calcium movement out of the tubule. Patients with high sodium intake may also fail to derive full benefits of thiazide treatment, as the intake may overwhelm the effect.

Calcium

The most common electrolyte abnormality found in the 24-hour urine collection is hypercalciuria. There are several possible etiologies for this finding: excess dietary calcium intake, excess dietary sodium intake, excess urea production from protein intake, and acidosis [49].

Calcium Stones: Oxalate and Phosphate

High oxalate usually suggests either a large oxalate load in the diet or malabsorption, as seen in short gut syndrome or after Roux-en-Y type gastric bypass. However, primary hyperoxaluria, a rare genetic condition, can also be a cause for this finding. Hyperphosphaturia may be indicative of high dietary intake or hyperparathyroidism.

Citrate

Citrate is a component of the 24-hour collection that can be important in further treatment of patients with calcium stones. Citrate binds free calcium in the tubule, decreasing the chance of calcium complexing with oxalate or phosphate. Hypocitraturia can be induced by hypokalemia or metabolic acidosis [53]. Thus, the finding of hypocitraturia should prompt examination of concurrent blood tests for these abnormalities.

Uric Acid

Monosodium urate is detected in the urine. Even if uric acid in the urine is high, alkaline pH keeps the uric acid soluble. It is controversial whether elevated uric acid increases risk of calcium oxalate stone formation or not [50]. Treatment with xanthine oxidase inhibitors has decreased the risk of calcium oxalate formation in randomized trials. Normal 24-hour uric acid levels do not rule out suggestion for kidney stones since low urinary pH is the most important risk factor for stone formation which may increase the supersaturation along with low urinary volume [54].

Assessment of Dietary Intake

In addition to sodium, as noted above, several other indices can help assess dietary risks. Elevated levels of sulfate or urea nitrogen are indicative of high protein intake [49]. Sulfate is a by-product of animal protein breakdown, and it is associated with uricosuria and low pH.

Supersaturation

Supersaturation is a measure of the likelihood of crystal precipitation and an important parameter for lithogenic risk determination. The calculation is greatly influenced by the concentration (and hence urine volume) of minerals in the urine and the pH [55]. It is defined as the ratio of the concentration of the salt in a solution to the salt's solubility concentration. If the value is greater than 1, then there is supersaturation of the salt, and if it is less than 1, it is undersaturated. In general, the lower the value, the less likely a crystal, or eventually stone, is to form [1]. On univariate analysis, without taking into consideration the other parameters on the 24-hour urinalysis, the type of the stone correlates with the supersaturated salt. Thus, a decrease in the supersaturation may be a guide to monitor therapy [56].

Summary

The 24-hour urine collection is an integral part of the workup of nephrolithiasis patients. For patients presenting for an initial evaluation after an episode of nephrolithiasis, as there are several potential sources of error in the 24-hour collection, we strongly prefer two 24-hour urine collections to help guide assessment of risk factors and plan for treatment. Even though there are reference ranges for the parameters, a normal level does not mean an optimal level to decrease risk. It is better to look at the trajectory of the levels on separate collections.

Serum Studies

Although usually less revealing than the data obtained in a 24-hour urine collection, serum studies are equally important in the initial evaluation and follow-up of patients with nephrolithiasis.

Initial Evaluation After First Stone

Much like the 24-hour urine collection, the initial serum evaluation should be comprehensive, searching for the most common modifiable risk factors of stone disease. We suggest all patients should have a basic metabolic panel,[1] phosphorus, magnesium, uric acid, parathyroid hormone (PTH), and 25-hydroxyvitamin D levels checked [25, 57]. Furthermore, for those patients with known or suspected sarcoidosis, or other granulomatous diseases where 1-alpha hydroxylase is overactive, a 1,25-dihydroxyvitamin D should also be checked [57]. The interpretation of any abnormalities found in the results of these tests is discussed in Table 5.6 with management discussed elsewhere in this book.

Table 5.6 Serum studies for the initial evaluation

Test	Interpretation
Basic metabolic panel	Sodium and potassium: allows to assess safety of prescribing medications such as thiazides or potassium citrate in treatment of stone disease Bicarbonate: low values are suggestive of an acidosis, a stone risk factor, which must be worked up Glucose: elevated values are suggestive of either undiagnosed or uncontrolled diabetes, a risk factor for stone formation BUN and creatinine: assess for any underlying renal disease
Magnesium	If low, it can precipitate or hinder the correction of hypokalemia
Calcium	Be sure to correct for albumin. When high (over 10 mg/dL), can suggest underlying hyperparathyroidism, vitamin D excess, or excess intake
Phosphorus	Hypophosphatemia may be indicative of poor nutrition, malabsorption, or primary hypoparathyroidism
25-Hydroxyvitamin D	Low values of vitamin D are stimulus for parathyroid hormone secretion. High values suggest excessive exogenous supplementation
Parathyroid hormone	If high, or not suppressed, in the setting of hypercalcemia and adequate vitamin D stores, hyperparathyroidism is present
Uric acid	If high, can be due to a purine-rich diet, alcohol consumption, or the metabolic syndrome. Elevated serum uric acid may be a risk factor for stone formation

Resources: [22, 51, 56, 58]

[1] A basic metabolic panel includes sodium, potassium, chloride, bicarbonate, BUN, creatinine, glucose, calcium, and albumin.

Follow-Up

Blood tests are also an integral part of follow-up, particularly in patients requiring medication for the treatment of their nephrolithiasis.

Kidney Stone Workup and Associated Diseases

Most kidney stones are idiopathic calcium-based stones or caused by extrarenal causes affecting the components of the urine and the urine volumes such as in inflammatory bowel disease. Occasionally however the metabolic workup of the kidney stones, characterized by serum electrolyte disturbances and concomitant abnormal urinary values on the 24-hour urine collection, can lead to discovery of rare disorders or diseases.

Primary Hyperparathyroidism

Nearly 5% of all stone patients will be found to have primary hyperparathyroidism [58]. Biochemically, these patients will have high-normal or, more likely, hypercalcemia, hypophosphatemia, and an elevated, or inappropriately normal, parathyroid hormone (PTH). Urine studies will reveal hypercalciuria and hyperphosphaturia. When determining if a patient may have primary hyperparathyroidism, it is also important to determine if vitamin D deficiency is present by checking the 25-hydroxyvitamin D level as a deficiency will increase PTH levels. PTH and serum calcium may have to be repeated if there is suspicion for hyperparathyroidism. Treatment for primary hyperparathyroidism is parathyroidectomy, and surgical resection decreases the risk of recurrent stones [59].

Bartter Syndrome

There are several different genetic disorders that can lead to the clinical diagnosis of Bartter syndrome, characterized by hypokalemic metabolic alkalosis, hypercalciuria, and polyuria. The hypercalciuria seen with Bartter syndrome increases the risk of developing nephrocalcinosis [60]. Type 5 Bartter syndrome, caused by an autosomal dominant gain-of-function mutation in the calcium-sensing receptor (CaSR), is occasionally termed “autosomal dominant hypoparathyroidism” as the mutation also interferes with PTH release from hypocalcemia. In the tubule, this mutation leads to hypermagnesuria, producing hypomagnesemia, which is unique from the other types of Bartter syndrome [61, 62].

Renal Tubular Acidosis (RTA)

Distal (type 1) RTA is associated with an increased risk of stone formation and nephrocalcinosis. RTA should be suspected in patients with a normal gap metabolic acidosis in the setting of an inappropriately elevated urinary pH of 5.3 or above. The high pH values limit the excretion of the filtered acid load and can be caused by several different causes such as Sjögren syndrome, lupus, medullary sponge disease, and even nephrocalcinosis itself.

Regardless of cause, several aspects of type 1 RTA enhance lithogenesis or nephrocalcinosis and calcium phosphate stone formation. First is the metabolic acidosis itself, as bone will buffer the excess hydrogen ions leading to an increased filtered load of calcium and phosphate ions. Next, the impaired tubular acidification allows a relatively alkaline urine, decreasing the solubility of calcium phosphate. Lastly, the hypocitraturia induced by increased citrate reabsorption in the proximal tubule secondary to tubule intracellular acidosis only further enhances the availability of unbound calcium ions for stone formation.

A related, but less understood, condition is the incomplete, or partial, type 1 RTA where there is impaired urinary acidification without leading to reduction in the serum bicarbonate. As with a complete type 1 RTA, these patients have hypocitraturia, inappropriate elevation of the urinary pH (usually a fasting pH > 5.8), and an enhanced risk of calcium nephrolithiasis. However, these patients do not have a metabolic acidosis, as they are able to excrete their usual daily acid load. This condition can be unmasked by an acute acid load in the form of 0.1 g/kg ammonium chloride or several days of enhanced dietary acid intake, both of which will result in a mild metabolic acidosis with a urine pH above 5.3[63]. The prevalence of incomplete dRTA increases with increasing stone composition of pure calcium phosphate [47].

Diabetes and Type 4 RTA

Type 2 diabetes mellitus is emerging as an important risk factor for nephrolithiasis. A significant proportion of this risk is derived from the type 4 RTA, or hyporeninemic hypoaldosteronism, seen with diabetes. Insulin resistance leading to impaired ammoniagenesis leads to the limitation of the urinary buffer capacity, ultimately resulting in decreased net acid excretion despite a low urine pH. This low pH is a strong risk factor for uric acid stones, and if the patient is also hypocitraturic, the tubule environment is such that a high risk for calcium oxalate stones may also be present [64].

Summary

Evaluation of patients with kidney stones is a multidisciplinary approach. Patients with renal colics are evaluated by emergency physicians and urologists depending on the stone burden. Patients with recurrence are evaluated further by comprehensive metabolic workup either by nephrologists, primary care physicians, or urologists. Imaging with initial CT scan and then follow-up with ultrasound play a role in determining stone burden and surveilling recurrence. Stone analysis when available is helpful in narrowing down therapy. Serum metabolic workup is effective in ruling out or suggesting certain metabolic syndromes. Twenty-four-hour urine collections have become a mainstay in the evaluation of recurrent kidney stones because its constituents are important in determining the risk factors in stone formation. Follow-up 24-hour collections can determine the efficacy of treatment and dietary interventions that are required to prevent future recurrence.

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Chapter 6
Kidney Stone Removal Procedures and Emerging Therapies

Lawrence T. Zhang and Peter L. Steinberg

Keywords Shockwave lithotripsy · Ureteroscopy · Percutaneous nephrolithotomy · Medical expulsive therapy · Ureteral stent · Nephrostomy tube

Key Points
- Most urinary stones pass spontaneously, although 10–20% do require surgical intervention.
- Initial management of symptomatic stones includes determining if immediate urinary tract decompression is needed, analgesia with NSAIDs/opiates, IV fluids, and antiemetics.
- Smaller stones in the distal ureter are more likely to pass spontaneously than larger stones located in the proximal ureter.
- Medical expulsive therapy for ureteral stones, with alpha-antagonists or calcium channel blockers, may be considered before surgical options are explored.
- Shockwave lithotripsy (SWL) and ureteroscopy (URS) are the most commonly employed interventions for treating kidney and ureteral stones. Percutaneous nephrolithotomy (PCNL) and open/laparoscopic surgery are reserved for more complex cases.

Introduction

Urolithiasis affects roughly 10% of the US population during his or her lifetime, with stone recurrence rates often over 50% within 10 years [14, 22]. The incidence of kidney and ureteral stones is estimated at 1–3% for the entire population and with white males having the highest rate [14]. Nephrolithiasis costs the US medical system billions of dollars annually [14].

The majority of urinary stones will spontaneously pass; however, between 10 and 20% of stone events will necessitate surgical intervention [2, 16]. The most common reasons for stone surgery are intractable pain, renal failure, infection associated with a renal or ureteral stone, failure of a ureteral stone to pass, or management of a large renal stone. There are a variety of techniques to surgically manage stones, including observation, medical expulsive therapy (MET), shockwave lithotripsy

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(SWL), URS (URS), or percutaneous nephrolithotomy (PCNL). In unusual situations, conventional surgical approaches are needed, though modern stone surgical techniques make ureterolithotomy and nephrolithotomy rare, though just a few decades ago these were commonplace [1, 2].

Initial Evaluation

The urologist is the gatekeeper of surgical stone management, and his or her involvement is critical in all stone patients. Initial evaluation is focused on determining if urgent urinary decompression is needed, if stone passage is likely, and if management is needed, how surgical therapy will be delivered. Initial management usually requires intravenous analgesics, IV fluids, and antiemetics as well [2].

During initial assessment, which is often during an emergency department (ED) visit, the key aspects of the history, exam, and lab studies will focus on pain management, evidence of renal failure, and whether or not the systemic inflammatory response syndrome (SIRS) is present. The presence of any of these conditions mandates emergent urinary tract decompression, with definitive stone management being a secondary consideration. Urgent urinary tract decompression is performed with either a ureteral stent or a percutaneous nephrostomy tube (PCN). Table 6.1 describes some key differences between ureteral stents and PCN tubes. Often local expertise and provider availability dictate which technique is utilized; however, a PCN is often preferred in patients who are critically ill.

Assuming the patient does not have SIRS/sepsis and has normal renal function, the key to initial management is usually analgesia. Acute management usually consists of nonsteroidal anti-inflammatory agents (NSAIDs) and opiates [18]. The combination of both agents has been shown to be superior to either alone [13]. Caution should be taken with NSAIDs as they may elevate the risk of renal impairment and of surgical bleeding.

Spontaneous Passage

The rate of spontaneous passage is mainly determined by stone size and location. As a general rule, smaller stones that are closer to the bladder are more likely to pass than larger and more proximal stones. The ureterovesical junction (UVJ) is the narrowest part of the ureter; thus the majority of stones become lodged at this location [23]. This anatomic feature makes spontaneous passage much less likely for stones that are lodged in the mid and upper ureter. Stones that are sizeable, in the proximal ureter, or at the ureteropelvic junction (UPJ) are notorious for low rates of passage.

Stones in the distal ureter are among those with the highest rate of spontaneous passage. Although it is often difficult to tell the exact fate of a singular stone, and an estimate of passage is usually the best a urologist can provide, there is evidence that the majority of stones under 4–5 mm usually pass [4, 10]. Furthermore, 95% of stones that will spontaneously pass will do so within 4–6 weeks of presentation [ibid].

Table 6.1 Devices for emergent stone decompression

Device	Anesthesia	Approach	Surgeon
Ureteral stent	Usually general; can be local	Retrograde, cystoscopic	Urologist
Percutaneous nephrostomy tube (PCN)	Usually local; general sometimes needed	Ultrasound guided puncture of flank/posterior body wall	Interventional radiologist

Overview of Management

Observation and Medical Expulsive Therapy (MET)

Beginning in the 2000s, interest in medical therapy to hasten expulsion of ureteral stones grew. Given that the ureter is a smooth muscle, mechanistic-based trials of calcium channel blockers and alpha-blockers (as the distal ureter has alpha receptors) were conducted, with the assumption being that relaxation of the distal ureter may allow stones that would otherwise require surgical intervention to pass and passage might be hastened [21].

Two meta-analyses support the role of both alpha-antagonists and calcium channel blockers to increase the rate of stone passage and to speed stone passage [3, 15]. The review from Hollingsworth et al. suggests a 65% increased rate of stone expulsion with either agent and a number needed to treat of four [3]. A study from the emergency medicine literature, pooling data from 16 alpha-blocker studies and nine calcium channel blocker studies, shows a 59% greater rate of passage with alpha-blockers and a 50% greater rate of passage with calcium channel blockers [15]. The number needed to treat with alpha-blockers was 3.3 and for calcium channel blockers 3.9 in this study [15].

Recently, a well-powered study from the UK suggested that MET with either alpha-blockers or calcium channel blockers provides minimal benefit over observation [12]. This study randomized over 1100 patients to placebo, nifedipine, or tamsulosin and showed that 80% of patients in each arm did not require surgical intervention. Interestingly, this trial accrued patients with stones in all ureteral locations, while prior work has focused on the distal ureter. In addition, only 1/3 of enrolled patients had stones >5 mm in size. Additionally, a sizeable randomized trial was reported in early 2018 from China, where nearly 3300 patients were randomized to tamuslosin versus placebo. The tamsulosin arm had a stone passage rate of 86% and the placebo arm 79% [20]. Once again, in the subgroup of patients with stones over 5 mm, the passage rate appeared enhanced by alpha-blockers, while minimal benefit was seen in smaller stones. Although the use of alpha-blockers in ureteral stones is debated and practices are variable among ED and urologic providers, it appears there may be a benefit in sizeable, distal ureteral calculi, as noted in the initial trials of this technique over a decade ago.

Operative Therapy

Shockwave Lithotripsy (SWL)

SWL is a noninvasive procedure that uses an external acoustic shockwave to fragment a stone. This came into clinical use in the 1980s, after fortuitous observations by engineers at the German aircraft company Dornier. The concept behind SWL is to direct an acoustic wave through the human body and crush a stone into small pieces and sand that can readily pass through the ureter. This technique involves generating the wave at F1 of an ellipse and then positioning the stone at F2 of the same ellipse. The shockwave can be generated by various types of arrays, with the initial device actually using a sparkplug and delivering the shock through a water-filled bathtub! Modern devices use electromagnetic or piezoelectric means to generate the wave and usually direct this via a specialized treatment head that is placed against the patient's flank and coupled with an ultrasound gel.

The initial devices actually obtained better stone-free rates than modern devices, because the initial lithotripters had a very low power, but wide acoustic wave. This led to improved treatment as the kidney moved with breathing during treatment. Modern devices have required adjuncts to improve therapy, such as general anesthesia, careful patient selection, and reducing the rate of shock delivery, to allow better stone fragmentation [26].

Table 6.2 Appropriate SWL candidates

Stone Attribute	Size	Stone number	Location	Density	Composition
Good SWL candidate	<1–2 cm	Solitary stone	Upper pole, renal pelvis, proximal ureter	<800–1000 Hounsfield units	Uric acid Calcium oxalate dihydrate
Poor SWL candidate	>1–2 cm	Multiple stones	Lower pole, mid and distal ureter	>1000 Hounsfield units	Calcium oxalate monohydrate, cystine

SWL is usually performed under intravenous sedation, similar to a colonoscopy; however, some providers prefer general anesthesia to better manage the patient's breathing and hence renal motion. Procedures take 30–60 minutes, depending on the shockwave rate, anesthetic choice, and if the patient moves during therapy and the stone needs to be targeted again. Most cases are done as a day procedure, and patients infrequently need to be hospitalized afterward.

SWL can be used to treat stones in the kidney and the ureter. SWL is generally best reserved for stones that are no larger than 1–2 cm. Stones in the upper pole of the kidney, renal pelvis, and upper ureter are best targeted with this technique. Lower pole stones clear at roughly 50% the rate of these other locations, due to fragments often settling in the lower pole and not passing into the ureter [2].

Success of SWL can be predicted in an individual patient, based on the stone size, location, density of the stone, and the distance from the stone to the patient's skin. The latter two measurements are a surrogate for stone composition—SWL is notoriously ineffective against calcium oxalate monohydrate and cystine stones—and the shockwave attenuates through adipose tissue [2, 7]. Table 6.2 describes the types of stones that SWL is best suited for.

The chief complication of SWL is that it will not fragment the target stone and re-treatment or a URS/PCNL will be needed [9, 17]. This occurs in roughly 1/3 of cases. Additional complications are renal hemorrhage, which is rare, but can lead to transfusion and possibly permanent renal damage. Steinstrasse, German for "street of stones," is a complication that occurs when multiple stone fragments pass simultaneously and obstruct the kidney. This is more commonly an issue with stones over 1–2 cm in size. In addition, some patients can have ventricular ectopy induced by SWL, and there are some concerns in performing this on patients with extensive cardiac disease. Finally, SWL is contraindicated in pregnancy and in the face of a coagulopathy or distal obstruction to the stone that will be treated.

Ureteroscopy (URS)

URS involves passing a scope through the urethra and bladder and into the ureter and/or kidney. The stone is viewed directly by the urologist on a video screen and then either fragmented, usually with a laser, or grasped with a basket/forceps and withdrawn. Ureteroscopes are either semirigid stainless steel and used in the distal ureter or flexible and used in the mid or upper ureter and kidney (Fig. 6.1). Digital scopes have come into clinical use, and Boston Scientific now markets a disposable flexible scope as well [26].

URS has gained in popularity in the last 10–15 years for several reasons [11]. Foremost, endoscopic skill has diffused among urology trainees, and nearly all urologists are now facile with the technique. Secondly, as time has elapsed, the lithotripter technology has become less effective, and the ureteroscopes have both become smaller and the advent of holmium laser lithotripsy, which will fragment every stone we clinically encounter, has made this a very competitive technique [9, 17].

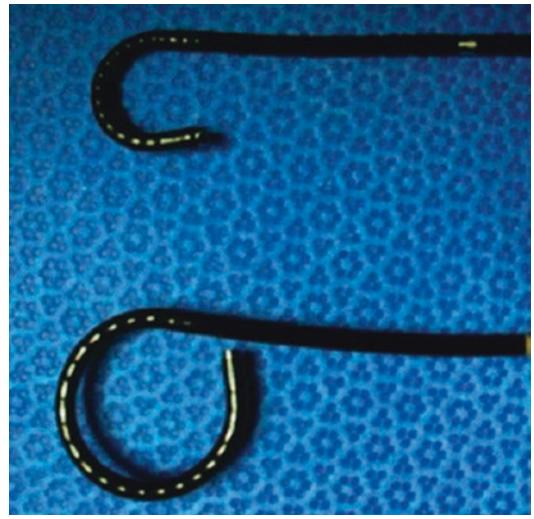

Fig. 6.1 Ureteroscopes with standard stand primary deflection (above) and exaggerated primary deflection (below). (From Campbell-Walsh Urology, Tenth Edition, Reprint permission by Elsevier)

Table 6.3 Comparison of URS and SWL

Technique	Pro	Con
SWL	Less invasive IV sedation No ureteral stent usually Fewer serious complications	High failure rate Many stones will not fragment Can only treat one stone at a time Limited by obesity and renal anatomy
Ureteroscopy	Can fragment any stone that can be reached Multiple stones can be treated Pregnancy, obesity, anticoagulation, and anatomy do not limit application	Risk of serious ureteral injury Ureteral stents usually needed and lead to temporary morbidity More invasive

The primary downside to performing URS is that most urologists leave a ureteral stent in the ureter afterward and this leads to substantial, though transient and reversible, morbidity. Most patients with a stent have complaints of urinary urgency, frequency, and often pain with urination and in the flank. Many patients wish to avoid URS solely because of this issue. In addition, there is a small but real risk of ureteral perforation and subsequent ureteral stricture formation from URS [6]. In modern series this risk is in the low single digits; however, even though rare, such complications are very distressing to patients and can require complex reconstruction to appropriately treat and resolve. More common issues after surgery are hematuria, urinary tract infection, dysuria, and other ureteral stent-related complaints [2].

URS is clearly superior in the management of distal ureteral stones, where success rates for single procedure clearance approach 90–95% and even higher in experienced hands. The rate of success for proximal ureteral stones is less, usually in the 80% range, often because instruments have issues traversing a narrow ureter in the same manner that a stone cannot advance distally [2]. Table 6.3 highlights some of the advantages and disadvantages of URS versus SWL.

URS is usually a day procedure, performed under brief general anesthesia. Most cases take between 30 and 90 minutes, and nearly all patients can be discharged the day of the procedure, barring infectious complications. URS can be performed during pregnancy, and some authors have reported minimal complications of such therapy [19]. In addition, although bleeding is increased when patients are

on anticoagulation or antiplatelet agents, URS can be performed with patients on these agents, and SWL is contraindicated in these cases.

Percutaneous Nephrolithotomy (PCNL)

PCNL is reserved for renal stones over 2–3 cm in size, including staghorn stones, complex anatomic situations (renal transplant, reimplanted ureters), ureteral stones over 2 cm, and lower pole stones over 1–2 cm in size [2]. This procedure is performed under general anesthesia and usually with the patient in a prone position; however, a modified flank position is gaining popularity in North America, after it has been extensively used in South America and Europe for over a decade [5]. The procedure lasts between an hour in simple cases, and complex procedures can require 4–6 hours of operative time. Patients are almost always hospitalized for at least 1 night, though some urologists have begun to perform very straightforward and uncomplicated cases as a day surgery.

The procedure is performed by puncturing a renal calyx with a needle under either fluoroscopy or ultrasound guidance. Contrast can be injected into the kidney via a retrograde ureteral catheteter placed cystoscopically. Either air or contrast can be used to do this. A calyx that will allow optimal access to the stone to be cleared is selected, considering preoperative CT characteristics of the stone, perirenal anatomy, and intraoperative factors, such as whether a rib is in the way of the desired site of puncture [26].

Once access has been achieved, a safety wire (similar to that used in central line placement or other Seldinger technique-based procedures) is placed into the bladder, and a high-pressure balloon is introduced into the kidney. This is inflated and creates a roughly 1 cm hole into the kidney. A rigid and hollow sheath is placed over the balloon, and this allows access for a rigid or flexible scope from outside the patient and into the collecting system. Instruments are passed through a nephroscope to fragment and remove the stone(s) [26].

The primary complications of PCNL are bleeding, infection, lack of stone clearance, and injury to adjacent organs. All patients have some bleeding from PCNL, but between 2 and 5% of patients in modern series bleed enough to need a transfusion [2]. Infectious complications are more common with large, potentially infected stones and in patients with a history of UTI or indwelling urinary tract stents and catheters, which are often colonized [26].

Stone complexity is a key factor in how well one PCNL will clear a stone. A variety of scoring systems exist to try and predict stone-free rate for individual patients [8]. Overall, success is highest for a single stone of low density in the renal pelvis. Success declines as total stone volume increases, the number of calyces increases, skin to stone distance increases, and stone density increases as well (ibid). Finally, a unique risk of PCNL is that adjacent organs can be injured during renal puncture: the colon, liver, spleen, and lung/pleura.

Laparoscopic/Robot-Assisted Stone Surgery/Open Surgery

With the availability of SWL, URS, and PCNL, ureterolithotomy and/or pyelolithotomy via conventional open or laparoscopic/robot-assisted surgery is rarely used. These procedures are responsible for <1% of all stone therapies and tend to be used when prior, less invasive efforts have failed or when a concomitant procedure such as repair of a ureteral stricture or UPJ obstruction is needed [2]. Occasionally these are offered as first line for an unusually complex and large ureteral stone; however, this remains infrequent in modern urologic practice.

Stone Composition

Calcium Oxalate

Calcium oxalate is by far the most common renal stone composition. Calcium oxalate monohydrate stones are notoriously resistant to SWL, and although they fragment during URS and PCNL, it takes more energy to pulverize these stones. A history of calcium oxalate monohydrate stones is a reason to modify the surgical plan away from SWL.

Struvite

Magnesium ammonium phosphate (struvite) stones are caused by infection with urease-producing bacteria, commonly *Proteus mirabilis*. Struvite stones should be suspected when patients have a history of persistent urinary tract infections and infections that seem to "recur as soon as antibiotics are stopped." Repeated infections with the same strain of bacteria are another clue as to the presence of an infected stone. Staghorn calculi can quickly form in the presence of urease-splitting bacteria. Management is with surgical removal of 100% of the stone, and PCNL is the mainstay of managing such stones.

Cystine

Cystine stones are also relatively resistant to SWL. Many patients have their first stone event early in life and often have undergone numerous procedures. The urologist must make every effort to preserve renal function in these patients, avoid performing a nephrectomy, and be aggressive in managing small stones before they grow and require PCNL and/or impair renal function.

Uric Acid

Unlike other stone types, uric acid stones are amenable to dissolution by urinary alkalinization. Potassium citrate, sodium citrate, or sodium bicarbonate should be given to increase urine pH to at least 6.5. Complete dissolution can be achieved in 2–6 months [24, 25].

Conclusion

The surgical management of kidney stones is a true triumph of minimally invasive surgical therapy. The modern urologist can manage almost all stones without making an incision and when needed, through a 1 cm scar in the patient's flank. Current practice in the management of stone disease requires that a urologist be facile with predicting the probability of ureteral stone passage and management with MET. In addition, the well-trained urologist can offer patients with stone disease SWL, URS with laser lithotripsy, PCNL for complex cases, and in rare circumstances, laparoscopic or robotic surgery.

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Part IV
Prevention, Medical and Nutritional Managements for Different Types of Stones

Chapter 7
Calcium Stone: Pathophysiology, Prevention, and Medical Management

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Keywords Calcium oxalate · Calcium phosphate · Hyperoxaluria · Obesity

Key Points

- Calcium stones represent the majority of cases in patients with kidney stones. Those with high risk of recurrence should be advised on specific therapy to prevent stone recurrence.
- Underlying medical conditions such as hyperparathyroidism, diabetes, hypertension, obesity, and conditions that promote hypercalciuria, hyperoxaluria, and hypocitraturia have been recognized as risk factors for stone recurrence.
- Diagnosis of calcium stone can be made by kidney ultrasound; radiography of the kidney, ureter, and bladder; and non-contrast computed tomography.
- Those with high likelihood of stone recurrence should undergo metabolic investigations so that specific advice can be given to avoid stone recurrence.
- Medical therapy for stone expulsion such as alpha-blocker may be useful in certain situations. Depending on the size and location of calcium stone, surgical treatment can be instigated for stone removal.

Epidemiology

The overall prevalence of nephrolithiasis kidney stone is 8.8% in the United States [2], and calcium stones represent the most frequent stone type (70–80%). Among the calcium stone subtypes, calcium oxalate is more common than calcium phosphate with the ratio 4:1 [3]. The trend of calcium stones is also most common in Middle Eastern as well as the Asian countries. For example, in China, the overall prevalence of calcium stone is 84% [4, 5].

Men are more likely than women to form calcium oxalate stone, while women are more likely than men to form calcium phosphate stone. Men may have higher protein consumption which may predispose to higher urinary oxalate excretion. Women are at increased risk of urinary tract infection, which

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may increase urinary pH and predispose to calcium phosphate precipitation. Calcium oxalate stones are more common among 40–70 years old, and calcium phosphate stones are more common among 20–29 years old [5–7]. Different ethnic backgrounds may also influence the rate of calcium stone formation. In a study in North America, patients of Arabic, West Indian, West Asian, and Latin American origin were more likely to develop calcium nephrolithiasis compared to the European origin, while patients of East Asian and African origin were less likely to form calcium stones [8]. In one study, Black women secreted less urinary calcium and more urinary citrate than Caucasian women [9]. Another study performed at Mayo Clinic has noted an association between summer months and calcium oxalate stone formation [7]. Medical condition such as obesity, diabetes, and hypertension are associated with a higher risk of calcium stone formation [10].

Given that calcium stones represent a majority of urolithiasis cases, the healthcare cost of treating kidney stones largely reflects the burden of treatment for calcium stone. In 2000, the total cost for stone treatment in the United States was estimated at $2.1 billion annually, majority of which spent on surgical treatment. It is predicted that the stone-related healthcare cost will increase annually by 25% in 2050 [11].

Risk Factors

Genetic

It is observed that patients with a family history of kidney stones have an increased risk of developing kidney stones [12]. The concordance rate for stone disease in monozygotic twins is higher than in dizygotic twins, suggesting an element of genetic predisposition. Studies on single nucleotide polymorphisms reveal an association between calcium stone formation and genes responsible for coding of vitamin D receptor, calcium-sensing receptor, and osteopontin.

Primary hyperoxaluria is a genetic metabolic disorder with a prevalence of 1 in 58,000. It is characterized by liver enzyme deficiency that results in overproduction of oxalate. More than 80% of cases present prior to the age of 20 years with recurrent calcium oxalate stone formation, or with nephrocalcinosis. The median age of onset of symptoms is at 5 years, and progression to end-stage kidney disease is at 33 years. Three known genetic causes of primary hyperoxaluria based on a cohort of 335 patients in the registry of Rare Kidney Stone Consortium are AGXT, GRHPR, and HOGA1 [13]. Patients with AGXT phenotypes accounted for two-thirds of the cohort, and they have earlier onset of end-stage renal disease. This is followed by GRHPR mutations (9%) and HOGA1 mutations (11%). Although patients with HOGA1 mutations presented the earliest, they had the slowest decline of kidney function [14].

Other studies have implicated many human genes in calcium stone disease. Many of these genes are responsible to promote high calcium load, such as mutation in SLC34A3, which causes hereditary hypophosphatemic rickets with hypercalciuria, or CYP24A1 mutation which causes infantile idiopathic hypercalcemia. Recently, mutation in SLC26A1 was implicated in hyperoxaluria [14]. A genome-wide association study showed an association between CLDN14 in chromosome 21 that codes for protein Claudin-14 and calcium stones. CLDN14 gene is involved in the regulation of paracellular permeability in kidney's tight junctions. Other important loci identified are SLC34A1 (coding for NPT2a, calcium phosphate co-transporter family), AQP1 (aquaporin-1), and DGKH (diacylglycerol kinase) [15].

A group of congenital tubulopathies affecting the proximal tubule (Dent's disease, Lowe disease), thick ascending loop of Henle (familial hypomagnesemia, Barter's syndrome), and distal part of nephron (renal tubular acidosis) are associated with calcium phosphate stone formation and nephrocalcinosis [16].

Inadequate Hydration

One of the main mechanisms of stone formation is supersaturation of urinary solutes, forming urinary crystals, which serve as a nidus for stone formation. Low fluid intake will lead to low urinary volume and promote stone formation. Summer season with higher temperature has been associated with increased urinary calcium concentration, which may predispose to calcium stone [17]. Having adequate hydration with a target urine volume of more than 2–2.5 Liters per day is an important step to prevent stone formation [18].

Hyperoxaluria

Oxalate component in calcium oxalate stone plays an important role in stone formation, as calcium is usually present in high concentration in urine and calcium oxalate crystallization occurs in 1:1 molar ratio. Hence, increased concentration of oxalate in urine will contribute to stone formation [16].

Oxalate can be found in many daily food items. Foods that contain very high oxalate are spinach, rhubarb, beetroot, black teas, chocolate, some tree nuts (almond, cashew, hazelnut), and legumes [19]. Normal western diet provides 200 mg/day of oxalate, although some may exceed 500 mg/day. Usually only 10–15% absorption occurs mainly in the small intestine, but this depends on many factors such as oxalate bioavailability from food and food calcium content. Calcium in food combines with oxalate and precipitates in the gut, reducing the absorption. Reducing calcium intake, which some patients may practice, actually increases the oxalate absorption further and promote calcium oxalate stone formation [20].

Experimental studies showed patients with small bowel resection have a higher proportion of oxalate being absorbed. The mechanism is probably related to poor absorption of fatty acid and bile salts, which leads to a more complex formation between fatty acid and calcium, leaving oxalate to be absorbed more easily. Fatty acid and bile salts also increase the permeability of oxalate in large intestine. It leads to increased urinary oxalate excretion and predisposes to calcium oxalate stone formation [20].

Inflammation and malabsorption in inflammatory bowel disease such as Crohn's disease and ulcerative colitis may promote calcium stone formation via a similar mechanism – malabsorption caused by inflammation or bowel resection promotes increased oxalate solubility in the intestinal lumen and permeability in colonic mucosa. Patients may also lose bicarbonate in liquid stool and become acidotic and dehydrated, subsequently causing low magnesium and citrate urinary excretion and promoting calcium stone formation [21]. Ileostomy is an additional independent factor for stone formation through a similar mechanism. In a retrospective study, patients with inflammatory bowel disease who had undergone ileostomy or J-pouch are observed to have a higher risk of calcium stone formation [22].

Patients who have undergone a bariatric surgery represent another at-risk cohort for calcium stone formation via hyperoxaluria mechanism. Patients with a prior Roux-en-Y gastric bypass develop kidney stones at a higher rate compared with obese patients who have not undergone a Roux-en-Y gastric bypass surgery [23]. The mechanism is like malabsorption, promoting increased oxalate absorption. In addition, a urinary study showed that patients develop hyperoxaluria, hypocitraturia, and hypercalciuria after gastric bypass surgery [21].

Hypocitraturia

Low urinary citrate level is present in 20–60% patients with kidney stones [24]. Citrate inhibits stone development by forming soluble calcium citrate, thus reducing the availability of free urinary calcium to bind with oxalate or phosphate. It is also hypothesized that citrate prevents adhesion of calcium oxalate to tubular epithelium.

Average daily excretion of urinary citrate ranges between 200 and 500 mg/day. Hypocitraturia is generally defined as urinary citrate level below 320 mg/day. Diets rich in animal protein may increase acid load, which then reduces citrate excretion. High sodium intake may also reduce citrate urinary excretion [24].

Traditionally, it was thought that citrate slows the growth of crystal formation. Newer study by Shang YF et al. suggested that potassium citrate potentially may dissolve the already formed calcium oxalate stone. The in vivo study also showed that potassium citrate changes the crystal morphology of calcium oxalate to be more rounded and smooth, reducing the tendency of crystal aggregation. Citrate also may convert calcium oxalate monohydrate to calcium oxalate dihydrate crystal, making it less pathological and less likely to recur [25].

Hypercalciuria

Increased excretion of urinary calcium increases the probability of stone formation in a supersaturated environment. About 30% of dietary calcium is being absorbed in the small intestine. Calcium metabolism is controlled by the interplay of the intestine, the kidney, vitamin D, and the parathyroid hormone. Normal urinary calcium excretion is less than 200–250 mg/day. In calcium stone formers, about 20–40% of patients have hypercalciuria [26].

Among patients with primary hyperparathyroidism, 20% develop symptomatic kidney stones, and as many as 55% may have asymptomatic stones. Hypercalciuria is the main risk factor for kidney stone in patients with primary hyperparathyroidism developing in up to three-quarter of primary hyperparathyroidism patients and may develop even in the absence of hypercalcemia. Although parathyroidectomy is one of the treatments for primary hyperparathyroidism, 30% of patients may still experience persistent hypercalciuria after surgery [27].

Sarcoidosis is a systemic granulomatous disease characterized by lung, lymphatic system, eye, and skin involvement. Ten percent of patients with sarcoidosis may have kidney stones, with calcium oxalate being more common than calcium phosphate stone. Sarcoidosis induces interferon release from macrophages and lymphocytes that enhance production of 1,25-(OH)2D3 [28] which results in elevation in calcium. Hypercalcemia occurs in approximately 5–10%, but hypercalciuria is more common with prevalence rate of up to 60% in patients with sarcoidosis [29]. Steroid therapy may normalize hypercalcemia, but its direct effect on the already formed kidney stone is unknown.

Although dietary calcium restriction may reduce excretion of urinary calcium, it will increase the urinary oxalate level through a secondary mechanism; hence it is not advisable for calcium stone formers to restrict dietary calcium intake [30].

Obesity and Metabolic Syndrome

Prevalence of obesity based on NHANES 2011–2012 data has increased to 34.9% in adult [31]. In Nurses' Health Study I and II, and in the Health Professionals Follow-Up Study, nephrolithiasis was associated with a higher body mass index [32]. As part of the metabolic syndrome,

obesity is associated with hypercalciuria, hyperuricosuria, hyperoxaluria, and hypocitraturia. Many obese patients also have diabetes and hypertension, risk factors for stone formation [33]. Another potential mechanism is that the serum level of adiponectin, which is produced in adipose tissue, seems to be low in obese individuals. Adiponectin is postulated to inhibit stone formation in mice [34].

Patients with metabolic syndrome are more likely to have hyperuricemia and hyperuricosuria, hence a uric acid stone. The association between calcium stone and hyperuricosuria has long been a subject of investigation. One-third patients with calcium stones have hyperuricosuria. Hyperuricosuria may promote calcium stone formation via epitaxy, the formation of one crystal on top of another. It is hypothesized that the more soluble, charged uric acid causes precipitation of poorly soluble, uncharged calcium oxalate, through a mechanism called "salting out." Salting out happens when non-electrolyte becomes less soluble (calcium oxalate) with increasing concentration of electrolyte (uric acid). This mechanism was shown in an experiment using healthy human urine. The urine was treated with increasing amount of sodium urate. Calcium oxalate spontaneous precipitation was observed with increasing urate concentration [35]. However, in a large cross-sectional study, uric acid excretion was not associated with calcium stone formation [36]. Interestingly, in an intervention trial to reduce calcium stone formation in patients with hyperuricosuria, patients prescribed allopurinol daily had significantly less new stone formations, compared to placebo [37]. Hence, the role of hyperuricosuria in calcium stone formation remains a subject of ongoing investigation.

Dietary Factors

In healthy nonpregnant adults, recommended daily allowance for calcium is 1000–1200 mg/day. Intuitively, patient with calcium stone may reduce the dietary calcium intake. However, the oxalate component plays a bigger role in promoting stone formation. Dietary calcium binds with oxalate in the gastrointestinal tract, preventing oxalate absorption. Reducing calcium intake will potentially leave unbounded oxalate available for absorption [38]. In a 5-year randomized controlled study involving 120 men with idiopathic hypercalciuria, normal calcium diet at 30 mmol/day (equivalent to 1200 mg/day) combined with a low protein and low salt diet showed a 50% reduction of calcium oxalate stone recurrence, compared to traditional low calcium diet (10 mmol/day) [39]. An intake of protein can be estimated based on 24-hour urea excretion:

$$\text{Protein intake}\ (\text{g}) = \text{Urine urea}\ (\text{mmol}/24\ \text{hours}) \times 0.18 + 13$$

A randomized controlled trial that included 210 patients with idiopathic hypercalciuria showed patients taking low-sodium diet had a significantly lower urinary calcium and oxalate excretion, compared to normal dietary habits. Both groups were advised to take beverages that amounted to 2 liters per day. Patients allocated to low-sodium diet were advised to eliminate kitchen salt and replaced it with herbs and spices. They were also advised to strictly limit consumption of food with high-salt content. The urinary sodium reduced from 228 mmol/day to 68 mmol/day after 3 months [40].

A higher intake of dietary protein may reduce urine pH and citrate level by inducing acid overload, inhibiting renal calcium reabsorption, and increasing calcium excretion. Furthermore, the excess acid promotes release of calcium phosphate from the skeleton and increases urinary calcium grapefruit juice seems to increase the risk, while dietary calcium, dietary phytate, caffeinated drinks and wine may reduce the risk of stone formation [41–43].

Medications and Supplements

The role of calcium supplementation in stone formation is controversial. The result from the large randomized trial of Women's Health Initiative Study showed a combination of 1000 mg elemental calcium plus 400 IU of vitamin D increased the risk of kidney stone by 17% [44]. Consistent result was found in Nurse's Health Study I, whereby subjects receiving calcium supplementation had an increased risk of stone formation by 20% [38]. Dietary calcium surprisingly decreased the risk of stone formation. It is theorized that dietary calcium has a higher binding affinity to oxalate, preventing oxalate absorption, which is the main factor for calcium oxalate stone [38]. A recent review suggested that the risk of stone formation was increased in healthy women taking calcium supplementation, but not in osteoporotic women and healthy men [45].

In a large prospective analysis of participants in the Health Professionals Follow-Up Study and in Nurse's Health Study I and II, there was no difference in kidney stone detection between participants who took vitamin D more than 1000 IU/day and those who took less than 1000 IU/day [46]. A recent meta-analysis of randomized controlled trials involving nearly 20,000 patients showed increased risk for hypercalcemia (relative risk 1.54 [95% confidence intervals 1.09–2.18]) and hypercalciuria (relative risk 1.64 [95% confidence intervals 1.06–2.53]) in those taking vitamin D, but no increased risk for kidney stone [47]. In contrast, an earlier Cochrane meta-analysis found that vitamin D supplementation, together with calcium supplementation, either for mortality or cancer prevention, increased the risk of kidney stone (relative risk 1.17 [95% confidence intervals 1.02–1.34]) [48, 49].

Vitamin C has been proposed as a risk factor for calcium oxalate stone formation as it gets converted to dehydroascorbic acid, which then gets converted to oxalate. However, it is possible that this conversion happens due to reaction in the collection vessel, but not in the body. Results from the analysis of the Health Professionals Follow-Up Study and Nurse's Health Study I and II with follow-up nearly 12 years showed vitamin C supplementation was associated with increased kidney stone development among men, but not among women [50]. The risk of kidney stone was found to be dose-dependent. The reason for gender differences is unclear, but it may be related to dietary consumption and potentially to differences in metabolism.

Infection

Apart from the well-known association between struvite stone and urease-producing bacteria, the relationship between infection and other types of stones is not well established. Many patients with stone disease have concurrent urinary tract infection, but causality is not confirmed. Interestingly, bacteria such as *E. coli* and *Pseudomonas* spp. can be cultured from calcium oxalate stones themselves in up to 40% of the cases. Gene sequencing analyses of the stones have identified multiple bacteria including pseudomonas, lactobacillus, and enterobacteria. The way bacteria may promote or potentiate stone formation is by reducing urinary citrate level with the production of citrate lyase, as well as their natural tendency to aggregate around calcium oxalate monohydrate [51].

Formation of Kidney Stones

A basic requirement for stone formation to begin in the urinary tract is the amount of stone-forming substance exceeds its solubility, a state of supersaturation. If no precipitation is formed within minutes of supersaturation or if the initial precipitates are removed promptly, it will end up as crystalluria.

However, if the precipitation is formed and prolonged, the retention particles will serve as nidi for stone formation [52].

Dr. Randall in 1937 observed two locations of calculus formation in renal papillae. The first site was in the interstitium, specifically in the papillary tips around the bends of loop of Henle. The initial step was thought to be the formation of calcium phosphate in the interstitium. These deposits increase in size with accumulation of organic materials and crystal components. Some of the calculi eroded through the urothelium and formed plaque in contact with urine. This is called fixed-particle mechanism. Another site was in the renal tubule at the end of collecting duct (duct of Bellini). Retention occurs when the precipitates are too large to pass or if they adhere to damaged cell possibly by oxidative stress. This is called free-particle mechanism theory [52–54].

The formation of stones depends on the delicate balance of the supersaturation of urinary electrolytes, such as calcium, oxalate, phosphate, uric acid, and cystine, and the lack of inhibitors of stone formation, such as citrate and magnesium. Calcium phosphate precipitation is favored when the urinary pH is over 6.5, while calcium oxalate stones are pH independent.

Evidence from clinical and experimental studies suggests that production of reactive oxygen species with the development of oxidative stress contribute to the formation of kidney stones. Decreased antioxidant capacity, together with persistent supersaturated urine, may lead to crystallization of calcium oxalate monohydrate. These crystals may adhere to the renal tubular epithelial cell and activate cyclophilin D that results in mitochondrial injury. Oxidative stress also causes apoptosis, further cell injury, and osteopontin expression. Osteopontin is identified as one of the organic components of urinary calcium stones, and it promotes stone formation. The cell debris from mitochondrial and microvilli injury condense into kidney stones [15].

Calcium Oxalate Stone

Calcium oxalate crystallizes as three hydrates, calcium oxalate monohydrate (COM), dihydrate (COD), and trihydrate. The trihydrate form has not been reported in kidney stones. COM usually exhibits hexagonal lozenge morphology, while COD exhibits bipyramidal structure [55]. In an experiment examining crystalluria formation by inducing dehydration in marathon runners, the Caucasian stone formers produced COM aggregates, while non-Caucasian non-stone formers produced COD bipyramid crystals [56–58]. It is possible that the increased proportion of COD formation in a non-stone former is a protective normal process, while COM is pathological, although this would not explain why there is still a significant proportion of calcium oxalate stones (up to 30%) in a dihydrate form [3]. The increased prevalence of COM compared to COD may be explained by its more pathogenic nature, greater adhesion to renal tubular cell, as well as to Randall's plaque and faster growth rate in supersaturated surrounding [55, 59].

Calcium Phosphate Stone

Calcium phosphate stones can be divided into calcium phosphate (apatite) and calcium hydrogen phosphate dihydrate (brushite). Calcium phosphate stones supersaturate in higher urinary pH, higher urinary calcium, and higher urinary phosphate. It forms not only kidney stones but also hydroxyapatite plug that causes inflammation and damages the kidney. Compared to patients with calcium oxalate that mostly have normal renal papillae, patients with calcium phosphate stones usually have damaged papillae, and it is worse in brushite type [60, 61].

Hydroxyapatite stones produce smaller deposits but more numerous than the brushite type. Brushite stone is the most soluble calcium phosphate phase that forms in the urine but later can foster nucleation of calcium oxalate and hydroxyapatite stones. Brushite stones have a tendency to recur more frequently, perhaps due to their association with distal renal tubular acidosis, which can be found in nearly one-third of patients with brushite stones [60, 62].

Management of Calcium Stones

Clinical Presentation and Evaluation

Patients with calcium kidney stones may have a variety of presentations, from being completely asymptomatic to typical one-sided colicky flank pain associated with gross hematuria. Patients may have an associated fever. A detailed history and examination is needed to evaluate the possibility of stone diagnosis or other causes of pain, to identify risk factors that may predispose to stone disease, and to identify the suitability of treatment for the patients. History taking should include information on both nutritional and lifestyle aspects, especially the intake of fluid and the consumption of calcium-, sodium-, protein-, and oxalate-rich food.

Ultrasonography could detect renal stone with a sensitivity of 70% and specificity of 94% (Fig. 7.1), but lower if the stone is in the ureter (sensitivity 57%, specificity 97.5%). Ultrasound had no radiation

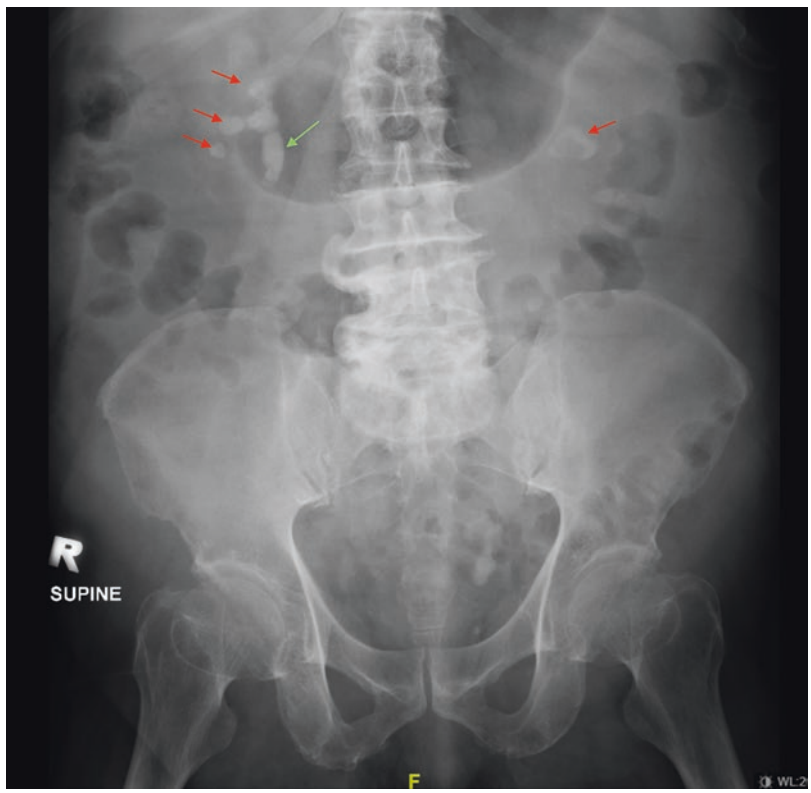

Fig. 7.1 X-ray plain film of the kidney, ureter, and bladder shows radiopaque multiple calculi in the right renal pelvis (red arrow) and proximal ureter (green arrow), as well as lower pole of left kidney (red arrow)

risk and inexpensive. Ultrasound may also detect nephrocalcinosis or polycystic kidney disease. As calcium stones are radiopaque (unlike uric acid stones), plain abdominal X-ray may be able to detect the stones, although its sensitivity ranges from 44% to 77% and specificity from 80% to 87%. Intravenous pyelography has been replaced with non-contrast-enhanced computed tomography, which has a higher sensitivity and specificity to identify the location, size, and maybe the composition of stones. A non-contrast computed tomography does not increase the risk of contrast-associated acute kidney injury and may be able to detect extra-urinary cause of abdominal pain and is the test of choice (Fig. 7.2) [61].

Many patients will have only one episode of symptomatic nephrolithiasis, but some will continue to experience recurrent stone formation. It is estimated that 10% of patients with calcium-type stones will have recurrence of symptomatic stones [63] more than three times throughout their lives, with brushite stone being the most common. Stone analysis should be performed in all first-time stone formers. Identification of the stone composition traditionally was made with a chemical method, but newer techniques such as infrared spectroscopy and X-ray diffraction have superseded the old method for better precision. While calcium oxalate stones are the most common, calcium phosphate or brushite stones may suggest an underlying renal tubular acidosis.

The intensity of investigation is determined by several factors such as the probability of recurrence, stone composition, and underlying medical risks. Blood analysis should be part of the initial investigation to identify abnormal kidney function, presence of hypercalcemia, hyperphosphatemia, or hyperuricemia. High fasting glucose is suggestive of diabetes. Low blood pH and low serum potassium suggest the presence of renal tubular acidosis. Causes of hypercalcemia may include hyperparathyroidism with high intact parathyroid hormone level.

Further metabolic evaluation should be continued in patients with risk factors for recurrence and may not be appropriate for all first-time patients with stones. The 24-hour urine collection should be

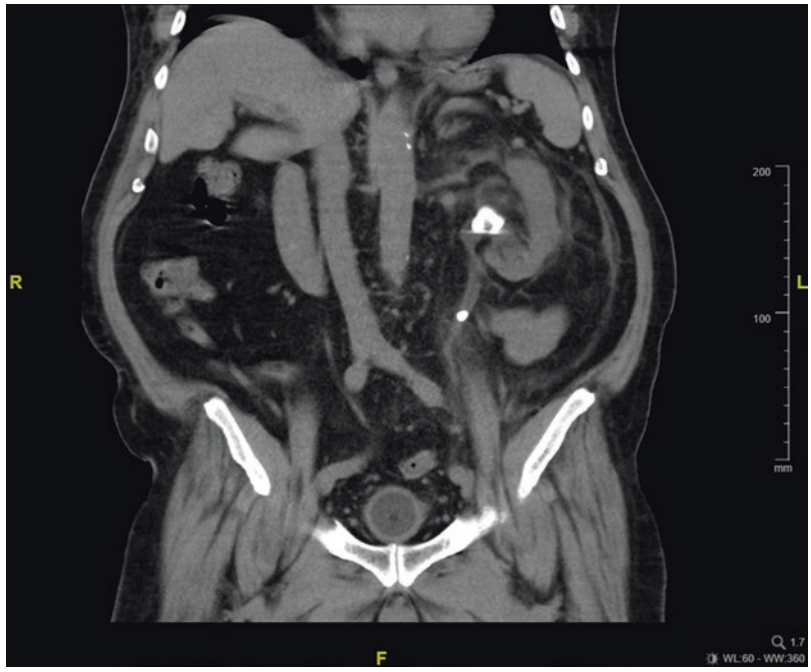

Fig. 7.2 Reconstitution of CT scan images shows hydronephrosis of the left kidney with large stone in the left renal pelvis measuring 1.0 × 2.0 × 1.9 cm and smaller stone in the left ureter at L4 level. There is also perinephric and periureteric stranding on the left side. The right kidney (not seen in this film) has shrunken in size

Table 7.1 Reference ranges for normal values on 24-hour urine collection

Analyte	Reference range (male)	Reference range (female)
Creatinine	18–24 mg/kg 13–18 mmol	15–20 mg/kg 7–13 mmol
Calcium	<200 mg <5 mmol	<250 mg <5 mmol
Citrate	>450 mg >2.5 mmol	>550 mg >2.5 mmol
Uric acid	<0.8 mg <5 mmol	<0.75 mg <4 mmol
Phosphate	0.6–1.2 g <35 mmol	
Oxalate	20–40 mg <0.5 mmol	

done under normal daily condition to correctly identify abnormalities in the urine. It can be done to identify patients with underlying medical conditions or to demonstrate individual urinary abnormality to guide specific treatment recommendations. Guidelines recommended two samples of 24-hour urine collection, although this can be difficult for patients. The collection containers should contain preservatives to avoid bacterial growth and prevent oxidation of ascorbate to oxalate. Using hydrochloric acid or boric acid or addition of thymol or toluene may achieve these objectives but at the expense of disrupting urinary pH level [64].

Table 7.1 lists suggested normal 24-hour urinary values. However, it is important to emphasize that the risk of stone formation has a linear association with urinary analytes and patients may form stones despite levels in the range below. Specific advice based on the results of investigations may give greater understanding on the reasons for stone formation and promote patient's adherence to treatment.

Medical Management

Pain relievers such as nonsteroidal anti-inflammatory drugs are effective in patients with colicky pain due to kidney stones and have better analgesic properties than opioids. This should be weighed against the potential adverse effect of such as worsening of kidney function and long-term risk of cardiovascular event. Opioids can be used in patients who have contraindications to other pain medications.

Fluid intake is the mainstay treatment for preventing stone, based on pathophysiology of stone formation. However, data from randomized trial is limited. A recent meta-analysis of two randomized trials and seven observational studies suggested the beneficial effect of high fluid intake [65]. In the first randomized trial in 1996 [66], 199 patients with history of kidney stones were asked to drink fluid to achieve urine output of more than 2 liters per day. The intervention group managed to achieve urine output more than 2 liters per day over 5 years, while the control group was achieving urine output just above 1 liter per day. In another randomized trial in 2006 [67], 70 patients with history of kidney stones were advised to drink fluid to achieve urine output of more than 2.5 liters per day. The pooled risk ratio of kidney stones in individuals with high fluid intake was 0.40 (95% confidence intervals 0.20–0.79). Since the difference between 24-hour urinary volume and the actual fluid intake is approximately 0.9 liter, patients may need to drink 3.0 liter or more per day [65]. Following these trials, the American Urological Association recommended stone-forming patients to drink fluid to achieve a minimum urine volume of 2.0–2.5 liters per day [68]. Randomized trial by increasing fluid intake as a primary prevention strategy against formation of calcium stone has not been performed [18].

Low urinary citrate is associated with the formation of calcium stones since citrate acts as an inhibitor by forming soluble calcium citrate instead of calcium oxalate or phosphate. A meta-analysis looking at citrate supplement usage (in the form of potassium citrate, sodium-potassium citrate, or potassium-magnesium citrate) in patients with calcium oxalate stones showed a 74% risk reduction in new stone formation, when compared with placebo. Common side effects with such treatment include upper gastrointestinal disturbance [69]. Sodium bicarbonate supplementation may increase urinary citrate levels and reduce calcium oxalate supersaturation, but is not as effective as potassium citrate [70]. Studies using commercial fruit juices (such as orange, cranberry, apple) have showed significant increase in urinary citrate level [24].

Hypercalciuria is associated with formation of calcium stones. However, discussed in the previous section, reducing calcium intake was paradoxically associated with more formation of calcium oxalate stones. Hence, restricting dietary calcium intake was not recommended as it can increase oxalate absorption from the gut. Additional calcium supplement is associated with stone formation, and its usage in a stone former should be reviewed. Another way to reduce calcium in urine (hypercalciuria) is by using thiazide diuretics. Thiazides cause modest sodium depletion, which then reduces calcium renal excretion. Animal studies have shown that thiazides are associated with an increase in sodium and calcium absorption in proximal tubule. There is also an upregulation of sodium-hydrogen exchanger and distal tubular calcium channel (TRPV5) with thiazide use. The net effect is positive calcium balance with hypocalciuria [71]. In a Cochrane meta-analysis of patients with idiopathic hypercalciuria, five trials were included comparing thiazide with standard treatment. There was a significant decrease in the number of new stone formation in those treated with thiazide (relative risk 1.61, 95% confidence intervals 1.33–1.96) [72].

Prebiotics and probiotics supplementations are increasingly being recognized as the potential treatment options in obesity, diabetes, and inflammatory bowel [73–75]. There are an increasing number of publications regarding microbiome and calcium renal calculi. As oxalate and calcium play an important role in the formation of kidney stones, increased oxalate breakdown in the gut by certain bacteria may reduce oxalate gut absorption and subsequently reduce oxalate excretion in the kidney. Another possible mechanism is that gut microbiome may also play a role in influencing the net alkali absorption and may increase citrate concentration in the urine. These mechanisms may eventually reduce the rate of stone formation [76].

Probiotics containing *Lactobacillus* spp. have been shown to reduce urinary oxalate level in small studies. However, a randomized trial comparing probiotics containing *Lactobacillus* spp. (Oxadrop) and placebo did not show significant difference in the reduction of urinary oxalate excretion. All patients were put on a low oxalate diet, which may explain the lack of differences between the three groups [77].

Another potential organism, *Oxalobacter formigenes*, utilizes oxalate as its energy and carbon source. It also promotes oxalate release in the gut by stimulating its transport through gut epithelium, potentially reducing gut oxalate absorption. An observational study showed higher *Oxalobacter formigenes* colonization in stone-forming patients, compared to non-stone-forming patients [78]. Initial small study in patients with primary hyperoxaluria suggested that *Oxalobacter formigenes* therapy reduced urinary oxalate significantly [79]. However, a subsequent 24-week randomized, placebo controlled trial of 36 patients with primary hyperoxaluria, although well tolerated, showed no difference in urinary oxalate excretion [80]. Hence, the clinical application of probiotics in calcium stone disease is still in its infancy.

Conclusions

Calcium stones represent majority of cases in patients with kidney stones. Many risk factors have been identified, and those with high risk of recurrence should be advised on specific therapy to prevent stone recurrence.

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Chapter 8
Nutritional Management of Calcium Stones

Donna E. Gjesvold

Keywords Citrate · Hypercalciuria · Hyperoxaluria · Hypocitraturia · Microbiome · Nephrolithiasis Oxalate · Potential renal acid load · Supersaturation · Calcium phosphate stones · Uric acid

Abbreviations

AHRQ	Agency for Healthcare Research and Quality
AUA	American Urological Association
CT	Computed tomography
DASH	Dietary Approaches to Stop Hypertension
NHANES	National Health and Nutrition Examination Survey
PRAL	Potential renal acid load
PTH	Parathyroid hormone
RCT	Randomized controlled trial

Key Points

- Calcium-containing kidney stones are common, increasing in prevalence and economic burden, and multiple dietary factors contribute to this phenomenon.
- Fluid intake has been clearly identified as an important focus for kidney stone risk reduction for all stone types including calcium-based stones.
- It is recommended that total daily calcium intake from preferred dietary sources, and supplements if needed, should meet but not exceed the adequate range of about 1000–1200 mg/day for most adults. Timing and dosing of dietary and supplemental calcium are important in reducing kidney stone risk.
- Calcium homeostasis is influenced substantially by both dietary sodium and nondairy animal protein, and both may contribute to formation of calcium stones. Dietary Approaches to Stop Hypertension is a reasonable intervention to modify sodium and protein for kidney stone risk reduction.

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- Diets that provide adequate calcium, lower nondairy animal protein and sodium, and higher amounts of fruits and vegetables and plant-based proteins reduce the risk of calcium oxalate stone formation and recurrence despite lack of oxalate restriction. In cases of enteric hyperoxaluria related to malabsorption, dietary oxalate restriction provides additional benefit.
- Urinary citrate is a powerful inhibitor of calcium stone formation. Diets rich in foods with a high potential renal acid load can result in decreased urinary citrate excretion and increased stone risk. Increasing dietary citrate may alleviate hypocitraturia similar to pharmacologic citrate.
- Treating calcium stones in the broader context of associated chronic diseases requires consideration of the unique needs of the individual patient and their nutrition history. Medical and nutrition therapies provide synergistic benefits and give the patient the best chance at satisfactory treatment outcomes and preventing recurrence of stone disease.

Introduction

From the earliest written records, we find evidence of kidney stone disease. The oldest known kidney stone dates back to about 4400 BCE and was discovered with the mummified remains of an ancient Egyptian in 1905.This stone was found to contain calcium oxalate and calcium phosphate [1]. Today around 80% of kidney stones in the United States contain calcium, and most calcium stones are primarily calcium oxalate [2]. Ancient Babylonian medical texts dating back as early as the second millennium BC provide additional historical references [3]. Treatments were mostly plant or mineral based and included ingredients such as myrrh, milky sap, and seed of tamarisk. These were combined with milk, juice, wine, beer, or oil and ingested, instilled, or applied in a variety of ways [3].

While medical and technological advancements have broadened treatment options beyond exotic plant and mineral potions, there remains an important role for nutrition therapy in supporting the medical management of kidney stone disease. True prevalence of kidney stones is difficult to determine for various reasons [4]. However, it is clear that kidney stones are common and increasingly so, affecting nearly 1 in 11 people in the United States during their lifetime [5]. Additionally, half or more people who have a kidney stone will develop a second stone within 10 years of initial event [6].Overall prevalence of self-reported kidney stones increased 70%, regardless of age or gender from 5.2% to 8.8%, for the periods 1988–1994 and 2007–2010 based on the National Health and Nutrition Examination Survey (NHANES) data [5]. As prevalence has risen over time, the financial toll of caring for patients with kidney stones has increased as well. In the year 2000, the total cost of healthcare plus days of missed work associated with kidney stones was estimated at $5.3 billion [7]. Dietary changes in recent decades are increasingly implicated as contributing to this phenomenon [4]. Humans eat and drink for survival and pleasure, and the details of how we do so appear to play a role in either raising or reducing kidney stone risk. In this chapter we will review the literature pertaining to calcium kidney stones and the prevailing concepts regarding dietary interventions, also known as medical nutrition therapy.

Nutrition in Medical Management of Calcium Stones

A review of the scientific literature on the topic of dietary intervention for calcium stones produces a multitude of possible options, but little conclusive guidance emerges. A fundamental complexity of nutrition therapy is the large amount of environmental and cultural variation in the simple act of eating

and drinking. These behaviors are essential for survival and do not easily lend themselves to the structure and control of high-quality clinical trials. Additionally, ethical dilemmas emerge when exposure to or denial of substances essential for health are tightly controlled or manipulated.

Recently there have been efforts to organize the existing knowledge regarding treatment of kidney stones. The Agency for Healthcare Research and Quality (AHRQ) embarked on a thorough and systematic review of existing literature on the topic to help establish best practices and guide healthcare decision-making. They published their comparative effectiveness review of preventive medical strategies for recurrent nephrolithiasis in adults in 2012. Their review selected studies based on quality and strength of evidence and compiled a body of 28 randomized controlled trials (RCT's) including 8 related to diet therapy. Regarding dietary intervention, the AHRQ concluded that increasing fluid intake and reducing soft drink consumption decreased risk of recurrent calcium stones. No other firm recommendations could be made regarding nutrition therapy due to mixed results of other interventions [8].

The American Urological Association (AUA) built on the AHRQ's work by distilling key findings from the highest-quality studies available into practice guidelines which were released in 2014. Despite literature searches producing thousands of possible references, the AUA's panel eventually selected a total of 46 studies as the basis of guideline development. A total of 27 guideline statements ensued and are supported by graded evidence or expert opinion. Dietary interventions for calcium stones are addressed in five of these guideline statements and give broad recommendations on fluids, sodium, calcium, oxalate, fruits and vegetables, and nondairy animal protein. Fluid intake was identified as an important focus for kidney stone risk reduction for all stone types (Table 8.1). The AUA guidelines for calcium phosphate and calcium oxalate stones are similar except with regard to recommendations to lower urinary oxalate. The AUA's guideline statements provide a solid launching point to build nutrition therapy recommendations on as more evidence becomes available [4].

Additional dietary interventions beyond these guideline statements may be important given the fact that a variety of systemic conditions including overweight and obesity [9], hypertension [10], and diabetes [11] are all associated with kidney stone disease. Pending further data it is reasonable to focus on well-documented nutrition interventions promoting healthy weight, blood pressure, and glucose control that might also decrease the risk of kidney stones. Any recommendations should be individualized based on the details of any one patient's kidney stone history. Calcium oxalate stones are the most common type of kidney stones [2], and implementing reasonable dietary interventions to treat such patients may provide substantial health and cost benefit with minimal risk of harm.

Interventions can be better targeted if basic serum chemistries, stone analyses, and 24-hour urine studies including calcium, oxalate, phosphate, sodium, total volume, and supersaturation levels are obtained. Supersaturation is defined as a state of the urine when it contains more of an element or compound than can be dissolved under normal conditions of urine volume and pH.

Table 8.1 AUA 2014 guideline statements pertaining to calcium stones

Guideline	Type of statement	Strength of evidence
Fluid intake to achieve urine volume of at least 2.5 liters per day for all types of stones	Standard	Grade B (moderate)
Limit sodium, and consume 1000–1200 mg per day of dietary calcium if stones are calcium based and urinary calcium is relatively high	Standard	Grade B (moderate)
Limit oxalate rich foods, and maintain normal calcium consumption if stones are calcium oxalate and urinary oxalate is relatively high	Expert opinion due to insufficient evidence	–
Increase intake of fruits and vegetables, and limit nondairy animal protein if stones are calcium based and urinary citrate is relatively low	Expert opinion due to insufficient evidence	–
Limit intake of nondairy animal protein if stones are uric acid or calcium based and urinary uric acid is relatively high	Expert opinion due to insufficient evidence	–

Data from Pearle et al.[4]

Fluid

Fluid intake is the main determinant of urine volume, which in turn affects concentration of stone-forming salts [4]. There is good evidence that higher fluid intake reduces the risk of stone formation [12]. AUA guideline statements advise enough fluid intake to produce at least 2.5 liters of urine daily with modifications tailored to the patient's clinical presentation [4]. Most patients require 3 liters or more of fluid intake to reach this urine volume goal, but this varies with patient-specific factors including non-urine loss of fluids. Routinely drinking fluids throughout the day is advised to prevent periods of decreased urine output that may allow urine crystals to begin forming. All beverages help increase urine volume and appear to lower risk of stone formation at least somewhat except for sugar-sweetened beverages including soda [13]. A generally advised rule of thumb is that water should make up the majority of one's fluid intake.

Calcium

Once fluids are optimized, assessment of calcium status is important for treating calcium oxalate and calcium phosphate stones. Ample evidence demonstrates that lower calcium diets generally increase risk of stone formation and may be explained by lower availability of calcium to bind with dietary oxalate in the gut. This may result in higher oxalate absorption and urinary excretion [4]. A study by Sorensen showed higher incidence of nephrolithiasis among individuals consuming <800 mg calcium/day. Persons consuming adequate dietary calcium, defined as 1000–1200 mg/day for most adults, clearly demonstrate reduced risk of stone formation [14]. Meeting the recommended intake of calcium with food alone may be difficult for some due to a variety of reasons. Supplemental calcium is a reasonable intervention to address dietary shortfalls and has been a mainstay of osteoporosis therapy for postmenopausal women for many years. There is evidence, however, that supplemental calcium may correlate with higher risk of kidney stone formation in older women. In The Women's Health Initiative clinical trial, an increased risk of stones was noted with calcium supplementation in subjects whose total calcium from both diet and supplements exceeded the recommended upper limit of 1200 mg daily for adults [15, 16]. Enough calcium, regardless of source, is needed, but excessive calcium from supplements in particular appears to increase stone risk. Timing of the supplements, as well as the actual dosing, may play a role in this finding, as calcium from either food or supplements must be consumed with meals for oxalate binding and reduced absorption to occur. It is recommended that total daily calcium intake from both diet and supplements should not exceed the adequate range of about 1000–1200 mg daily for adults. Assessing 24-hour urine collections for supersaturation levels may help determine whether calcium supplements are beneficial or problematic for this patient group [4].

Sodium

Calcium homeostasis is influenced substantially by both dietary sodium and nondairy animal protein, and both may contribute to formation of calcium stones. Lower sodium and nondairy animal protein paired with adequate calcium in diet can reduce urinary calcium excretion in hypercalciuric stone formers [17]. Based on the available evidence, the AUA recommends a dietary sodium limit of no more than 100 mEq or 2300 mg daily for most adults [4]. Nutrition strategies and tools to help the patient achieve this in a step-wise fashion over time are widely available and well-known as interventions for hypertension and cardiovascular disease.

A reasonable intervention to modify sodium and protein (which is discussed below) is to implement a comprehensive heart-healthy eating plan, such as the Dietary Approaches to Stop Hypertension (DASH)[18]. Large studies have demonstrated significantly reduced risk of kidney stones in groups consuming diets consistent with the DASH guidelines [19]. The DASH has multiple advantages. It limits sodium intake, it is lower in nondairy animal protein, and it is higher in fruits, vegetables, nuts, legumes, whole grains, and dairy compared to a typical western diet. Regarding protein, animal sources appear to convey more kidney stone risk compared to plant-based proteins, and the DASH eating plan provides about 4–6 oz animal protein per day which appears adequate for most people. While strict adherence to DASH is not the only way to reduce kidney stone risk, it is a reasonable intervention to help patients address multiple risk factors in a systematic way, and resources to help implement the plan are widely available at no cost to the patient or provider. Importantly, the DASH eating plan has also shown potential benefit in reducing risk of chronic kidney disease, type 2 diabetes, cardiovascular disease, and stroke [20].

Oxalate

Treating hypercalciuria by addressing possible dietary factors may be effective in shifting urine supersaturation to lower risk of calcium stones. If urinary oxalate is relatively high despite adequate dietary calcium, restricting oxalate in diet may be warranted especially in patients with confirmed calcium oxalate stones. The Harvard School of Public Health maintains an extensive online oxalate database to provide guidance in managing a low oxalate diet restriction [4]. Nevertheless, dietary intake of oxalate is not the only factor influencing urinary oxalate (Fig. 8.1), and most high oxalate foods provide other health benefits, so overly restrictive low oxalate diets are not generally recommended [21, 22].

Additionally, there is no single gold standard oxalate reference, and there is great variation in reported values (Fig. 8.2) across references which may confuse both patients and providers when attempting a low oxalate diet intervention [22, 23]. There are logical explanations for at least some of the variability noted in food oxalate data (Fig. 8.3). How the food item was analyzed in the laboratory accounts for some variation. Multiple other aspects related to the plant itself, ripeness when picked, and soil characteristics are also challenging in oxalate restriction [22, 23].

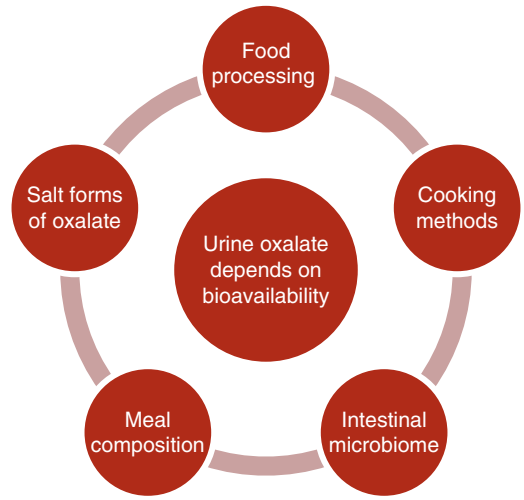

Fig. 8.1 Urine oxalate depends on factors that regulate absorption from food. (Adapted from Massey with permission from Elsevier [22])

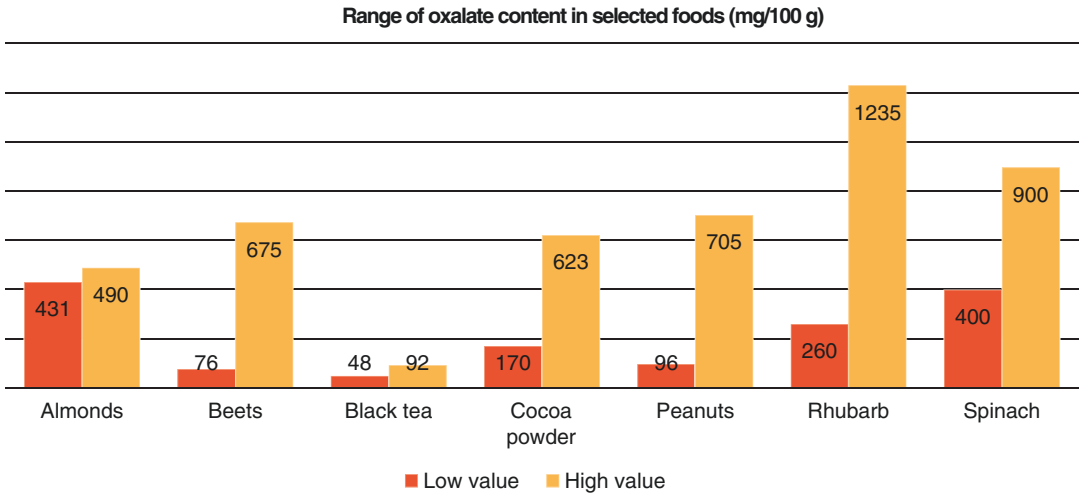

Fig. 8.2 Variation of published oxalate values. (Adapted from Massey with permission from Elsevier [22])

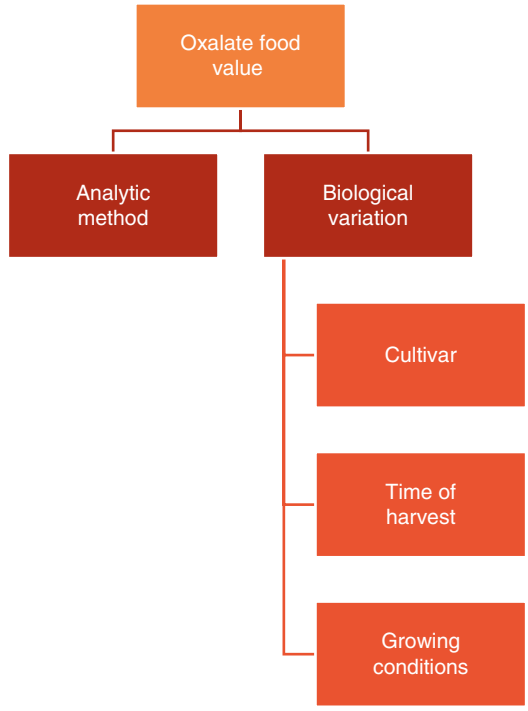

Fig. 8.3 Variables affecting oxalate food values. (Adapted from Massey with permission from Elsevier [22])

Given the difficulties of dietary oxalate restriction, hyperoxaluria treatment is often focused on adequate calcium intake to modulate oxalate absorption rather than decreased oxalate in the diet [21, 24]. Diets that provide adequate calcium, lower nondairy animal protein and sodium, and higher amounts of fruits and vegetables and plant-based proteins can reduce the risk of calcium oxalate stone formation and recurrence despite lack of oxalate restriction [19]. So while the DASH eating plan may

be high in oxalate, depending on individual food choices, it is rich in fiber and phytate which help inhibit absorption of oxalate in the gastrointestinal tract. In cases of enteric hyperoxaluria related to malabsorption (i.e., Roux-en-Y gastric bypass or inflammatory bowel disease [25, 26]) with very high urinary oxalate excretion, a more restrictive low oxalate diet may provide benefit. Higher calcium intake and lower fat intake may also help prevent increased oxalate absorption (see Chapters 12 and 13). This may require calcium supplements provided with meals to promote oxalate binding.

A variety of oral supplements may contribute to elevated urinary oxalate. Ascorbic acid from high-dose vitamin C supplements is metabolized to oxalate [27], and turmeric and cranberry supplements have been associated with higher oxalate levels in urine [28, 29]. The AUA advises avoiding vitamin C supplements due to calcium oxalate stone risk. Other supplements have been suggested as beneficial in reducing urinary oxalate in idiopathic calcium oxalate stone formers. Probiotics, omega-3 fatty acids, vitamin B6, or pyridoxine have not been sufficiently studied at this point to justify recommendations by the AUA, but completing 24-hour urine studies before and after dietary interventions like these may provide guidance in specific situations [4].

Acid-Forming Foods or Animal Protein

Hypocitraturia is seen in about 20–60% [30] of calcium stone formers. Urinary citrate is a powerful inhibitor of calcium stone formation [31]. Acid-base status drives urinary citrate excretion, and dietary acid load can result in reduced urinary citrate excretion. While medical conditions and some medications may cause hypocitraturia, a diet rich in foods with a high potential renal acid load (PRAL) can trigger acidosis [32]. Meats, fish, poultry, cheese, eggs, and grains contribute more of an acid load compared to most fruits and vegetables, which provide an alkali load. Dietary fat, milk, and yogurt are considered to have a neutral PRAL (Table 8.2) [33, 34].

If nutrition assessment indicates diet is contributing a high PRAL and likely contributing to hypocitraturia, the patient may benefit from increasing fruits and vegetables and decreasing meats, fish, poultry, cheese, eggs, and grains. Increasing fruits and vegetables as a singular intervention may be adequate [35], but weight gain may result if other foods are not adjusted to balance calories. Hypocitraturia may also be addressed with increased dietary citrate [36]. Citrate from fruits and juices may alleviate hypocitraturia similar to pharmacologic citrate [37]. Although data is insufficient for specific recommendations at this time, it appears that the juice from two medium-sized fresh lemons

Table 8.2 Average potential renal acid loads (PRAL) of certain food groups (related to 100 g edible portion)

Food group	PRAL (mEq)
Cheese – more than 15 g protein per 100 g	23.6
Meat and meat products	9.5
Cheese – less than 15 g protein per 100 g	8.0
Fish	7.9
Grains – flour	7.0
Grains – pasta	6.7
Grains – bread	3.5
Milk and non-cheese products	1.0
Fats and oils	0
Vegetables	−2.8
Fruits and fruit juices	−3.1

Data from Remer and Manz [34]

consumed daily may provide a level of dietary citrate that is comparable to typical pharmacologic interventions at lower cost and without gastrointestinal side effects [38].

The AUA recommends patients with calcium stones and relatively high urinary uric acid to limit nondairy animal protein to reduce stone recurrence risk. Low urine pH is a risk factor for both calcium oxalate and uric acid stones. They may coexist in some patients, and there is speculation that uric acid crystals may form a nidus for calcium stones. Urinary uric acid is a product of exogenous and endogenous input with diet contributing about 30% which comes mostly from high-purine animal sources in the typical western diet [39]. While there is no good data to support nutrition therapy targeting urinary uric acid in calcium stone formers, it is probably reasonable to limit higher-purine foods. High-purine foods typically contain more than 150 mg per 3-ounce serving and include anchovies, sardines, herring, mackerel, scallops, and mussels, water fowl, organ meats, glandular tissue, gravies, and meat extracts. Moderately high-purine foods include other shellfish and fish, game meats, mutton, beef, pork, poultry, and meat-based soups and broths [4].

Nutrition therapy may be the only needed intervention to prevent recurrence of calcium stones. However, medications are often required to sufficiently mitigate risk. An awareness of how diet supports and enhances pharmacologic therapy may optimize outcomes further, as in lower sodium diets paired with diuretic therapy.

Calcium Phosphate Stones

While most calcium stones are calcium oxalate stones, calcium phosphate stones can sometimes be found on stone analysis. They occur when the supersaturation of calcium phosphate is elevated in the setting of alkaline pH (>6.3) and hypercalciuria. Calcium phosphate stones are associated with certain diseases such as primary hyperparathyroidism and renal tubular acidosis, but they can be found in the absence of metabolic acidosis. Treatment should focus on decreasing the supersaturation of calcium phosphate by increasing fluid intake and decreasing urinary calcium. Caution is advised when treating hypocitraturia in patients with these stones especially if the pH is elevated because it may create an environment that favors calcium phosphate crystal formation [40].

Summary

Calcium stones are the most common type of kidney stones and have been documented in the historical record for thousands of years. Stone disease is an increasing problem, and finding new ways to provide high-quality care for the best outcomes while minimizing risk of harm is a priority. Although there is a shortage of high-quality studies to guide nutrition therapy for treatment and prevention of calcium stones, it is possible to target interventions with available serum and urine chemistries paired with results of stone analysis. The AUA's current guideline statements regarding dietary modification provide a reasonable start for a coordinated approach that supports and complements medical interventions. Treating calcium stones in the broader context of associated chronic diseases requires consideration of the unique needs of the individual patient and their nutrition history. Medical and nutrition therapies provide synergistic benefits and give the patient the best chance at satisfactory treatment outcomes and preventing recurrence of stone disease.

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Chapter 9
Medical Management of Uric Acid Stones

Shimontini Mitra and Robert A. Cohen

Keywords Uric acid · Urolithiasis · Urate · Alkalinization · Hyperuricemia

Key Points

- Uric acid stones are the second most commonly occurring form of kidney calculi.
- Uric acid stone formation occurs commonly when urinary pH and/or volume is low. A high-purine diet exacerbates stone formation.
- Dietary changes and pharmacological approaches are the mainstay of prevention of uric acid stone formation.
- Increasing fluid intake, adopting a more plant-based diet, and decreasing alcohol consumption are some of the dietary approaches that prevent urolithiasis.
- Alkalinizing urine with oral citrate and use of xanthine oxidase inhibitors to decrease uric acid production are pharmacological methods for preventing uric acid stone formation.
- Surgical intervention is rarely needed as dietary and medical therapy is generally effective.

Introduction

The incidence of uric acid nephrolithiasis has risen in the United States in the last few decades. The treatment of patients with uric acid stones is based on pathophysiology. The following management approaches are commonly used: increasing urinary volume, alkalinizing the urine, reducing uric acid excretion, or any of these combined. We will focus on nutrition and pharmacotherapy approaches, for stone prevention. Surgical treatment of uric acid kidney stones is addressed in Chap. 5.

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Urinary Volume

It is generally accepted that increased fluid intake is associated with a reduction in recurrence of nephrolithiasis in stone formers. In one trial, stone formers were randomized into two groups [1]. One group consumed a higher volume of fluid (amount of water needed to produce at least 2 liters of urine a day) compared to the other group. The lower volume group had an increased rate of stone recurrence and increased levels of urinary calcium as well as higher supersaturation of calcium oxalate, brushite, and uric acid compared to the high fluid volume group. Another consideration is diurnal variation in urinary pH and volume [2]. The early morning and early evening hours are times of day when both urine pH and volume are lowest and concentration of solute is greatest. Therefore, the total concentration of uric acid can be reduced with higher fluid intake, particularly during those intervals, with the expected reduction in crystal formation [3].

Urinary Alkalinization

Urinary pH plays a fundamental role in uric acid crystallization. Humans lack uricase, an enzyme found in other mammals, which converts uric acid into soluble allantoin. In humans, the reaction that converts uric acid to a more soluble form of urate takes place at a p*K*a of 5.35 [4]. Therefore, it is advisable to maintain a higher urinary pH greater than 6.5, at which level most uric acid will be in the more soluble form of urate [5]. However, caution should be exercised with increasing urinary pH greater than 7.0, as this has the potential to promote calcium phosphate stone formation in predisposed patients.

Diet

In patients consuming a typical American diet, without gout or a myeloproliferative disorder, about 300–400 mg/dL uric acid is produced daily. About two-thirds of the uric acid is excreted in the urine [6]. In stone formers, this level tends to be greater than 600 mg/dL [5]. Exogenous sources of uric acid in the typical Western diet are mainly found in animal proteins like meats and fish, in the form of purines. Purines are metabolized in the intestine to form uric acid, commonly referred to as acid ash [5, 7, 8]. Thus, a diet high in animal protein is associated with a more acidic urine. Moving away from a high-protein diet and adhering to no more than 1.5 g/kg/day are advisable for uric acid stone formers [8]. This approach results in an increase in urine pH [5] and a reduction in net uric acid excretion.

Alcohol is also high in purine content. Beer, in particular, has an elevated concentration of purines, about 5–8 mg/100 mL [9]. It has been shown to increase levels of serum uric acid, whereas small quantities of wine do not [9, 10]. Increased alcohol intake can also lead to dehydration, another risk factor for stone formation in general. No studies, however, have found a direct association between alcohol consumption and urolithiasis.

Citrate-derived salts from citric acid minimize uric acid stone risk by increasing urinary pH. Citrates also chelate urinary calcium and therefore reduce the risk of calcium stone formation. A vegetarian diet, which is also lower in purines and animal protein, tends to be higher in citrate concentration. Citrate, derived commonly from citrus fruits, serves as an alternative to pharmacological citrate compounds. Citrate content differs among fruits. One study compared the impact over a duration of 1 week of orange juice to lemonade on kidney stone risk factors [11]. Orange juice resulted in the greatest increase in urinary pH and citrate compared with lemonade. The authors argued that potas-

sium from oranges forms a complex with citrate, whereas protons from lemons form a complex with citrates. A drawback of using orange juice as a preventive measure is its high calorie content. The former should be kept in mind when treating diabetics with uric acid stones and the latter for individuals also prone to calcium oxalate stones. Another study by Kang et al. looked at the effects of long-term dietary lemonade compared with oral potassium citrate supplementation [12]. Although the change in urinary pH was higher in the potassium citrate group, the urinary citrate levels were comparable in both arms, about 700 mg/day for lemonade and 800 mg/day for potassium citrate.

Other beverages have been evaluated. Coffee and tea intake was examined in a survey [13], with the results showing lower levels of serum uric acid in coffee drinkers. In this study, however, urinary uric acid was not investigated. Coffee is thought to decrease uric acid levels through its high concentrations of a polyphenol, chlorogenic acid, which has insulin-sensitizing effects [14, 15].

Mineral water, with varying concentrations of bicarbonate, has also been studied in terms of its effects on urinary pH [16, 17]. Patients with calcium oxalate stones were assigned to either consuming lower bicarbonate content mineral water or higher bicarbonate content mineral water for 3 days. Urinary pH and urinary citrate levels were higher, and supersaturation of uric acid was significantly lower in the group consuming mineral water with a higher bicarbonate content.

Another consideration is dietary fructose consumption, which, due to its presence in many processed foods, has increased significantly in the recent past. Fructose metabolism produces purines which are metabolized to uric acid. Epidemiological studies have revealed an association of hyperuricemia and gout with increased fructose consumption [18]. In one large prospective study, fructose was established as an independent risk factor associated with the development of stones while non-fructose carbohydrates were not [19]. In animal models, fructose infusions have been shown to increase insulin resistance [19, 20]. This has been theorized to be a primary contributor to lower urinary pH and therefore a potential kidney stone risk factor.

In aggregate, the evidence suggests that a vegetarian diet may be most beneficial for preventing recurrence of uric nephrolithiasis. The Dietary Approach to Stop Hypertension (DASH) diet focuses on citrate-rich foods, which generate an alkaline urine. In one study, individuals who adopted this diet exhibited higher urinary citrate and pH levels [17, 21]. However, propensity for stone development was not studied. The DASH diet may have additional benefits as it is associated with weight loss and possible improvement in the metabolic syndrome, resulting in improved insulin sensitivity and higher urinary pH.

Pharmacotherapy

Prescription of citrate compounds is the pharmacologic cornerstone of uric acid stone management. As noted, dietary citrate leads to urinary alkalinization with a higher urine pH. Numerous studies have shown the benefits of potassium citrate salts in reducing stone risk [22]. Pak et al. showed that treating patients with daily potassium citrate at an average daily dose of 60 mEq increased urinary citrate, urinary pH, and the amount of undissociated uric acid. Stone recurrence rate decreased significantly. The study's results were consistent with the average increases in urinary citrate excretion found in the study by Kang that evaluated dietary citrate consumption [12]. One drawback of potassium citrate is expense. Another is the possibility of developing hyperkalemia, particularly in individuals with impaired renal function, those taking medications that inhibit the renal angiotensin aldosterone axis, and transplant patients taking calcineurin inhibitors [23]. Finally, some patients experience gastrointestinal side effects from potassium citrate, limiting its usefulness in treating a low urinary pH.

Potassium citrate dosing is dependent on urinary pH and supersaturation of urinary uric acid found with 24 hour urine determinations. The question of dosing interval is also important. Given the data

on diurnal variation in uric acid excretion and pH [3, 24] dosing should probably be done intermittently (two to four times daily) rather than once daily to maintain a higher urinary pH more consistently. Once initiated, further dosing adjustment should reflect changes in urinary pH, keeping in mind that very high urine pH in some individuals may predispose to calcium phosphate stone development. Dosing is also altered based on gastrointestinal intolerance, with the need to adjust doses according to the presence of symptoms.

Sodium citrate is an alternative drug to potassium citrate for uric acid nephrolithiasis [26]. One study compared the use of sodium citrate to potassium citrate for patients with urolithiasis [26] with the finding that both interventions comparably raised urinary pH and citrate levels. However, urinary calcium levels were higher with sodium citrate in contrast to potassium citrate, likely reflecting the calciuric effect of increased urinary sodium excretion. Thus, sodium citrate could prove problematic for those individuals who are also prone to hypercalciuria. In addition, solubility of urate tends to be lower with sodium salts when compared to potassium salts [25, 26]. The presence of concomitant heart failure or hypertension may also limit the use of sodium salts. However, in circumstances in which uric acid stones are considered related to diarrhea or other gastrointestinal conditions resulting in volume depletion, sodium salts may be preferable for preventive treatment [25].

Another potential treatment for alkalinizing the urine is sodium bicarbonate supplementation [27]. Each 650 mg tablet contains approximately 8 mEq of bicarbonate. Potential reasons to avoid sodium bicarbonate, especially at higher doses, include higher sodium excretion with concomitant hypercalciuria and the development of metabolic alkalosis.

Other Medications

Xanthine oxidase inhibitors are used to prevent uric acid nephrolithiasis. Allopurinol, one such xanthine oxidase inhibitor, reduces xanthine and hypoxanthine conversion to uric acid. Hypoxanthine is also converted back to purine ribotides which inhibit enzymes that ultimately affect de novo purine synthesis [28]. Xanthine oxidase inhibitors have also been shown to decrease uric acid excretion into the urine [29]. However, no randomized studies have examined whether allopurinol prevents uric acid stone development.

Allopurinol has been investigated with regard to calcium oxalate stone prevention; a medication may also have a beneficial impact on uric acid stone formation. In a study published in the *New England Journal of Medicine* [30], patients with a previous stone history were randomized to taking allopurinol or a placebo. The allopurinol arm showed a decreased percentage of calculi as well as longer time to recurrence. The study also showed significantly decreased serum uric acid and urinary uric acid levels in the intervention group, leading some to use allopurinol for stone prevention in those with a history of uric acid nephrolithiasis. The use of febuxostat, another xanthine oxidase inhibitor, has also been efficacious in lowering both serum uric acid and urinary uric acid values [31]. Allopurinol has also been used as a treatment in individuals who continue to have uric acid stones despite correction of urinary pH. Primary gout or tophaceous gout is another indication for xanthine oxidase inhibitors. Gastrointestinal side effects are common with allopurinol. Rare but very serious side effects of allopurinol treatment include Stevens-Johnson syndrome or allopurinol hypersensitivity syndrome (AHS), consisting of fever, rash, transaminitis, peripheral eosinophilia, and acute renal failure [7, 36]. Chronic kidney disease may predispose to AHS [36]. Therefore, allopurinol should be used with caution in patients with chronic kidney disease and should be started at low dose with careful dose escalation.

Patients with myeloproliferative disorders, tumor lysis syndrome, and certain congenital disorders require xanthine oxidase inhibition due to net high uric acid excretion of >1000 mg/day [32]. In addi-

tion to the high uric acid production potentially leading to kidney stone development, microobstructions in the kidney and decreased eGFR have been reported in this context [33]. In settings of anticipated heightened uric acid production, rasburicase, a recombinant urate oxidase that catalyzes the conversion of uric acid to allantoin, has been deployed. This intervention has been shown to decrease serum uric acid levels within 4 hours. Rasburicase is very expensive, limiting its use [34]. In addition, it has not been studied for the prevention of uric acid nephrolithiasis.

Acetazolamide, a carbonic anhydrase inhibitor, is not considered a treatment for uric acid stone prevention. Due to its ability to raise urinary pH, it has been used in patients receiving high doses of methotrexate as a preventive measure for methotrexate-induced crystal nephropathy [37]. However, using acetazolamide routinely for urinary alkalization is not recommended since it tends to produce hypocitraturia [7, 38] and is associated with the formation of calcium phosphate stones [39].

Finally, of note, losartan has been associated with increased hyperuricosuria [40] in both normotensive and hypertensive patients. This appears to be a unique feature of losartan rather than for other angiotensin II antagonists or ACE inhibitors. The mechanism is unclear, but it is thought to be an effect of the parent drug rather than its active metabolite, E-3174 [41]. It is unclear whether patients with uric acid nephrolithiasis should avoid this medication.

Surgical

Surgery for urolithiasis is often not needed since medical therapy is usually very effective. Indications for surgery are similar for all forms of kidney stones: persistent urinary infection, symptomatic discomfort, and failure of medical therapy. Lithotripsy, ureteroscopy, and percutaneous nephrolithotomy have all shown to be effective in the surgical management of urolithiasis [7]. Surgical management is addressed in Chap. 5.

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Chapter 10
Nutritional Management of Uric Acid Stones

Anne-Marie Desai

Keywords Uric acid · Fluid intake · Dehydration · Obesity · Protein · pH · Alkalization · Citrate Purines

Key Points

- Maintaining a healthy body weight and avoiding rapid weight loss are important in prevention of uric acid stone formation.
- High output ostomies and dehydration can increase the risk of uric acid stone formation.
- Urine alkalization using either dietary citrate or potassium citrate can prevent uric acid stone recurrence.
- Individuals at risk of uric acid stone recurrence should aim to drink greater than 3 liters of water per day. Ideally spread evenly throughout the day.
- A diet moderate in protein and high in fruit and vegetables may assist to prevent uric acid stone recurrence.
- Excessive intake of purine-rich foods, such as meat, seafood, yeast, yeast extract, and beer, may contribute to uric acid stone formation.

Prevention

Dietary modification is a key component of uric acid stone prevention and requires first a thorough patient risk assessment. Table 10.1 summarizes uric acid stone risk group.

Table 10.1 Summary of at risk groups

Summary of at-risk groups
1.1 Overweight and obese [2]
1.2 Rapid weight loss [8, 9]
1.3 High protein "Atkins style" dieters [8, 11, 12]
1.4 Chronic diarrhea or high output ostomies [13]
1.5 High fructose intake [17]
1.6 Working or living in hot climate/conditions (dehydration) [21–24]

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Low urine volume, hyperuricosuria, and low urine PH are the three most importation risk factors amenable to dietary intervention [1]. Low urinary volume and low urine PH are generally viewed as the most modifiable contributing factors to stone formation.

At-Risk Groups

Overweight and Obese

Being overweight or obese has been shown to be a significant risk factor in uric acid stone development [1, 2]. Metabolic syndrome and type 2 diabetes are both associated with uric acid nephrolithiasis [3]. Additionally, there is an increased risk of stone formation in patients with truncal or central obesity as opposed to those patients who have increased leg fat mass [4]. The exact mechanisms of uric acid stone formation in the overweight and obese are unclear; however it is thought that insulin resistance and impaired glucose metabolism play a role [5, 6]. There is evidence that higher body mass index (BMI) correlates with high urinary excretion rates of uric acid and therefore a lower urine pH [2, 7] and an increased likelihood of stone formation.

Prevention of the metabolic syndrome and obesity through dietary and lifestyle measures may assist in the prevention of uric acid stone formation.

Weight Loss Diets

The risk of uric acid stone formation must also be considered during weight loss. Individuals who experience rapid weight loss whether intentional or unintentional are at risk of uric acid stone formation due to the loss of lean muscle tissue [8, 9]. When the aim of nutritional therapy is for rapid weight loss, such as in those individuals placed on the very low-energy diet (VLED), adequate hydration of at least 3 liters a day should be recommended.

Recently, high protein diets for weight loss have become more popular both in the general public and within the medical establishment [10]. There is some evidence that a high protein diet such as an Atkins style diet could result in increased levels of uric acid and hence increase the risk of stone development probably due to the decease of urine pH [8, 11, 12]. Individuals on high protein, low carbohydrate diets should be warned of the risk of stone formation and counseled to ensure fluid intake is greater than 3 liters daily.

Gastrointestinal Diseases

In disorders that result in non-urinary loss of fluids from the GI tract, the urine volume may decrease, and urinary uric acid becomes more concentrated resulting in the formation of uric acid crystals. Patients with chronic diarrhea or high output ostomies have an increased risk of uric acid stone formation. There may also be loss of alkali in certain conditions including chronic diarrhea resulting in a metabolic acidosis and decreasing the urine pH. Overall the net loss of fluid and alkali leads to uric acid supersaturation [13]. These patients often require alkalization of the urine through the use of

potassium citrate or sodium bicarbonate. Adequate hydration to prevent stone formation must be matched to the often large stoma output for ileostomy patients.

Fructose

Fructose has become more prevalent in the western diet [14], and there have been emerging concerns of the health implications of increased fructose consumption including kidney stone formation. Two mechanisms are thought to contribute. First, fructose increases insulin resistance and if diabetes is present may cause a low urinary pH and decreased ammoniagenesis. Second, fructose intake results in the stimulation of adenosine monophosphate (AMP) deaminase resulting in raised uric acid levels [15, 16]. Both of these adverse outcomes can lead to the development of uric acid stones [17–19]. Avoidance of excessive fructose is becoming increasingly difficult particularly in the USA where the use of high fructose corn syrup is used in the production of many foods such as soft drinks and pancake syrup. Table 10.2 shows examples of processed foods containing high amounts of fructose in the US diet. Advising patients to limit processed foods and to enjoy fresh and freshly cooked foods can reduce dietary intake of fructose.

Dehydration

Individuals living in hot desert climates such as those in the Middle East, Australia, or the southern states of America may be at increased risk of uric acid and all stone formation due to dehydration. Evaporative skin losses can lead to reduced urine volume and hence increase the risk of stone precipitation [21–23]. Individuals working in manual labor under hot conditions are also at risk [24]. Access to clean drinking water and encouraging good water intake of at least 3 L per day as a public health message can help reduce the risk.

Treatment

For patients who have already been diagnosed with uric acid stones, there are several dietary precautions that can be taken to help prevent stone recurrence. General recommendations include slow weight reduction and maintenance of a healthy BMI, avoiding high protein diets, maintaining adequate hydration, and limiting intake of high fructose containing foods. Additionally, patients with

Table 10.2 Processed foods containing high amounts of fructose in the US diet [20]

Processed foods containing high amounts of fructose in the US diet
Soft drinks (soda)
Sweetened breakfast cereals
Bread, cookies, and pop tarts
Condiments such as ketchup and pancake syrup
Low fat and fat-free flavored yogurt

gastrointestinal disorders resulting in the loss of fluids or alkali should receive appropriate nutritional counseling to minimize the risk of further stone formation.

There are three strategies employed to prevent recurrent uric acid stones:

1. Urine alkalization
2. Increasing urinary volume
3. Decreasing uric acid production

Urine Alkalization

It is known that a higher urinary pH can reduce stone recurrence and promote stone dissolution [25]. Therefore, the most important and clinically effective way to prevent stone recurrence is to ensure that urinary pH is between 5.8 and 6.2. This can be achieved through the prescription of potassium citrate or sodium bicarbonate and the frequent monitoring of urinary pH [26, 27]. Potassium citrate is generally preferable to sodium bicarbonate as adding a sodium load may be associated with calciuria in calcium stone formers or may not be tolerated in patients with heart disease or hypertension [25, 27]. Additionally, bicarbonate is broken down into carbon dioxide gas in the stomach and may lead to gastrointestinal complaints [26]. However, sodium bicarbonate is often cheaper and more readily available than potassium citrate and may be used when potassium citrate cannot be obtained. Sodium bicarbonate can also be considered in patients with concurrent sodium loss from the GI tract.

Dietary citrate may also be used to raise urine pH and when in the form of citric acid may prevent crystal formation and aggregation in the urine [26, 28, 29]. Lemons and limes have the most citric acid, followed by oranges, melon, grapefruits, and berries. Adding lemon or lime juice to water with the aim of a daily half-cup (4 ounces of pure lemon/lime juice) may be as effective in providing the same amount of citric acid as pharmacological therapy. See Table 10.3 for tips on how to increase dietary citrate.

Increase Urinary Volume

Inadequate fluid intake leads to low urine volume. In those individuals at risk of uric acid stones, low urine volume and high concentration of uric acid lead to supersaturation, and uric acid crystal formation can occur [30].

Table 10.3 Methods to increase dietary citrate

Methods to increase dietary citrate
Add fresh lemon or lime juice to dishes such as grilled fish or salads
Add a squeeze of lemon or lime juice to your drinking water
Squeeze lemon or lime juice on top of fruits such as watermelon or papaya for an extra zing
Eat a fresh orange every day
Make a smoothie out of fresh or frozen berries

Increasing urine volume should be a primary goal in the treatment of individuals with uric acid stones. The consensus opinion is that urine volume should exceed 2.5 L per day [21, 30, 31] requiring at least 3 liters of fluid a day. This volume is best consumed over the course of the day, rather than episodically, to prevent periods of increased urine concentration, so it requires a concerted effort on behalf of the patient. Patients should be educated they will need to urinate more frequently and that this might cause some inconvenience and increase the likelihood of nocturia. See Table 10.4 for strategies to assist patients increase their fluid intake.

Water is the most appropriate and safest fluid choice. There is some evidence to suggest that grapefruit [32] and apple juice [33] should be avoided for patients with uric acid stones. As previously discussed adding lemon or lime juice may be of benefit to raise urine pH but does not provide significant volume by itself. Orange juice has been shown to decrease insoluble uric acid excretion [34, 35], and black current juice has been shown to increase urine pH [36, 37]. However, the potential negative effect of excessive juice consumption, [38] including increased sugar intake, could outweigh the potential benefit of extra orange juice with regard to kidney stone reduction especially in someone who is already overweight or suffers from diabetes. There may also be some merit in bicarbonate-rich mineral waters to assist with the alkalization of urine [36, 39].

Decrease the Production of Uric Acid

Decreasing the production of uric acid can be managed through pharmacological agents such as allopurinol, a xanthine oxidase inhibitor that inhibits the degradation of purines to uric acid [25]. A reduction of urinary uric acid levels is only effective if low urine pH is corrected and urinary uric acid levels are high [26].

Dietary measures to reduce the production of uric acid and increase urinary pH can be achieved through the reduction of animal protein in the diet. Uric acid production can be reduced by directly limiting the intake of dietary purines.

Moderate Protein Intake

Reduction in dietary intake of animal proteins may assist in treatment of recurrent uric acid stones. There is currently a lack of strong evidence showing that limiting protein in the diet will reduce the rate of stone recurrence [40]. The recommendation for a moderate protein intake is based on the knowledge that a diet high in animal proteins leads to a reduction of urinary pH, increased uric acid

Table 10.4 Methods to increase fluid intake

Methods to increase fluid intake
Fill a 3 L bottle of water every day as a visual reminder to drink
Use digital technology, e.g., “health apps” with reminders
Drink a glass of water immediately after voiding
Drink a glass of water with every meal and snack
Don’t forget to add lemon or lime to your water to increase citrate intake

excretion, and therefore an increased likelihood of uric acid precipitation (stone formation) [41–43].

The current recommendations for protein intake in the treatment of recurrent uric acid kidney stones are in line with the Dietary Reference Intake (DRI) for protein for the general population this being 0.8–1.0 g/kg/day [44]. A high protein diet (>2 g/kg/day) can reduce urine pH and may increase risk [21, 44]. See Table 10.5 for strategies to assist patients decrease their protein intake.

There is also some evidence that following a vegetarian diet may be protective against all stone formation [11, 45]. Historically a diet rich in fruit and vegetables was referred to as an alkaline ash diet, and a diet rich in animal proteins was referred to as an acid ash diet. Although these terms are not commonly used, the principle is that fruit and vegetables, when metabolized, result in an alkaline urinary load, whereas the metabolism of animal proteins results in an acidic urinary load.

Raising the urine pH of individuals with recurrent uric acid kidney stones is one of the main goals of medical therapy. It has been found that a higher intake of fruit and vegetables may also raise the urine pH and hence reduce the risk of uric acid stone formation [46]. This is supported by epidemiological studies showing vegetarian diets to be protective against recurrent kidney stones [47]. There are currently no formal recommendations for the exact proportion or amount of fruit and vegetable consumption. Current evidence suggests that greater than five servings of fresh fruit and vegetables per day (greater than 400 g mixed fresh fruit and 300 g mixed fresh vegetables) is optimal [48]. Table 10.6 shows methods to increase fruit and vegetable consumption.

Reduced Intake Dietary Purines

There are two sources of purines in our bodies:

1. Exogenous, from protein in our diet

Table 10.5 Methods to decrease protein intake

Methods to decrease protein intake
Have two or three vegetarian style meals each week
Swap your turkey sandwich for hummus and salad
Avoid steak houses or share large portions with a friend
Make sure your protein serving size is no larger than your smart phone

Table 10.6 Methods to increase fruit and vegetable consumption

Methods to increase fruit and vegetable consumption
Have two or three vegetarian style meals each week
Shop at your local farmers market
Aim for three different vegetables on your plate each night for supper
Grow your own vegetables if you can
Have a fruit bowl in your kitchen

2. Endogenous from tissue nucleotide synthesis and metabolism (cell breakdown)

The average adult consumes approximately 2 mg of purine/kg/day, which produces 200–300 mg of uric acid daily. In addition, endogenous production of uric acid is about 300 mg/day [21]. Regardless of the source of purines, all purines eventually breakdown to uric acid through metabolic pathways (Fig. 10.1). A reduced intake of purines can lead to a decreased excretion of uric acid in the urine and is recommended when serum uric acid is elevated [21, 26, 44].

Examination of data from a nationally representative sample of men and women in the USA suggests that higher levels of meat and seafood consumption are associated with higher levels of uric acid, whereas dairy consumption was inversely associated with serum uric acid levels [49].

Based on this evidence, it is prudent to recommend a low purine containing diet for recurrent uric acid stone formers. However, not all purines are equal in terms of their potential to contribute to lower urinary uric acid excretion. We are therefore recommending that only purines from meat, seafood, yeast, yeast extracts, and beer be excluded or reduced [42, 45, 49]. Table 10.7 shows high purine foods to avoid or limit.

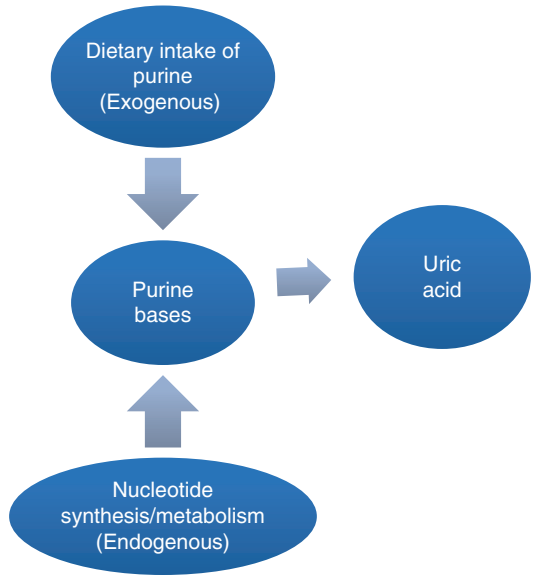

Fig. 10.1 Simplified uric acid metabolism

Table 10.7 High purine foods to limit or avoid

High purine foods to limit or avoid
Organ meats, such as the liver, kidneys, sweetbreads, and brains [49]
Large servings of meats, including bacon, beef, pork, and lamb [44, 49]
Game meats [49]
Anchovies, sardines, herring, shrimp, mackerel, and scallop [44]
Beer, yeast, and yeast extracts [42]

Summary

The goal of dietary management of uric acid kidney stones is to modify the three main risk factors which include low urine volume, low urine pH, and high urine uric acid concentration.

Patients should be encouraged to drink water primarily and consume 3 liters or greater of liquid a day to generate at least 2.5 liters of urine. Alkalization of the urine can be achieved through increasing intake of citrate and a moderate protein intake. Fruit and vegetables should be encouraged to assist with alkalization. Patients should be advised to avoid purine-rich foods that are known to increase uric acid production.

Together with appropriate medical management, these relatively simple dietary measures can assist in the treatment of recurrent uric acid stones. A renal dietitian is able to provide patient-specific treatment advice which when paired with medical management can be of significant benefit in preventing recurrent uric acid kidney stones.

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Chapter 11
Struvite Stones

Walter P. Mutter

Keywords Struvite · Infection stones · Staghorn · Urinary tract infection · Magnesium ammonium phosphate · Calcium carbonate apatite

Key Points
- Struvite stones are rare but associated with significant morbidity and mortality.
- Struvite stones are associated with urinary tract infection and may grow to large staghorn calculi.
- Definitive treatment is surgical, but medical management with antibiotics and urease inhibitors may be helpful.
- Metabolic analysis for stone-forming risk factors may be appropriate in selected patients.
- Currently, no dietary or medical intervention has been shown to decrease the risk of recurrence.

Introduction

Struvite stones contain the compound struvite which is composed of magnesium ammonium phosphate. However, some stones may also contain calcium carbonate-apatite [1]. Historically, struvite stones were known as "infection stones" and were believed to be exclusively associated with genitourinary infection. The term "infection stones" is often used to describe struvite stones in contrast to "metabolic stones" which are related to a primary disturbance of stone-forming urinary compounds such as calcium, oxalate, and urate. Because struvite stones were thought to be related to bacterial growth and not metabolic abnormalities formal evaluation for stone-forming risk factors has not been routinely pursued.

Before the advent of current surgical treatment modalities, struvite stones were associated with significant morbidity and mortality. For example, a recent report identified large bilateral staghorn calculi in the skeleton of a young woman buried in Illinois in the mid-nineteenth century. Chemical analysis was consistent with struvite, and the authors speculate that the kidney stones may have played a role in her young age at death [2]. Struvite stones are now relatively uncommon, and their incidence may be decreasing, probably because of improved medical treatment of genitourinary infection and improved surgical care.

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Staghorn Calculi

Staghorn calculi are large branching calculi that fill the urinary space and may be unilateral or bilateral. By definition they send branches into at least two calyces [3]. The name derives from their characteristic shape resembling deer (stag) antlers. Historically staghorn calculi have been thought to be mostly composed of struvite because it is soft and amorphous and fills the urinary space. Uric acid and cysteine may also form staghorn stones, but calcium oxalate and phosphate are much less likely to do so [4]. Often the literature combines the discussion of staghorn and struvite stones legitimately assuming significant overlap. Early data, mostly prior to 1990, suggest an infectious etiology in 59–68% of cases with higher rates up to 74% in women with bilateral staghorn calculi [5, 6]. The 2005 American Urology Association (AUA) guidelines state that most staghorn calculi are composed of struvite and/or calcium apatite [7]. However, staghorn stones may contain other chemical components. For example, a single-center US study from 2011 looked at the composition of Staghorn calculi in 48 patients and found that most (56%) were "metabolic" with the following breakdown: 56% calcium phosphate, 21% uric acid, 14% calcium oxalate and 10% cysteine. The remainder, only 44% were struvite or "infection stones" [5]. Recent data suggest that staghorn calculi are not necessarily related to infection, and do not necessarily contain struvite. Some authors speculate that there has been an evolution of staghorn composition over the last 20 years [5].

Pathophysiology/Bacteriology

Struvite was first described in 1845 by a Swedish geologist who identified the compound in bat guano and named it after his mentor Baron H.C.G. von Struve [1, 4, 8]. The formation of struvite is dependent on high concentrations of ammonia and an elevated pH in the urine. In such circumstances, phosphate solubility decreases. Clinically this usually occurs in the presence of urease-producing bacteria. The most common species are Proteus, Klebsiella, Pseudomonas, and Staphylococcus [4]. Struvite stones may grow rapidly in the right circumstances resulting in staghorn formations in weeks [4, 9].

The association of genitourinary infection and kidney stones has been known for millennia, but only recently has the mechanism been defined. On pathologic analysis, the stones are a conglomeration of crystals, protein, and bacteria. Bacterial infection is believed to be necessary for the formation of struvite stones, although not all patients have a positive urine culture. Specifically, struvite stones require the presence of a urease-splitting organism to provide the necessary ammonium substrate and local urine pH to initiate supersaturation and subsequent crystallization [4, 10]. Interestingly, there are emerging data which suggest that bacterial infection may also play a role in the formation of both calcium oxalate and calcium phosphate stones [11]. A recent study compared struvite and non-struvite stone cultures and found that 72% of struvite stones were culture positive (of which 36% were a urea splitting organism), whereas 23% of non-struvite stones were also culture positive [12].

The detection of a urease-splitting organism is common, but not always possible. A recent single-center US study of 1191 struvite stone formers treated with percutaneous nephrolithotomy (PCNL) struvite stone microbiology revealed that such organisms are not always identified. Stone cultures were positive in only 72% of patients [12]. Overall 12% of patients had negative urine and stone cultures with 52% growing urease-producing organisms at least once and 36% growing non-urease-producing organisms. Also, urease-splitting organisms accounted for only one-half of the positive cultures. Most common organisms were enterococcus 18%, proteus 18%, and *Escherichia coli* 12%. The majority, 67%, were resistant to first and second-generation cephalosporins [12].

A theory to explain negative stone cultures for urease-producing bacteria is that some struvite stones are rendered sterile by prior antibiotic therapy or may become secondarily infected with non-urease-producing organisms. This is supported by the fact that one-half of the struvite stone formers previously had a urine culture positive for a urease-producing organism within a year prior to stone culture [12].

Many authors argue for vigilance with culturing struvite stone formers with recommendations to culture the urine in the renal pelvis when possible and making sure the lab identifies and reports slow-growing and fastidious organisms [10]. Some authors recommend looking for *Ureaplasma urealyticum* if standard cultures are negative [8, 10]. Many factors may contribute to the absence of a positive culture in struvite stone formers including improper collection, laboratory policies regarding urine culture, and prior antibiotic exposure [10].

Epidemiology

Struvite containing stones are relatively rare. In a Mayo Clinic study of 2961 stone formers, struvite components were identified in only 0.9% of patients [13]. This is somewhat less than previously published estimates which range anywhere from 2% to 30% of all stones [1, 8, 10, 14]. Struvite stones are more common in women by a factor of about 2:1. This is assumed to be because of the increased risk of urinary tract infection in women. In addition to gender, risk factors include urinary tract obstruction, indwelling catheters, neurogenic bladder, and immobility [4, 15]. Although immobility predisposes to struvite stones, patients with musculoskeletal abnormalities and immobility interestingly tend to have more non-struvite stones, especially calcium phosphate stones [15]. Also, there may be geographic variation in stone composition. For example, one study showed less struvite and more calcium present in staghorn calculi in Japan compared with other populations [16].

Metabolic Evaluation

The standard treatment of struvite and staghorn calculi is surgical, but metabolic evaluation may be warranted in some patients. It is important to note that staghorn stones may not contain struvite or be related to infection. Also, struvite stones, even if associated with infection, may be associated with metabolic abnormalities.

A number of studies have shown that staghorn stones often contain other components, including calcium oxalate, calcium phosphate, and urate. Additionally, patients who present with struvite and staghorn calculi may have abnormalities of urinary stone-forming risk factors. In pure struvite stones, the rate of metabolic abnormalities has been reported to be low at 14.2% in one study [17]. However, a more recent study of 33 patients in Sweden identified calcium phosphate in 30 of 31 staghorn stones, and 59% of patients had a 24 h urine showing an elevated calcium oxalate risk index [3]. In a US case series of 48 patients with staghorn calculi, the authors characterized 56% as metabolic and *the remaining* only 44% as infection stones. Therefore they suggest metabolic evaluation of staghorn stone formers [5]. Another US study of 75 patients with struvite stones found hypercalciuria in men, but not in women, compared with controls. Also, men tended to present with stones of mixed composition. They speculate that struvite stones in women may be mostly related to infection, whereas in men calcium stones may be secondarily infected causing subsequent struvite stone formation [18]. Other investigators looked at 75 patients with struvite stones and divided them into three groups. Group 1 (7 patients) had pure struvite

stones with metabolic evaluation, Group 2 (32 patients) had mixed stones with metabolic evaluation, and Group 3 (17 patients) had pure struvite stones without metabolic evaluation. Metabolic abnormalities were found in 57% of Group 1 and 81% of Group 2 patients. A follow-up Group 3 (without metabolic evaluation) tended toward a higher stone activity rate.

The 2005 AUA guidelines support metabolic evaluation for non-struvite staghorn kidney stones, but they do not recommend metabolic evaluation for pure struvite stones [7]. However, considering more recent data, it may be reasonable to perform standard metabolic analysis to look for stone-forming risk even in patients with pure struvite stones [5]. It is not known whether modifying such risk factors prevents future stones.

Management

Natural History of Conservative Management

Prior to 1970 there was a belief that staghorn stones should be managed conservatively without surgery [19]. However, a landmark study from 1976 showed that conservative management was associated with 28% mortality vs. 7.2% mortality in patients who received surgical intervention [20]. Another study found 11.5% mortality and 36% with renal failure in the conservative group vs. 5% mortality and 17.5% renal failure in the group treated with various surgical procedures [21].

Most data support aggressive surgical management of staghorn kidney stones, and this is the accepted clinical approach [7]. However, in patients who decline surgery or who are medically unfit, conservative management may be acceptable. For example, a single-center study in the United Kingdom of 22 patients showed that conservative management was associated with progressive renal failure in only 14% of patients with 9% requiring dialysis. Nevertheless, there was still a 9% disease-specific mortality rate [22].

Surgical

Surgical management of kidney stones is addressed in Chap. 5. Common approaches to struvite stones (often in a staghorn formation) include PCNL, ureteroscopy (URS), open surgery, and shock wave lithotripsy (SWL). It is generally agreed that PCNL should be the preferred treatment modality as it has shown better clearance than extracorporeal shock wave lithotripsy (ESWL) and less complications than open surgery [7, 19]. The goal of any surgical intervention is complete stone removal which may be difficult for large or staghorn stones, and repeated procedures may be needed [7].

Medical and Surgical Combined

Recently there is renewed interest in combined medical and surgical management of struvite stones. A recent retrospective study of 43 patients out of Duke with pure or mixed struvite stones examined a strategy of PCNL or URS followed by medical therapy [23]. Notably, current data is limited, and the authors comment that theirs was the first article in 20 years to address the medical management of

struvite stones. Medical therapy in this study included antibiotic therapy and/or the urease inhibitor acetohydroxaminic acid (AHA). AHA was studied in the 1980s and 1990s but largely abandoned because of significant side effects including nausea, vomiting, tremors, anxiety, headaches, anemia, rash, hepatotoxicity, and venous thrombosis [23–25]. The AUA guidelines for medical management of kidney stones from 2014 recommending offering AHA only after surgical options have been exhausted [26].

Metabolic/Dietary

The role for metabolic manipulation for management and prevention of struvite kidney stones is unknown. No dietary modification has proved effective at preventing or treating struvite stones. Logically a diet that could decrease the urine pH would potentially decrease stone formation, but this has not been shown. Metabolic evaluation has traditionally not been performed for struvite stones as earlier data suggested few metabolic abnormalities in pure struvite stone formers [17]. However, recent data suggest an excess of metabolic abnormalities in such patients [27]. Certainly, for mixed stones metabolic evaluation with urine and serum chemistries as per typical stone formers may be of benefit.

Antibiotics

The use of antibiotics and documented clearance of infection is important for the prevention of struvite stones [4]. But specific guidelines about the choice and duration of antibiotics are lacking [28]. One group has reported complete dissolution of a struvite stone with prolonged antibiotics alone [28]. However, surgical therapy and complete removal of any infected stone fragments remain the cornerstones of therapy [4, 7, 8]. Usually antibiotics are tailored to urine or stone culture results understanding that some may be culture negative. The 2014 AUA guidelines state that patients are at risk for persistent or recurrent infection and should be monitored closely, and long-term antibiotic therapy should be considered [26].

Stone Dissolution

Currently, the standard of care for struvite stones is surgical management and eradication of infection. Improved surgical management has made treatment safe and successful. Several studies have looked at stone dissolution both in isolation and in conjunction with surgical therapies. Some techniques have been abandoned, but interest in the concept remains. The pathophysiology of struvite stone formation requires the presence of bacterial urease so therapies looking at inhibition of this enzyme have made logical sense. There was an early interest in acetohydroxaminic acid (AHA), but adverse reactions and toxicity have prevented its widespread clinical use [24, 29]. Hemiacidrin chemolysis has been attempted with success and low complication rate but requires a nephrostomy tube and prolonged treatment [30, 31]. More recently, combined treatment with PCNL and hemiacidrin has been reported with success [32].

New Directions

Currently complete surgical removal combined with antibiotics tailored to culture results to prevent reinfection is the gold standard of treatment. Ideally it would be helpful to have non-surgical options especially for patients at high surgical risk. Interestingly other mammals may develop struvite stones. There is a significant literature about struvite stones in house cats and this has provided some insight for treatment in humans. There are data in cats which suggest than an acidifying calculoytic diet inducing a urine pH <6.5 may help prevent struvite stones [33]. In vitro data show that the Juice of *Citrus medica* Linn, a citrus fruit, may help inhibit struvite crystal growth [34]. Additional in vitro data suggest that Vitamin C may decrease the number, size, and growth rate of struvite crystals in the presence of pseudomonas [35]. Enzymatic stone dissolution has also been tested. In one study purine nucleoside phosphorylase could dissolve struvite minerals in vitro [36]. Unfortunately, none of these promising avenues of investigation are applicable yet to clinical practice.

Conclusion

Struvite stones are relatively rare but cause disproportionate morbidity and mortality. The pathophysiology of stone formation is well established. Surgical stone removal is a cornerstone of therapy. This is used along with antibiotics to eradicate bacterial infection and prevent recurrence or infectious complications. Some patients with struvite stones may also have concurrent metabolic abnormalities, and metabolic workup may be appropriate in selected cases. Medical therapy is focused on proper identification of a causative organism(s), appropriate antibiotic choice and administration to clear infection, and close follow-up.

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Chapter 12
Cystine Stones

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Keywords Cystine stone · cystinuria

Key Points

1. Cystine stones are caused by cystinuria, a rare hereditary disorder with autosomal inheritance. Cystine nephrolithiasis and related kidney diseases are usually the only clinically pertinent manifestation of this disorder.
2. Patients with cystinuria usually present with first kidney stone in their early teens although presentation may be as early as infancy or as late as the fifth decade.
3. Diagnosis is made by stone analysis and measurement of very high cystine levels in urine.
4. Cystine capacity, a new urine assay, is used as a measure of cystine saturation in urine and is helpful in guiding the ongoing management of cystine stones.
5. High urine volume, urine alkalization, and cystine-binding drugs are the three pillars of medical and nutritional management.
6. The two cystine-binding agents in clinical use are D-penicillamine and tiopronin, both of which have a high incidence of adverse reactions.
7. Frequent follow-up of patients is needed to ensure compliance with burdensome dietary recommendations, to re-assess the need for management adjustment based on urine studies, and to look for adverse effects of the medications.

Introduction/Physiology

Cystine stones, as the name suggests, are formed by high concentration of the amino acid cystine in the urine. It is due to a rare genetic disorder called cystinuria, which occurs due to a defective transport mechanism in the tubular lumen allowing for a large amount of cystine and other cationic amino acids (cystine, ornithine, arginine, lysine (COAL)) to appear in the urine.

After glomerular filtration cystine normally undergoes near complete reabsorption in proximal tubule via a cystine transporter, with a fractional excretion of about 0.4% [1]. This can increase to more than 100% in patients with cystinuria (suggestive of tubular secretion) [2]. These large amounts

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of unreabsorbed cystine in the urine crystallize at usual human urine pH of 5.5–7.0 and cause stone formation. The other three amino acids (see above) are also present in high quantities in urine but do not precipitate at normal urine pH and thus lack clinical significance.

The cystine transporter consists of a heavy subunit, rBAT encoded by *SLC3A1*, and a light subunit, bo,$^{+}$AT encoded by *SLC7A9*. The light subunit is the actual transporter, whereas the heavy subunit is responsible for trafficking of the light subunit to the apical membrane of the cells [3, 4]. In addition to renal proximal tubule, this transporter is also expressed in the intestine where its malfunction is compensated by peptide transporter 1 (PEPT1), which is not present in nephron tubular lumen. Thus cystine stones are the only clinically relevant feature of this disorder.

The normal excretion of cystine in urine, which is less than 30 mg/day, exceeds 400 mg/day in patients with cystinuria [5]. Patients with cystinuria usually present with first kidney stone in their early teens (median age of 12 years) although the age of presentation may be as early as infancy or as late as the fifth decade [6–8]. In fact, 80% of symptomatic patients experience their first stone episode by the end of the second decade [7]. Compared with other stone formers, patients with cystinuria tend to have stones earlier, more often, more bilateral, and more of the staghorn variant that require more urological interventions [8–10]. They also have a higher risk of chronic kidney disease (CKD) and lower quality of life compared with non-cystine stone formers [10–12]. The higher prevalence of CKD is, however, variable across different studies. In a 2002 study looking at the International Cystinuria Consortium (ICC) data, impairment of the renal function was noted in 17% of the patients [7]. In a 2015 study from France, whereas only 22.5% of the patients had glomerular filtration rate (GFR) > 90, 27% of the patients had GFR below 60, and in 0.6%, the GFR was below 15 [13]. In addition, cystinuria patients were almost five times more likely to have nephrectomy compared with patients with calcium oxalate stones; 14% vs. 3%, respectively [11].

In the past, cystinuria was classified phenotypically as type I–III or type I, and non-type I, based on the level of cystine excretion in parents, type I being the group where parents had normal cystine in urine and non-type I where parents had high cystine excretion. However, after identification of the genes behind cystinuria, it was found that this classification had poor correlation with the genotypes, and hence a genotypic classification has been adopted [7]. *SLC3A1* and *SLC7A9* are the two gene mutations which can be identified in the vast majority of patients. Patients with *SLC3A1* and *SLC7A9* mutations are called type A and type B, respectively. Rare patients with single mutated allele in both genes are called AB and usually have mild disease.

Prevalence, Inheritance

Cystinuria was first described in the 1800s [1] and was one of the disorders used by Sir Archibald Garrod in 1908 to illustrate the concept of inborn errors of metabolism [14]. The prevalence of cystinuria varies from 1/2500 in Libyan Jewish population to 1/100,000 in Swedish population [2]. The average prevalence is estimated to be about 1/7000 [15]. Nephrolithiasis and related complications are the only clinically significant manifestation of this disorder.

Up to 1% of adult stone formers and 5–10% of pediatric stone formers have cystinuria [13, 16]. A recent study also noted an increasing trend of cystine stones as a proportion of all stones in males [17]. About 6% of patients with cystinuria never present with urolithiasis [15].

Cystinuria has autosomal inheritance with *SLC3A1* or type A showing to be autosomal recessive and *SLC7A9* showing to be autosomal dominant with variable penetrance pattern [8]. Most patients are homozygotes of either of these gene mutations: 100% of homozygotes have high cystine excretion, and 94% of the homozygotes develop kidney stones in their lifetime [15]. Whereas heterozygotes of type A have normal urine cystine, heterozygotes of type B usually have higher than normal

levels of urine cysteine in 86–90% of cases and kidney stone formation in 2–18% of cases [8, 15]. There is no good correlation between the concentration of amino acids in the urine to stone event frequency [7, 18].

Although in a large cohort [19] type A accounted for about 45% of the patients with cystinuria and type B for about 53%, this proportion varies among different cohorts; type AB constitutes 1.2–4% of the cases [20]. Type A and type B homozygotes have similar clinical manifestation [7] although males seem to be affected more severely for as of yet unclear reasons [21]. So far, 160 and 116 different mutations have been reported in *SLC3A1* and *SLC7A9*, respectively [20].

Diagnosis

The diagnosis of cystinuria is essentially based on high urine cystine levels. It should especially be suspected in younger patients with high stone burden and high recurrence.

In the office, examination of urine sediment for cystine crystals and sodium nitroprusside test may be helpful. Under microscopy, cystine crystals are colorless, refractory, and hexagonal and are pathognomonic of the disease. But they are identified in only 25% of patients [5]. Sodium nitroprusside test can identify urine cystine concentration of more than 75 mg/L (urine turns purple) and may be used as a screening test with sensitivity of about 70–80% and specificity of approximately 83–95% [22, 23].

All patients with suspected cystinuria should undergo a 24-hour urine collection to assess cystine excretion along with other metabolic factors that affect crystallization and stone formation. Of these, urine pH and volume are the two most important factors. Considering a relatively fixed total cystine excretion per day, the concentration halves as the volume of urine doubles. The solubility of cystine is highly affected by the urine pH as cystine is much more soluble in alkaline urine. As a rule, at pH of 7, cystine is soluble at concentration of 250 mg/L. This doubles to 500 mg/L at pH 7.5 and goes up further at pH of 8 [2, 24].

It is hard to determine cystine supersaturation based on cystine concentration and pH alone given high inter-patient variability. Therefore, cystine capacity, a new solid phase assay, has been developed to determine urine's cystine saturation. In this assay, a known amount of solid phase cystine is added to urine. In supersaturated urine, cystine precipitates onto added crystals, thus the recovered solid phase after incubation will be more. A negative cystine capacity implies oversaturated urine and vice versa [25].

Cystine stones are less radio-opaque than oxalate, and X-ray may miss small stones. Computed tomography (CT) scan may help not only in identifying but also in managing small stones as it can differentiate "rough stones" from "smooth stones" based on the appearance and lower Hounsfield units in rough stones [1]; rough stones tend to be more fragile and amenable to lithotripsy. Renal ultrasound is a good noninvasive test to identify and monitor stone formation.

Genetic testing is not routinely performed as it does not affect the management or clinical course of the disease.

Management and Prevention

Cystinuria is a highly morbid disease given recurrent stone formation, requiring frequent procedures and pain management, and for increasing the risk of CKD development. If poorly managed, the risk of forming new stones is about 1/patient-year, requiring urological procedure every 3–4 years [24]. Although medical therapy is often met with poor compliance and fails to achieve the desired control, it certainly helps in reducing the number of stone events and procedures required [10, 24] by up to 78% and 52%, respectively [24].

Also, in patients with cystinuria the stone composition may be mixed [26]. Therefore, stone analysis (for composition) is an important part of medical evaluation and management of these patients.

The goal of medical management in cystinuria is to reduce the recurrence of stones and minimize the burden of urological procedures and chronic kidney disease. It is aimed at achieving low cystine concentration in urine and modifying the milieu to promote its solubility with a goal to achieve urine supersaturation of <1 or a positive cystine capacity.

High urine volume, urine alkalization, and cystine-binding drugs are the three pillars of medical and nutritional management.

Nutritional Management

(a) High fluid intake is the cornerstone of nutritional management. The goal is to bring the cystine concentration to below 250 mg/L. A fluid intake of at least 3–4 L is recommended. Emphasis should be given on staying well hydrated at night and drinking water before bed and in the middle of the night.
(b) Low protein (particularly of animal source) diet may help urine alkalization in addition to reducing cystine production by lowering the supply of its precursor methionine [27]. Children and adolescents require normal protein intake for their overall growth.
(c) Low sodium diet can help reduce cystine concentration in urine, the mechanism of which is not clear [28].
(d) Diet rich in fruits and vegetable is recommended as it may help with increasing the urine pH [29].

Medical Management

Urine Alkalization

Potassium citrate is the preferred choice to increase urine pH. Citrate may also reduce the risk of calcium phosphate stone formation associated with alkaline urine.

Sodium bicarbonate is another option but is less desirable due to its sodium load. Acetazolamide is used by some as the last resort, although it is poorly tolerated, has questionable efficacy, and may have adverse effect(s) on bone health due to metabolic acidosis.

High Urine Volume

This is achieved through high fluid intake, as discussed above. Tolvaptan has been proposed as an option in patients with low volume but comes with high expense, risk of liver disease, and unclear benefit [30, 31].

Cystine-Binding Thiol Drugs

Often patients are refractory to nutritional changes and urine alkalization and require cystine-binding thiol drugs (CBTDs). These drugs reduce the insoluble cystine to cysteine monomer and form complexes with it. This complex is about 50 times more soluble than cystine [1, 20], thus preventing crystallization and stone formation.

The two agents in clinical use are D-penicillamine and 2-meracptopropionylglycine (tiopronin). D-penicillamine and tiopronin are similar agents with tiopronin having the advantage of fewer side effects; drug withdrawal of 69% vs. 31%, respectively [32]. Studies have consistently shown reduction in stone size and dissolution of stones with D-penicillamine and tiopronin. Compared with conservative management, treatment with one of these two drugs decreased stone events by 32–65% [33]. In one study, they reduced new stone formation or enlargement of existing stones from 1.6 per year to 0.5 per year [34]. In another study with median daily dose of 900 mg D-penicillamine or 750 mg tiopronin, the mean decrease in free cystine excretion was 32% (35% and 29%, respectively) [24].

The dose of D-penicillamine in adults ranges from 0.5 to 2 g/day (20–40 mg/kg per day in children) in 3–4 divided doses. Tiopronin initial dose is 250 mg/day, gradually increasing to 400–1200 mg/day in 3–4 divided doses with maximum dose of 2 g/day (10–15 mg/kg per day) [20].

Both agents have a high incidence of adverse reactions that limit their tolerability although the incidence is lower for tiopronin [1]. They include abnormal taste, fever, arthralgia, skin rash, leukopenia, and proteinuria among others [35]. In fact, D-penicillamine is known to cause proteinuria and nephrotic syndrome mainly due to membranous nephropathy and minimal change disease although other lesions including crescentic glomerulonephritis have been reported [36–39]. D-penicillamine causes vitamin B6 (pyridoxine) deficiency and requires supplementation of 50 mg/day of vitamin B6 [20]. Most adverse effects are dose-dependent and more common during the first year of therapy, hence the recommendation for gradual dose escalation. Of note, autoimmune and hypersensitivity-related side effects are not dose dependent and typically occur in patients with other autoimmune disorders [1].

Captopril is also a potential CBTD. Captopril has good cystine binding *in-vitro*, but it is of little clinical value given its low urinary concentration [25]. Multiple studies have produced contradictory results on its ability to improve cystine concentration in urine even at high doses of 75–150 mg/day [40, 41]. However, it may be utilized as a preferred anti-hypertensive agent.

Although pH does not appear to affect the maximum effect of CBTDs, it has been shown that it does affect the time by which they reach the maximum effect; the higher the pH, the faster the effect. This higher rate of action at higher pH is attributed to higher deprotonated (active) form of the drug. This may have clinical implications given that urine transition time through renal pelvis may be short and only a few minutes. Therefore, it is very important to remember that the effects of CBTDs and high urine pH are complimentary, and one should not be considered as a substitute for the other [42, 43].

Follow-Up

Compliance with strict nutritional, medical, and follow-up requirements is difficult, and studies have shown poor compliance with subsequent treatment failure [44, 45].

Frequent follow-up of patients is recommended to insure compliance with burdensome dietary recommendations, to re-assess the need for management change based on urine studies, and to look for adverse effects of the medications. A patient with severe disease should be followed up every 3 months with radiological studies [20]. Patient with mild disease and minimal or no stone activity can be followed every 6 months. A 24-hour urine analysis should be done at least annually and preferably more frequently. Isolated overnight collection may be necessary in refractory cases [46].

Management in specialty clinic may help reduce recurrence and the need for urological procedures [47].

Cystine stones do not occur post-transplant as the graft kidney does not have the genetic defect [48].

Genetic testing of siblings is not done routinely but may be helpful if they have not been diagnosed with cystinuria. Genetic counseling of siblings and spouse may be beneficial.

Future Direction

Structural mimics of cystine (cystine dimethyl ester (CDME) and cystine methyl ester (CME)) are being studied for their potential to inhibit cystine crystallization and crystal growth by steric inhibition [49]. In one study, *SLC3A1* knockout mice treated with CDME demonstrated smaller but more bladder stones [50].

SCL3A1 and *SCL7A9* knock out mice and a proximal tubular cell line derived from normal human kidney mimicking cystinuria phenotype have been developed allowing for further investigation [1].

Atomic force microscopy is a new technique to study crystal growth and is being used to identify molecules which may inhibit crystal growth [51].

Formation of Rare Kidney Stone Consortium, which studies primary hyperoxaluria, cystinuria, adenine phosphoribosyl transferase (APRT) deficiency, and Dent disease, and the establishment of an International Cystinuria Registry may help in further understanding of the disease and to facilitate clinical trials [43].

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Chapter 13
Medical Management of Unknown Stone Types

Eric S. Kerns, Kenneth Ralto, and Adam M. Segal

Keywords Unknown stone composition · Diagnostic tests · Calcium oxalate · Calcium phosphate Uric acid

Key Points
- The majority of patients with a new kidney stone will have a calcium-based stone.
- Most patients with uric acid stones do not have a concurrent diagnosis of gout.
- A 24-hour urine collection can help guide therapy and should be considered in the evaluation of a patient with kidney stones.
- Initial laboratory testing should include a serum calcium, and if this is elevated or in high-normal range, a parathyroid hormone level should be checked to assess for hyperparathyroidism.
- When the stone type is not known, dietary recommendations should include increasing fluid intake to target a urine volume of at least 2 liters/ day and limiting dietary sodium, animal protein, and oxalate intake.

Introduction

Management of the patient with kidney stones of unknown composition is a common scenario in the clinic. Despite the use of urine strainers, many patients are unable to collect a specimen and on occasion, surgically removed stones are not sent for analysis. Moreover, patients may have stones that are incidentally diagnosed on abdominal imaging that was obtained for other purposes. This chapter will discuss the management of patients with nephrolithiasis in whom the type of stone has not yet been determined.

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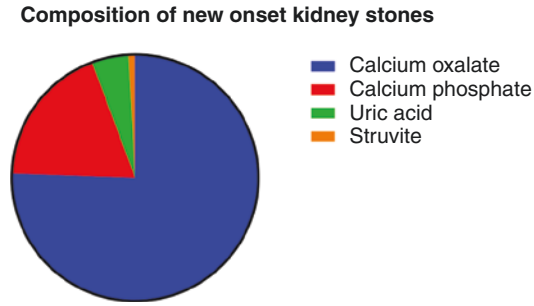

Fig. 13.1 Composition of new onset kidney stones. The majority (94%) of newly-diagnosed kidney stones in the Unites States are calcium-based, with 76% calcium oxalate and 18.9% calcium phosphate. Uric acid and struvite stones make up a minority of first-time stones. (Data adapted from Singh et al. [1])

Diagnostic Considerations

Epidemiologic data from the United States suggest that the vast majority of patients with new onset nephrolithiasis will have calcium-based stones, with calcium oxalate being the most common finding [1] (Fig. 13.1). Certain comorbidities raise the likelihood of calcium-based stones. These include gastrointestinal malabsorptive disorders such as pancreatic exocrine insufficiency, inflammatory bowel disease, or Roux-en-Y gastric bypass surgery, all of which predispose to hyperoxaluria and the formation of calcium oxalate stones. Hyperparathyroidism should heighten suspicion for calcium-based stones, both calcium oxalate and calcium phosphate, as should other systemic diseases that alter calcium metabolism, such as vitamin D excess and sarcoidosis [2]. A diagnosis of medullary sponge kidney is a risk factor for calcium-based stones, which should also be considered in young women with new onset nephrolithiasis. Distal renal tubular acidosis, which is associated with autoimmune diseases like Sjögren syndrome or medications like acetazolamide, predisposes to calcium phosphate stone formation via hypercalciuria, low urine citrate, and high urine pH [2].

Persistently acidic urine (pH less than 5.5) promotes the precipitation of uric acid crystals, whereas urate solubility increases at a pH greater than 6.5. Chronic diarrhea results in the formation of concentrated and acidic urine due to gastrointestinal losses of water and bicarbonate. While a patient with gout is more likely to have uric acid stones than someone without gout, it should be noted that most patients who form uric acid stones do not have a concurrent diagnosis of gout [3].

Struvite stones are among the least common types of stones and typically occur in patients with upper urinary tract infections caused by the bacterial species *Proteus* or *Klebsiella*. These urease-producing organisms cause an alkaline urinary pH, typically greater than 8. Patients with evidence of staghorn calculi on imaging should be suspected of having struvite stones. Cystine stones are also uncommon and typically present in childhood with characteristic hexagonal crystalluria.

Diagnostic Evaluation

There is ongoing debate as to the cost-effectiveness of obtaining a full metabolic evaluation for patients after the first stone passage. The tests can be particularly useful for patients in whom the stone type is unknown, as they often provide clues as to which type of stones a patient is at risk for forming, findings which can then guide therapy. The following section will describe the diagnostic approach when the decision is made to pursue a full metabolic evaluation.

As with all cases of nephrolithiasis, one of the most important aspects in the initial work-up is a thorough medical and dietary history. The medical history should focus on risk factors mentioned above, including gastrointestinal disorders, gout, age at onset of nephrolithiasis and family history. A thorough dietary history should include the average daily volume of fluid, sodium, calcium, animal protein, and oxalate-rich foods. A thorough supplement history should also be obtained with attention to calcium and vitamin D supplements.

Obtaining a stone or stone fragment is another important step in the diagnostic evaluation. This is typically accomplished by having the patient strain the urine through a commercially available mesh strainer. Alternatively, if the patient has a large ureteral stone that requires urologic intervention, a sample can often be obtained during the procedure.

The appearance of nephrolithiasis on imaging may be useful in distinguishing among types of stones. In contrast to calcium-based stones, uric acid calculi are radiolucent on plain radiographs but visible on ultrasound and computed tomography (CT). Using CT, stone measurement in Hounsfield units (HU) can further help to differentiate among stone types. In one study, calcium oxalate stones were found to have a higher Hounsfield measurement (approximately 650 HU) when compared to uric acid stones (approximately 350 HU) [4]. Additionally, the presence of staghorn calculi on CT suggests struvite stones, whereas nephrocalcinosis supports a diagnosis of calcium phosphate stones.

Initial laboratory testing includes a basic metabolic profile to assess electrolytes, including calcium, as well as blood urea nitrogen and creatinine to assess kidney function. If the serum calcium level is elevated or in the high end of the normal range, intact parathyroid hormone should be measured to assess for primary hyperparathyroidism. Measuring uric acid level is also helpful, especially in a patient with a history gout or risk factors for this disease. Depending on the initial laboratory results and clinical history, additional testing for causes of hypercalcemia and/or renal tubular acidosis should be pursued (Table 13.1).

A 24-hour urine collection often provides useful information in patients with unknown stone composition as there may be significant abnormalities which predispose to a particular type of stone. Typically, two 24-hour samples are collected at baseline because diet is variable from day-to-day and a single collection may not be representative. It is recommended to wait a few weeks after passage of a stone to collect the 24-hour sample. While many patients may have abnormalities of calcium, oxalate, uric acid or citrate urinary excretion without nephrolithiasis, identification of specific abnormalities can provide a starting point for management. The measured urine supersaturation of calcium oxalate, calcium phosphate, and uric acid have also been shown to correlate well with stone composition [5].

The urinalysis and microscopic examination of urine sediment are other valuable diagnostic tools in the work-up of a patient with unknown stone composition. Polarized light can identify a variety of crystals suggestive of a specific type of stone, including calcium oxalate, calcium phosphate, uric acid, cystine, or drug crystals. A persistently acidic urine pH favors the formation of uric acid or calcium oxalate stones whereas an alkaline urine pH supports the precipitation of calcium phosphate. Evidence of a urinary tract infection with leukocyturia and bacteriuria in combination with an alkaline urine pH raises the possibility of struvite stones from infection with a urease-producing organism such as *Proteus* or *Klebsiella* species.

Dietary Management

Dietary interventions should target the most likely etiology for kidney stone formation after completing the above work-up. The specific changes for each stone type are discussed in detail in the preceding chapters. Increasing fluid intake to achieve a urine volume of at least 2 liters/day is effective for

Table 13.1 Blood, urine, and imaging tests useful in the evaluation of new-onset nephrolithiasis

Specimen or imaging modality	Test	Significance of findings, advantages, and disadvantages
Blood	Electrolytes	Abnormalities may suggest malabsorptive gastrointestinal disease (low serum bicarbonate) and/or distal renal tubular acidosis (hypokalemia), which favor calcium stone formation
	BUN and creatinine	Assess renal function
	Calcium	Diagnose disorders of calcium metabolism, such as primary hyperparathyroidism, sarcoidosis, or malignancy
	Phosphorus	Hyperphosphatemia suggests primary hyperparathyroidism
	Uric acid	Hyperuricemia supports a diagnosis of uric acid nephrolithiasis
	Intact PTH	Primary hyperparathyroidism leads to hypercalciuria and calcium stone formation
	1,25OH-D and 25OH-D levels	Hypervitaminosis D causes hypercalciuria
	TSH, ACE level, PTHrP, SPEP/UPEP	Additional testing, as indicated, in hypercalcemia
Urine (spot sample)	Urine pH	Acidic urine (pH < 5.5) favors uric acid or calcium oxalate stone formation, whereas alkaline urine (pH > 7.0) favors calcium phosphate or struvite stones
	Urinalysis	Identification of leukocyturia or bacteriuria suggests struvite stones
	Urine sediment microscopy	Light microscopy and polarized light allow for identification of specific urine crystals (hexagonal = cystine; coffin-shaped = struvite; pyramid or dumbbell shaped = calcium oxalate; rectangular or rhomboidal = uric acid)
Urine (24-hour collection)	Volume	Less than 2 liters/day increases risk for stone formation
	Calcium	Greater than 200–250 mg/day (women) and 250–300 mg/day (men) increases risk for stone formation
	Oxalate	Greater than 40–45 mg/day increases risk of stone formation
	Uric acid	Greater than 750 mg/day increases risk of stone formation
	Citrate	Less than 450 mg/day (men) and 550 mg/day (women) increases risk of stone formation
	Sodium	Low sodium diet (<2400 mg/day) reduces risk of stone formation
	Creatinine, urea nitrogen, potassium, phosphorus, sulfate, magnesium	Assess completeness of urine collection, adherence to medications and diet, and protein intake
Imaging	Plain radiograph (KUB)	Determines whether stones are radio-opaque and can be used to monitor disease activity; may miss a stone in the ureter or kidney and provides no information on obstruction
	Renal ultrasound	Avoids radiation and provides images of the kidney and proximal ureter, though ureteral stones and stones <3 mm diameter may be missed
	Helical computed tomography (HCT) of the abdomen and pelvis	Offers the highest sensitivity and specificity for diagnosing stones

reducing the recurrence of all types of stones as this will dilute the offending salts and reduce the risk for precipitation. Generic dietary advice for all patients with stones of unknown composition is to reduce sodium (to less than 2000 mg per day), limit oxalate-rich foods, limit animal protein, increase fruit and vegetables, and reduce sugar. Notably, high dietary calcium intake does not appear to be a risk factor for calcium-based stone formation. In contrast, higher dietary calcium intake is correlated with a *reduced* risk of forming kidney stones [6], and the combination of normal calcium intake with

reduced animal protein and salt confers a decreased risk of recurrent calcium oxalate nephrolithiasis compared to a low-calcium diet [7]. There is conflicting data on whether calcium supplements are a risk factor for calcium stones, and the risk of calcium oxalate stones may in fact be lower when calcium pills are taken with meals rather than on an empty stomach [8].

Medical Management

Medical management of the unknown stone can be challenging, but there are basic strategies which can reduce the risk. As discussed above, an attempt should be made to collect a stone or stone fragment for laboratory identification in order to tailor therapy. When a specific type of stone has not been identified and there are no obvious risk factors for the formation of a particular stone type, therapy should focus on treating abnormalities identified in the metabolic evaluation (Fig. 13.2). It should also be noted that the upper limits of normal for 24-hour urine findings are somewhat arbitrary, and values in the "normal" range do not rule out a particular stone type. This was highlighted by research showing that there is an incremental increase in the risk for kidney stone formation with increasing degrees of urinary calcium excretion or a decreasing degree of urinary citrate excretion, even when the values are within the "normal" range [9, 10].

The upper limit of normal for 24-hour urine calcium excretion is commonly defined as 250 mg in men and 200 mg in women. As mentioned above, these ranges are not absolute and patients with values in the "normal" range may still benefit from therapies to reduce calcium excretion. The most common strategy is the use of a thiazide diuretic, particularly a long-acting thiazide such as chlorthalidone which can be started at a dose of 12.5–25 mg per day. Many patients will require uptitration to 50 or 100 mg per day to achieve adequate reductions in calcium excretion [11]. Follow-up examination should occur 4–6 weeks after initiation of therapy with the goal to measure blood pressure, assess serum chemistries for hypokalemia or hyponatremia, and repeat 24 urine studies to monitor for efficacy in reducing calcium excretion.

Elevated urinary oxalate excretion (defined as greater than 40–45 mg per day) increases the risk for calcium oxalate stone formation. Dietary approaches for reducing oxalate excretion have been discussed previously. High doses of vitamin C supplements can increase urinary oxalate and should be

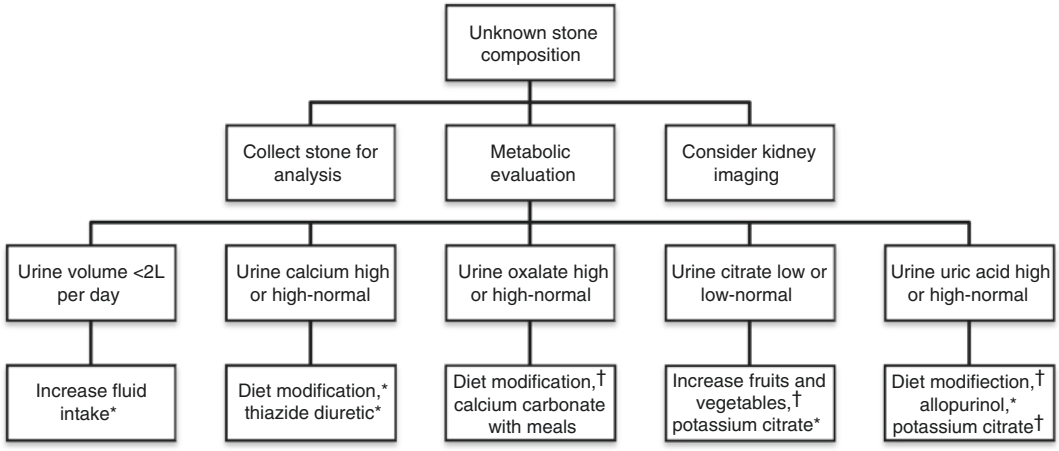

Fig. 13.2 The diagnostic, dietary and medical approach to treating patients with kidney stones of unknown composition (*AUA Guidelines* 2014; 192: 316–324). (*Evidence Strength: Grade B, †Evidence Strength: Expert Opinion)

discontinued if possible. If dietary changes alone are insufficient, then calcium carbonate supplementation with meals can be used to increase binding of dietary oxalate in the gastrointestinal tract, reducing systemic absorption and urinary excretion [8].

A low or low-normal urinary citrate on 24-hour urine collection also increases the risk for calcium-based stone formation. Daily excretion of less than 450 mg in men or 550 mg in women increases the risk for stone formation; however, patients with values only marginally above this cutoff may also benefit from citrate supplementation. Potassium citrate administered at doses of 10–20 mEq three times per day can effectively raise urinary citrate to chelate calcium. One potential downside to this therapy in the patient with unknown stone composition is that the urine alkalinization that occurs when citrate is converted to bicarbonate can in theory increase the risk for calcium phosphate precipitation and stone formation. In patients with calcium phosphate stones, it is not clear whether the benefit from calcium chelation outweighs the risk of urinary alkalinization, though potassium citrate therapy should still be offered to calcium phosphate stone formers with hypocitraturia (*Evidence Strength = Grade B*) [12].

Urinary uric acid excretion of greater than 750–800 mg per day, particularly in patients with acidic urine, increases the risk for both uric acid and calcium oxalate stones. The initial approach in this situation is dietary modification to reduce uric acid production. If uric acid excretion remains elevated despite these efforts, allopurinol (100–300 mg per day) can be prescribed to reduce the production of uric acid. This may be of particular benefit for patients with concurrent gout who will also benefit from lowering of serum uric acid levels. In theory, urinary alkalization with potassium citrate may also be beneficial, as this will facilitate dissolution of urate crystals [11].

Follow-Up and Monitoring

After making a dietary modification or starting a new medication, it is essential to monitor whether there is improvement in the desired urinary parameter. A repeat 24-hour urine collection should be performed approximately 6 months after changes to therapy. Upon reaching a satisfactory change in the urine results, repeating a 24-hour urine collection annually is recommended for ongoing surveillance. Additionally, annual imaging should be obtained to assess the stone burden and monitor for new stone formation (*Expert Opinion*) [12]. Ideally, this is done with plain radiograph renal ultrasonography to limit exposure to ionizing radiation, but only if the stones are visible with this modality. Otherwise, periodic imaging with low dose computed tomography of the pelvis can be considered for surveillance. If the patient continues to experience the formation of new stones, efforts should be increased to send a stone sample for analysis and tighten control of the aforementioned risk factors.

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Chapter 14
Nutritional Management of Unknown Types of Stones

Diana El Jundi and Zeina Younes

Keywords Nephrolithiasis · Nonobstructive · Urolithiasis · Unknown kidney stones · 24-hour urine Calcium oxalate

Abbreviations

BMI	Body mass index
CT	Computed tomography
DASH	Dietary Approaches to Stop Hypertension
US	Ultrasound

Definition and Prevalence

Unknown Types of Stones

Unknown stones are stones that are known to be present but not analyzed in the laboratory either because they were not collected, they were not sent to the lab, or they remain in the urinary collecting system. Often stones are incidentally found on imaging. Those can also be referred to as nonobstructive as they did not block urinary flow. These stones may however start moving at some point and become obstructive.

Renal colic is typical of stone passage and usually begins as a feeling of discomfort, which reaches a plateau 30–60 minutes later. Stones that obstruct the utero-pelvic junction lead to dysuria and urinary frequency. Colic is evident regardless of the position or motion of the body and is typically associated with nausea and vomiting, malaise, fever, and occasionally chills [1, 2]. Stones that measure <5 mm in diameter have been shown to have a high chance of passage, whereas larger stones pose a greater risk of obstruction [3]. Majority of large stones (>5 mm) need stone removal procedures such as shock wave lithotripsy (SWL) or extracorporeal shock wave lithotripsy (ESWL) [4]. Many patients who had stone removal procedures know the type of stones because the removed stones are sent to the lab to be analyzed but this is not always the case.

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While most of the nonobstructive stones occur in the kidney, some smaller stones in the ureter may also cause minimal, if no obstruction at all, with smaller stones being reported to pass spontaneously in 90% of patients [2, 5]. Due to this, patients may sometimes pass kidney stones without their knowledge or without experiencing pain, making it challenging to identify the type of stone that they had [6]. It is good medical practice to provide patients with strainers to try to collect a kidney stone if they have symptoms of stone passage or have recently undergone lithotripsy or another urologic procedure that might result in stone passage out of the body.

Diagnosis

Prevalence of kidney stones has increased worldwide [5]. Lifestyle factors, including both diet and obesity have been reported to be responsible for this increase in prevalence in all stone types [7]. Calcium-containing stones make up the majority of kidney stones followed by uric acid. Together they account for about 80–90% of kidney stones. Unless there are factors to suspect struvite stones (staghorn calculi or urinary infection) or cysteine stones, a reasonable assumption is that the stone is either calcium or uric acid containing.

A complete medical and physical examination is performed during the initial evaluation of patients. Symptoms of acute renal colic present with intermittent colicky flank pain, which could span to the lower abdomen or groin, and is usually associated with nausea and vomiting. Once the stone has entered the ureter, lower urinary tract symptoms such as dysuria, urgency, and frequency begin to occur [8].

Diseases that may increase the risk of kidney stone formation or that may affect the clinical course of the disease must be identified.

A personal or family history of kidney stones that have been previously treated and analyzed, as well as any anatomical abnormalities or surgeries of the urinary tract should be obtained. Some disorders can lead to clues to the type of stones that the patient may have. Patients with malabsorptive disorders such as inflammatory bowel disease, celiac disease, and chronic diarrhea with Roux-en-Y surgeries more likely have calcium oxalate stones. Medications can also contribute to kidney stones through the formation of urine crystals and by changing the characteristics of urine [2]. As such, medication history and any current medications that are known to increase the risk of kidney stones should be noted (please refer to table in Chap. 4) [8].

Imaging methods to diagnose kidney stones now include non-contrast computed tomography (CT) and ultrasonography (US). The gold standard for initial imaging in patients where nephrolithiasis is suspected is non-contrast CT. This is because ultrasonography displays lower sensitivity and higher user dependence [5]. Ultrasound can be useful in follow-up of resolution of urinary obstruction and to avoid further exposure to cumulative radiation from repeated CT scans. It is not recommended to use ultrasonography because small stones sized <5 mm and more distal stones are likely to be missed with ultrasonography [5]. Most kidney stones are visible through computed tomography, with the exception of stones that are induced by certain drugs (e.g., Indinavir) [8]. Ultrasound analysis may be reasonable for serial monitoring or if there are contraindications to CT scanning.

Kidney Stone: Assessment

A comprehensive metabolic evaluation including a basic metabolic panel, serum calcium, phosphorus, parathyroid hormone level, vitamin D, uric acid, and 24-hour urine composition is recommended for stone formers [9].

The rationale behind a kidney stone risk panel is to:

- Evaluate the risk of kidney stone development
- Determine underlying reason for kidney stone formation
- Aid in monitoring and treatment

Past Medical and Social History

Patient's past medical history is obtained, as stones may be associated with a variety of medical conditions (Table 14.1). In addition, a number of current as well as past medications or supplements taken by the patient can aid in the differential diagnosis of stones, as certain medications and supplements can increase the risk of kidney stone recurrence. Patient's family and social history are also of significance, as certain work environments (those working in construction, schools, etc.) do not allow for frequent hydration and toilet use resulting in a decreased output of urine and placing patients at risk for stone formation. The same applies for patients residing in hot climates, which places them at risk for lower urine volumes [10].

Diet History

A detailed history of the patient's diet is essential to understand the possible risk factors for stone formation, through which dietary modifications, aimed at preventing recurrent stone formation, can be prescribed [10].

Dietary Risk Factors for Kidney Stones

Changes in urine composition can play a role in the incidence of nephrolithiasis since kidney stone formation is dependent on urine's physiochemical properties [5]. As a result, other than medications, dietary habits should be evaluated when evaluating kidney stone formation.

Table 14.1 Medical disorders associated with kidney stones [8]

	Medical disorders	Associated stones
Systemic illness	Primary hyperparathyroidism	Caox and CaP stones
	Renal tubular acidosis	CaP stones
	Cystinuria	Cystine stone
	Gout	Uric acid stones
	Diabetes mellitus	Uric acids and CaOx stones
	Inflammatory bowel disease	Predominantly CaOx
	Sarcoidosis	CaP and CaOx
	Medullary sponge kidney	Nephrocalcinosis
Anatomical features	Presence of horseshoe kidney	CaOx and CaP stones
	Obstruction of the ureteropelvic junction	CaP and struvite stones
	Previous renal or ureteral surgery	Staghorn stones and struvite stones
Previous kidney and urinary track disease	History of urinary tract infection or pyelonephritis or both	Staghorn, struvite, and CaP stones
	Family history of urolithiasis	CaOx

CaOx calcium oxalate, *CaP* calcium phosphate

Body Weight and Caloric Intake

Obesity is a pro-inflammatory state that is correlated with imbalances in electrolytes and an altered urine chemistry [2]. A higher body mass index (BMI) is linked with a lower urine pH and a higher uric acid stone prevalence. It is also associated with a higher urine oxalate excretion, leading to an increased risk of calcium oxalate stone formation [11]. With obesity, the changes in body composition pose biophysical challenges that are associated with a disturbance in thermogenesis as well as dehydration [2]. As a result, weight loss can serve to reduce the risk of stone formation of any type if done correctly. The opposite holds true if weight loss is associated with a high animal diet, laxative abuse, the rapid loss of lean tissue, and/or hydration [2, 8].

High Salt Diet

High sodium intake (>4000 mg/day), as opposed to lower sodium diets (<2000 mg/day), has been shown to result in excessive excretion of calcium. Due to their high sodium content, processed and packaged foods should be limited [10, 11].

Protein

High animal protein intake is associated with a higher risk of kidney stones as opposed to vegetable protein. The latter has a smaller effect on calcium, uric acid, and citrate excretion as a result of their lower sulfur content, leading them to generate less acid [12]. Animal protein may lead to hypercalciuria, hyperoxaluria, and hyperuricosuria, which all increase the risk of calcium kidney stone formation. Moreover, protein increases net acid excretion and contributes to the low urine pH seen in uric acid stone formers. All diets that are rich in animal protein should be limited in patients with kidney disease [10].

Fructose and Sucrose

Fructose-rich foods and beverages (especially high fructose corn syrup) have been found to be associated with increased risk of stones [10–12]. Sucrose has been shown to increase risk of kidney stone as its intake increases urine calcium, independent of dietary calcium intake [13].

Citrate

Citrus fruits (lemon orange and lime) increase citrate excretion which alkalinizes the urine and decreases uric acid stone risk. Citrate can also bind to calcium in the urine, which lowers the crystallization of calcium oxalate [12]. Some caution should be considered with citrate administration if there is suspicion for calcium phosphate stones which form in an alkali urine.

Calcium

A low dietary calcium intake has been described with a higher risk of stones, possibly due to its effect on allowing more dietary oxalate absorption by the intestine [10]. According to recent literature, it is no longer recommended that dietary calcium be restricted for hypercalciuria due to the lack of evidence that lowering calcium intake will prevent stones and concern for the risk of bone demineralization especially in patients who are at risk for bone loss. Also lack of calcium in gastrointestinal (GI) track will cause more oxalate absorption; therefore adequate amount of dietary calcium intake of 1000–1200 mg/day will lower the risk of calcium oxalate stone [12]. On the other hand, calcium supplementation has not been shown to be effective in preventing recurrent stones and may slightly increase the risk of stone formation among older women [13].

Oxalate

Dietary sources of oxalates should be limited, and this is especially true for bariatric surgery patients due to their effect on increasing urinary levels of oxalate [14]. Examples of oxalate-rich foods include spinach, rhubarb, potatoes, as well as peanuts, cashews, and almonds. It is recommended that foods high in oxalate be avoided among all calcium oxalate stone formers irrespective of urine oxalate because there may be a period of high urinary oxalate excretion shortly after the food is consumed [13]. One should be cautious though when following an overly restrictive low oxalate diet as it consequently leads to lower intake of fruits and vegetables. Consumption of dairy products at the same time with high oxalate foods may help lower oxalate absorption.

Vitamin C

Vitamin C supplements have been shown to increase oxaluria, and in turn increasing the risk of stone formation especially calcium oxalate stone in men but not women. As a result, it is recommended that vitamin C supplements be limited to less than 1000 mg/day [14].

Fluids

Hydration is crucial for management of kidney stone patients. Fluid intake, mostly water, is indicated for patients with all kinds of stones if their urine specific gravity is greater than 1.015 [2]. Lower intake of fluids leads to lower urinary output, promoting stone formation by increasing supersaturation of lithogenic factors such as calcium, oxalate, phosphate, and uric acids [13]. People living in hot climates are at a risk of kidney stone formation due to low fluid intake that leads to high concentration of lithogenic substances in the urine [5].

The type of fluid consumed is also important despite conflicting reports on their effect on urine composition and stone risk.

Caffeinated Beverages

Caffeinated and decaffeinated coffee or tea has been associated with a reduced risk of stone formation, and alcohol (specifically beer) has been considered protective against stone prevalence. This could be related to alcohol's inhibition of antidiuretic hormone secretion, leading to a decrease in the concentration of urine. Colas have been linked to a greater stone risk due to their effect on acidifying the urine [12].

Cranberry Juice

When ingested in large amounts (1 L/day), cranberry juice has been found to increase the urinary excretion of oxalate but not necessarily the increased risk of kidney stone formation [12].

Sugar-Sweetened Beverages

Observational studies have found a positive association between sugar-sweetened beverages and stone formation. Patients are advised on avoiding sugar-containing beverages such as sweetened sodas [12].

Laboratory Evaluation

An assessment of the patient's blood and urine is an essential component of the evaluation. Serum levels of phosphorus, calcium, parathyroid hormone, vitamin D, magnesium, and uric acid should be measured to determine the risk factors of stone formation. A urinalysis assessing specific gravity, urine pH, presence of protein, blood cells, and/or bacteria can help in the differential diagnosis of the causes of kidney disease and stone risks [15]. Concurrent blood and urine tests provide correlation of patient's dietary and other stone risk factors.

24-Hour Urinalysis

The rationale for obtaining 24-hour urine samples is to analyze patients' specific urine composition in order to identify the risk factors for stone recurrence as well as to make recommendations for recurrence prevention [10].

The standard urinary parameters that are tested include sodium, calcium, citrate, creatinine, uric acid, oxalate, potassium, phosphorus, magnesium, sulfate, pH, urea nitrogen, urine volume, super saturation calcium oxalate, calcium phosphate, and uric acid concentrations [9, 15]. For the first evaluation of recurrent stone formers, one or two 24-hour urine collections are recommended. The urinalysis will guide dietary and medical treatments. For follow-up, one 24-hour urinalysis is acceptable on a regular basis. It is recommended to follow 3–6 months after the prescribed treatment [15].

Nutritional Treatment and Prevention of Kidney Stones

Diet plays a fundamental role in kidney stone formation. The two most common dietary deviations that have been found to increase the risk of nephrolithiasis are a high salt and high protein diet [16].

Diet prescription for kidney stones is dependent on the type of kidney stone at hand [2, 8]. However, when the type of kidney stone is unknown, the following recommendations can be prescribed to patients:

Fluids

To prevent the recurrence of kidney stones, the urinary balance between crystal forming and crystal inhibiting substances needs to be improved [17]. The basis for kidney stone management focuses on an increase in urine volume.

The recommended fluid prescription for patients is 3 L/day to produce at least 2.5 L of urine [10, 18]. Moreover, as mentioned in the diet history section, the type of fluid intake is very important. Lemon juice in water is high in citrate which inhibits calcium oxalate crystallization and increases urinary pH that in turn prevent uric acid stone formation [14]. However, high urine pH can increase risk of calcium phosphate stone formation. Caution should be advised in this, when the stone is unknown and calcium phosphate stones are considered likely.

Protein

A high protein diet (>2.0 g/kg/day) can lead to a reduction in the pH of the urine and can increase hypercalciuria and uric acid levels, leading to a greater risk of uric acid kidney stones. As such, it is recommended to follow a low-to-moderate protein diet, which translates to 0.8–1.4 g/kg/day [19]. Moreover, if the patient is at a high risk for uric acid stone formation, it is recommended to limit animal protein, and to focus on plant sources of protein.

Sodium

Sodium recommendation can be varied between 2000 and 2300 mg per day. Patients with hypertension would benefit from lower sodium diet, <2000 mg per/day, but healthy individuals with stone can consume 2000–2300 mg per day [18].

Calcium

Adequate amount of calcium intake of 1000–1200 mg per day is advised and that equals 2–4 servings of dairy products. However, calcium supplements are not recommended. Patients who have malabsorption problems, lactose intolerance, or history of gastric bypass surgery can take calcium supplement with close monitoring [18].

Weight Loss

For patients with a body mass index (BMI) >25 kg/m^2, healthy weight loss is recommended as part of kidney stone management [2]. Rapid weight loss, such as that resulting from bariatric surgery might actually increase stone risk. In their systematic review and meta-analysis, Thongprayoon et al. [20]

Table 14.2 Dietary recommendations to prevent kidney stones [18, 19]

Nutrients	Recommendation
Ca	1000–1200 mg/day
Oxalate	40–50 mg/day
Na	2000–3000 mg/day
Protein	0.8–1.4 g/kg/day
Fluid	3 L/day
Vitamin D	Low dose (if vitamin D insufficiency or deficiency, 1000–2000 IU/day)
Vitamin C	Dietary reference intake

found risk of kidney stone formation to differ depending on the procedure performed. Malabsorptive procedures such as Roux-en-Y gastric bypass, as compared to restrictive procedures have been shown to lead to an increased risk [20].

High protein/low carbohydrate weight loss diet is not appropriate for stone formers because high animal protein intake can lead acidic urine, and high uric acid production; therefore it can increase stone risk [19].

The Dietary Approaches to Stop Hypertension (DASH) diet is associated with a lower risk of kidney stones due to the following [10]:

- It is high in fruits and vegetables that contain citrate.
- It is moderate in low fat dairy.
- It is low in animal protein.
- It contains sources of oxalate (nuts, legumes, and whole grains).
- It is low in sodium, sweetened beverages, and red and processed meat.

Although DASH diet may be high in oxalate, adequate amount of dietary calcium with meals will help lower stone risk by reducing oxalate absorption from the gastrointestinal track.

Table 14.2 has summary of dietary recommendation to prevent kidney stones.

Summary and Recommendations

- Kidney stones are unknown if passed spontaneously or uncollected for analysis. Ongoing efforts should continue to collect a stone for chemical analysis.
- Nutritional recommendations for unknown type of stones are based on blood and 24-hour urinalysis.
- Risk factors for most kidney stone formation include a high BMI, high salt diet, fructose-rich beverages, low calcium intake, high dose vitamin C supplement use, and high protein diet.
- Fluid intake of 3 L/day is essential for kidney stone prevention and recurrence.
- Adequate amount of dietary calcium intake (1000–1200 mg/day, 3–4 servings of dairy products) is recommended to prevent Ca-based stones.
- Total protein of 0.8–1.4 g/kg/day with limiting animal protein.
- Weight loss when the BMI is >25. High protein low carbohydrate weight loss diet however is not recommended for stone patients.

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Part V
Special Consideration

Chapter 15
Bariatric Surgery and Stone Risk

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Keywords Bariatric surgery · Kidney stones · Urolithiasis · Roux-en-Y gastric bypass · Sleeve gastrectomy · Laparoscopic adjustable gastric banding

Abbreviations

BMI	Body mass index
BPD/DS	Biliopancreatic diversion with duodenal switch
CaOx	Calcium oxalate GI Gastrointestinal
LAGB	Laparoscopic adjustable gastric banding
PCC	Potassium citrate and calcium citrate
RYGB	Laparoscopic Roux-en-Y gastric bypass
SG	Laparoscopic sleeve gastrectomy
SS	Supersaturation

Key Points

- Obesity is a complex disease that affects over one-third of the US adult population. It is linked to a variety of health conditions including diabetes, hypertension, sleep apnea, and a number of cancers including kidney.
- Bariatric surgery is the most effective treatment option for obesity. The four main procedures performed in the United States are the adjustable gastric band, Roux-en-Y gastric bypass, vertical sleeve gastrectomy, and the biliopancreatic diversion with duodenal switch.

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- The risk of kidney stone formation increases after bariatric surgery, especially with malabsorptive procedures such as the Roux-en-Y gastric bypass. This is likely due to hyperoxaluria, hypocitraturia, and low urine volume.
- The most common type of stone formed after bariatric surgery is calcium oxalate.
- Treatment options to manage kidney stone formation include increased fluid intake, dietary modification, and use of medications as necessary.

Introduction

National data now shows that greater than one-third (36.5%) of the US adult population has obesity based on their BMI. Higher rates of obesity are seen in women (38.3% vs 34.3% in men) and in the age range of 40–59 (40.2%) [25]. Currently there are no states with a prevalence of obesity less than 20%, and four states have obesity prevalence rates greater than 35% (Louisiana, Alabama, Mississippi, and West Virginia) [6].

Obesity's associated comorbidities include hypertension, type 2 diabetes, hyperlipidemia, coronary artery disease, stroke, arthritis, sleep apnea, obesity-related cancers (including esophageal, pancreatic, colon, breast (after menopause), endometrial, kidney, and gallbladder), stress urinary incontinence, gastroesophageal reflux disease, and pregnancy-related issues and infertility [28]. Importantly, this list includes several of the current leading causes of death in our country [23]. Previous estimates state that the financial implications of obesity in the US could be as high as $147 billion dollars per year and that individuals with obesity spend about 42% more on health care than those with normal weight [9].

Bariatric Surgery

Weight loss surgery has emerged as one of the only available methods for patients with obesity to lose weight and sustain lower weight over the long term. Subsequent comorbidity resolution is significant with these procedures, and most obesity-related comorbidities have been found to improve or resolve after surgery [17].

National Institutes of Health NIH consensus guidelines for surgery include adult patients with a BMI greater than 40 or patients with a BMI between 35 and 39 with comorbidities (diabetes, hypertension, sleep apnea, hyperlipidemia). Patients should have undergone a trial of medically supervised weight loss before surgery, surgery should be performed by a multidisciplinary team, and patients should be committed to lifelong surveillance after their procedure [24].

As a result of patients' weight loss success and comorbidity resolution after bariatric surgery along with a greatly improved safety profile; case volumes for bariatric surgery have increased to over 200,000/year in the United States. The breakdown of case types has significantly changed in the past 5 years. The laparoscopic adjustable gastric banding (LAGB) procedure was previously one of the most popular weight loss operations but is now done in less than 4% of cases due to its lack of durable weight loss. Another relatively recent change has been the increase in laparoscopic sleeve gastrectomy (SG) volume due to lower morbidity rates, equivalent weight loss, and comorbidity resolution when compared to Roux-en-Y gastric bypass (RYGB). As of 2017, The SG now accounts for more than half (58.11%) of all bariatric procedures performed in the United States. The RYGB now accounts for less than one-fifth (18.69%) of bariatric procedures and the biliopancreatic diversion with duodenal switch accounts for <1% of cases [7].

The sleeve gastrectomy and RYGB make up the majority of primary bariatric procedures. The two operations have been shown to carry equivalent weight loss and comorbidity resolution [4]. However, the surgeries achieve these results with different mechanisms of action. The RYGB involves creation of a small gastric pouch causing a restrictive component and an intestinal bypass that leads to an additional malabsorptive benefit. The SG on the other hand shares a restrictive component by removing 60–80% of the lateral stomach, but there is no malabsorptive component. It has been found to significantly decrease circulating levels of the hunger hormone known as "Ghrelin" which explains its success despite lacking a malabsorptive component [18].

The LAGB involves placement of a fluid-filled band around the proximal stomach to create a small gastric pouch and restrict flow through the lumen. The band can be individually filled with differing amounts of fluid for each patient and tailored to their tolerance (Fig. 15.1).

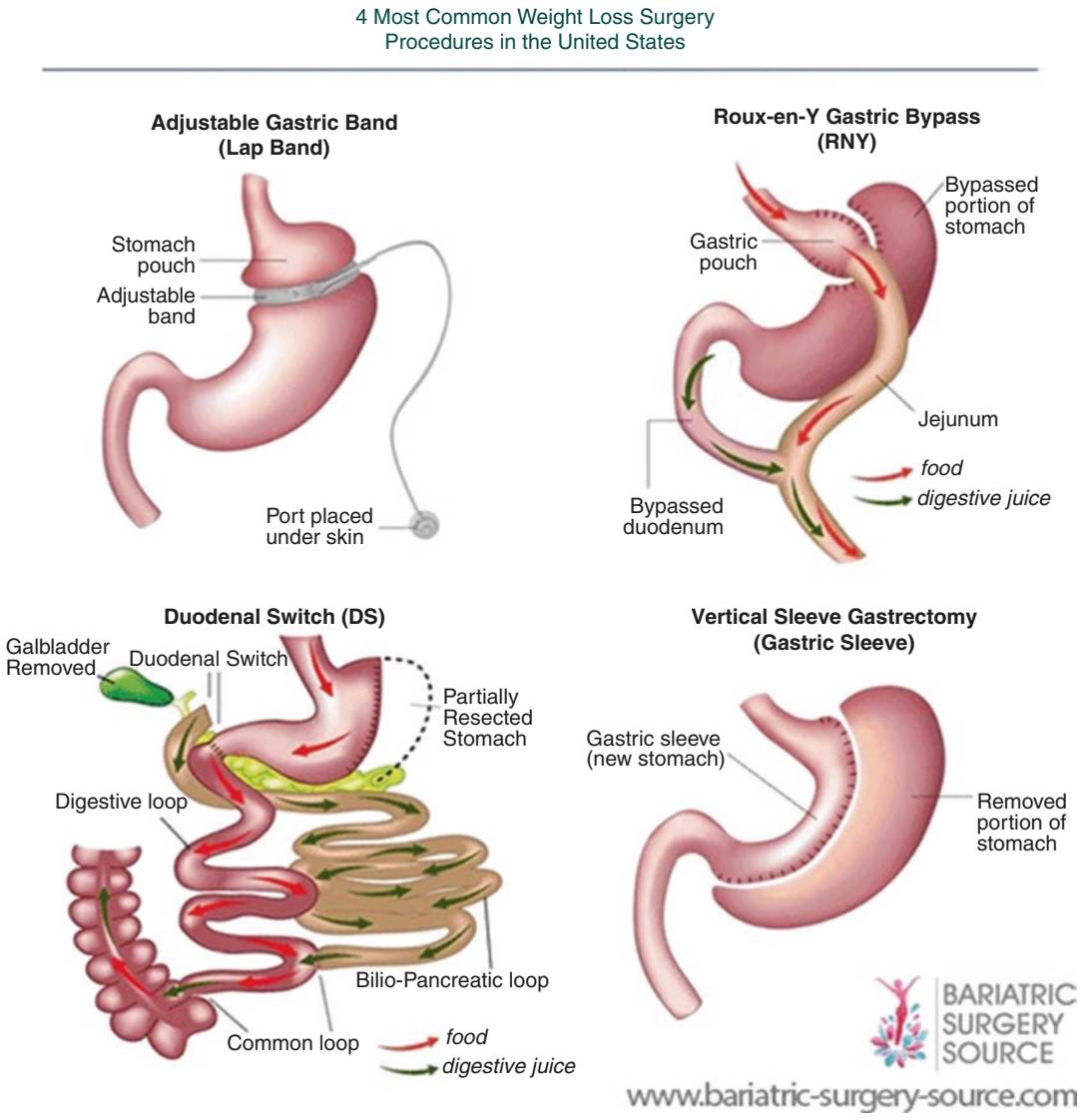

Fig. 15.1 Most common bariatric surgery procedures. (Permission to reprint from The Bariatric Surgery Patient's Essential Guidebook, www.bariatric-surgery-source.com)

Dietary Changes After Surgery

Patients seeking bariatric surgery meet with a multidisciplinary team consisting of dietitians, behavioral health providers, nurse practitioners, physician's assistants, and surgeons prior to their surgery in order to prepare for the changes ahead. While bariatric surgery limits the volume of food that can be ingested at one time, it does very little to impact the quality of the food consumed. Consequently, the team's role in assessing patients' readiness for change, evaluating patients' current nutritional status, and guiding patients toward necessary, lifelong dietary habits is crucial to long-term success [21, 22].

Postoperatively, patients follow a protocol-derived diet progression to promote proper tissue healing, preserve lean body mass during weight loss, and minimize any potential for gastrointestinal symptoms. Due to reduced stomach volume, patients may need to consume 3–6 smaller, low-calorie meals and snacks per day in order to meet daily nutrition needs. Many GI symptoms can be avoided by taking small bites of food, chewing well, and eating slowly. Consuming fluids 30 minutes after meals will ensure maximum comfort and hydration [22].

The dietary composition for a bariatric patient will differ from that of the general population. With limited stomach volume, there is emphasis on meeting protein targets to support lean body mass and satiety when eating. Protein needs should be individualized and guided by a dietitian with at least 60 g/day and up to 1.5 g/kg ideal body weight coming from high biologic value sources [22]. Commercially available protein supplements such as protein shakes and powders are used to support daily intake and frequently used as meal replacements shortly after surgery. Excess fats such as that in fried foods or concentrated sources of sugar such as juices should be avoided due to the risk of dumping syndrome in RYGB, and excess calorie intake with any procedure. Adherence to the general principles of healthy eating such as eating multiple servings of fruits and vegetables, complex carbohydrate sources, and lean proteins is advised [22].

Bariatric surgery patients require daily, lifelong vitamin and mineral supplementation in order to support normal body functions and reduce the risk of deficiencies. Table 15.1 summarizes the specific recommendations for each procedure. Of particular concern are iron, thiamin, vitamin B12, calcium, and vitamin D in all procedures as well as zinc and vitamins A, E, and K in the BPD/DS (full word used earlier in text so can abbreviate) biliopancreatic diversion with duodenal switch [27]. Patients start with chewable or liquid vitamins for the first 3 months and then advance to a swallowable form as tolerated. Routine lab monitoring at 1, 3–6, and 12 months postoperatively is recommended until the patient is stable in their weight loss and then on a yearly basis and anytime there is a question of deficiency [22].

Table 15.1 Post-operative vitamin supplement recommendations

Supplement	LAGB	SG	RYGB	BPD/DS*
Multivitamin, complete (%DV) specific nutrients: • 12 mg thiamin • 8–22 mg zinc • 1–2 mg copper • *At least* 18–36 mg iron • 400–800 mcg folate • 15 mg vitamin E • 90–120 mcg vitamin K • 5000–10,000 IU vitamin A	100	200	200	200
Calcium (mg)	1200–1500 Any form	1200–1500 Citrate preferred	1200–1500 Citrate preferred	1800–2400 Citrate preferred
Vitamin D (IU)	At least 3000	At least 3000	At least 3000	At least 3000
Vitamin B12 (mcg)	350–500	350–500	350–500	350–500

*Due to malabsorption, nutrient recommendations for BPD/DS may be higher than listed

Pathophysiology of Kidney Stone Formation After Surgery

Obesity is a risk factor for nephrolithiasis. The mechanism for increased risk of nephrolithiasis in patients with obesity is not entirely clear. Increased insulin resistance and dietary factors may be associated with lithogenic changes such as increased urinary excretion of calcium, uric acid, oxalate, and decreased urine pH which contribute to calcium-containing stones [34]. The risk of kidney stone formation increases two- to threefold in patients with malabsorptive bariatric surgery compared to controls. Mostly, stones in bariatric patients consist of calcium oxalate (CaOx). Urinary CaOx supersaturation (SS) is increased after malabsorptive bariatric surgery, and it leads to agglomeration of calcium oxalate crystals and stone formation.

24-Hour Urinary Chemistry Profiles

Urinary chemistry profiles are altered after RYGB surgery. Studies have shown 50% increase in urinary oxalate, 40% reduction in urinary citrate, and 30% reduction in urinary volume after RYGB surgery. Urine pH is also noted to be lower in RYGB patients. In 277 patients at 11 months post-RYGB, urinary oxalate increased from a mean of 28–44 mg/day with concomitant increase of CaOx SS from baseline of 1.5 to 2.3 [5]. Hyperoxaluria is the main determinant of high CaOx SS in bariatric patients. Other factors responsible for high CaOx SS are reduced urinary volume and low urinary citrate. In one study, after RYGB, a 40% reduction in urinary citrate at month 6 and 30–60% reduction in urinary volume, immediately post-op was noted [3]. These changes in urinary profiles promote CaOx stone formation.

Hyperoxaluria, Hypocitraturia, and Reduced Urine Volume

Hyperoxaluria In normal individuals, calcium and oxalate within the lumen of the intestine combine to form insoluble CaOx complexes that are excreted in the stool. In malabsorptive bariatric surgery, a part of small intestine is bypassed which leads to fat malabsorption. The presence of intraluminal fatty acids leads to saponification of calcium ions. Reduced calcium availability leads to decrease CaOx binding, hence increased free oxalate load in intestinal lumen. This free oxalate is absorbed by active or passive absorption. Once absorbed, it is filtered and excreted by the kidney. Permeability of GI tract to oxalate is increased by exposure to unconjugated bile salt and long chain fatty acids. Malabsorption of bile salts and fatty acids hence leads to hyperoxaluria, also called "enteric hyperoxaluria." In one study, dietary oxalate load leads to a twofold elevation in urinary oxalate in bariatric patients compared to controls which is suggestive of increased oxalate absorption [10]. Increased fecal fat excretion is noted in RYGB patients.

Hypocitraturia Hypocitraturia is defined as urinary citrate excretion lower than 320 mg/day. Urinary citrate is a potent endogenous inhibitor of CaOx stone formation. Citrate reduces CaOx SS in urine by forming soluble complexes with calcium ions and by inhibiting crystal aggregation. Low urine citrate in RYGB patients is secondary to systemic metabolic acidosis. There is increased mitochondrial citrate utilization in patients with acidosis. Lower intracellular citrate leads to increased citrate absorption in the proximal convoluted tubules and decreased urinary citrate excretion. In animal models, metabolic acidosis by arterial blood gas is noted after RYGB surgery [1]. Effervescent

potassium citrate and calcium citrate (PCC) raised urine pH and lowered CaOx agglomeration by direct crystal testing in RYGB patients [30]. This further suggests the role of chronic metabolic acidosis in hypocitraturia and stone disease in the bariatric population.

Decreased Urine Volume After bariatric surgery there is reduction in urine volume. Reduced stomach volume and gastrointestinal losses are responsible for reduced urine volume. In most studies urine volume is reduced by approximately 30%. Reduced urine volume contributes to higher CaOx SS and increased stone risk.

Incidence of Stone Formation After Surgery

Data from a review article published in 2014 revealed interesting trends regarding kidney stone formation following bariatric surgery. There were two main determinants related to risk. The first of which was the type of bariatric surgery performed (malabsorptive, RYGB, vs restrictive, SG and LAGB), and the second was personal history of previous stone formation.

Roux-en-Y gastric bypass patients were found to have stone formation rates after surgery ranging from 8.4% for patients with no history of stone formation to 16.7% for patients with recurrent stone disease. This is in comparison to SG and LAGB patients with a stone incidence after surgery from 1.3% to 4.7%. Overall this translates to RYGB patients having a two- to threefold higher risk of kidney stone formation after surgery when compared to SG/LAGB patients. Sleeve gastrectomy and LAGB patients' stone formation risk is similar to that of other patients with obesity who have not undergone surgery [5].

A group of 151 prospectively studied RYGB patients were evaluated for risk factors associated with stone formation. Data were obtained before surgery and 1 year after. Analysis revealed higher urinary oxalate and uric acid levels to be the only predictors identified for increased risk of stone formation [35].

Dietary Management of Kidney Stones in Bariatric Patients

Dietary intervention may prove to be an effective and inexpensive way for patients to manage kidney stones following bariatric surgery. Table 15.2 provides a summary of the current prevention and management strategies.

Table 15.2 Dietary management of kidney stones

Dietary modification	Recommendations for management
Fluid intake	Increase to produce urine volume of >2 L/day
Oxalates	Avoid excessive intake of foods high in oxalate content such as spinach, nuts, legumes and chocolate etc.
Calcium	Consume low-fat dairy and calcium-containing foods daily Take calcium citrate supplements with meals (1200–2400 mg/day depending on surgical procedure)
Protein	Consume a moderate amount of protein (0.8–1.4 g/kg/day) Choose a variety of protein sources, both plant and animal
Sodium	Limit sodium intake to <2300 mg/day
Fat	Limit intake of high-fat foods, such as fried foods, cream-based soups and sauces, and rich desserts etc.

A reduced stomach volume, the potential for lower fluid intake, diarrheal losses, and decreased urine volume following surgery pose a risk for stone formation due to an increase in urine SS from solutes such as calcium, oxalate, phosphorus, and uric acid [5, 11]. Increasing daily fluid intake is considered the first dietary line of defense when attempting to manage kidney stones. Patients should be advised to drink fluids such as water and other low-calorie beverages to support hydration and increase fluids to achieve at least 2–2.5 L/day of urine output volume [2, 11]. All sugar-sweetened sodas, juices and punches should be avoided as they may increase the risk of stones [8, 32].

Following a diet low in oxalates is commonly recommended to reduce urinary oxalate excretion though current research in this area remains controversial [26]. Urinary excretion of oxalate from foods depends on the bioavailability and solubility of oxalate, as well as ingestion of other nutrients in the diet such as calcium (decreases urinary excretion) and vitamin C (increases urinary excretion). Some studies suggest that the proportion of urinary oxalate derived from dietary oxalate may range from 10% to 20%, having at least some impact on stone risk [13, 36]. Patients with CaOx stones should be advised to limit habitually high intake of oxalate-containing foods such as spinach, nuts, legumes, and chocolate and consider pairing calcium-containing foods or calcium citrate supplements with meals to help bind oxalate in the intestine. Dietary calcium should not be restricted in these patients [11, 29, 32].

A diet emphasizing protein is often prescribed following surgery though may increase the risk of stone formation due to an increase in uric acid and calcium excretion and lowering of urine pH [11]. In particular, animal proteins such as red meat, poultry, and pork seem to carry the most risk while dairy and vegetarian sources of protein such as yogurt, whey based supplements, and beans may have more of a protective effect [32]. Consuming a moderate amount (0.8–1.4 g/kg body weight) of both plant and animal sources of protein will help to meet baseline needs of the patient without favoring a stone-forming environment [11].

Excess sodium in the diet increases renal calcium absorption and urinary calcium excretion, while concurrently lowering urinary citrate excretion, therefore increasing the risk of kidney stones [26]. Limiting meals eaten at restaurants, reducing intake of highly processed foods such as luncheon/deli meats, avoiding added salt on foods, and following a DASH-style eating plan are established ways to reduce dietary sodium intake. Additionally, following the Institute of Medicine's Dietary Reference Intake (DRI) guidelines of approximately 2300 mg/day of sodium or less is recommended [15].

Malabsorption of fat following RYGP and BPD/DS is common and can result in binding of calcium in the intestine, leaving free oxalate to be absorbed and processed by the kidneys [20]. Consuming a diet low in fat while increasing fluid intake and meeting needs for dietary and supplemental calcium may help to modify stone risk commonly seen with these procedures. While there are no specific guidelines on fat intake for the bariatric patient, it is reasonable to recommend a range of 20–35% of total calories from fat as proposed by the DRI [16].

Dietary therapy to manage kidney stones in the bariatric patient should be individualized and tailored specifically to the patient's current risk factors, stone formation history, and laboratory analysis of the type of stone formed.

Medical Management of Kidney Stones in Bariatric Patients

Medical therapy for prevention of stone formation is targeted at underlying metabolic abnormalities leading to stone formation. Refer to Table 15.3 for a summary of these management strategies. As previously discussed, bariatric patients have low citrate in their urine likely from systemic metabolic acidosis. Low urinary citrate leads to higher CaOx SS. Potassium citrate, 60–120 mEq per day in two to three divided doses, should be given to patients with recurrent kidney stones and urinary findings of low pH and hypocitraturia. Liquid formulation of potassium citrate is preferable as it is likely to

Table 15.3 Medical management of kidney stones

Medication	Recommendations for management
Potassium citrate	60–120 mEq/day in 2–3 divided doses Use for patients with high CaOx SS and hypocitraturia despite dietary intervention
Allopurinol	Use for patient with uric acid stone and hyperuricosuria
Probiotics	Colonization with *O. formigenes* and probiotics has potential but requires further study
Pyridoxine	Use for patient with primary hyperoxaluria type 1

have better absorption compared to slow release pills in patients with fast gastrointestinal transit. Potassium citrate should be cautiously used in patients with reduced kidney function as patients may develop hyperkalemia. One study looked at a new combined formulation of potassium citrate and calcium citrate (Use abbreviation only as PCC was previously used in the text) (PCC). It found that PCC increased urinary pH and citrate levels. Calcium in PCC can replace malabsorptive losses and prevent bone resorption [31]. However, this formulation is not commercially available.

Allopurinol can be considered in patients who have elevated serum uric acid and uric acid stones that do not respond to alkalization of urine with potassium citrate. Alkalization of urine increases uric acid solubility in urine and is the most effective treatment of uric acid stones. Thiazide diuretics are generally used in the treatment of nephrolithiasis for patients with hypercalciuria. However, bariatric surgery patients have low urinary calcium and thiazide diuretics are not helpful in this patient population.

Potential Future Treatment Approaches

The anaerobic bacterium *Oxalobacter formigenes* is a gut commensal, and its deficiency has been thought to be a potential etiology of hyperoxaluria in CaOx stone formers. It uses oxalate as a source of energy and has been indicated to interact with intestinal mucosa to promote the excretion of oxalate [12]. Animal models have shown improvement in urinary oxalate levels after esophageal gavage with *O. formigenes* [33]. In one study, the use of a probiotic (lactic acid and bacteria mixture) in ten patients with enteric hyperoxaluria including four patients with RYGB showed 20% reduction in urinary oxalate [19]. *O. formigenes* and other probiotic preparations may offer future potential therapy for patients with enteric hyperoxaluria. More studies are required to establish their role in prevention of CaOx stone in bariatric patients.

Pyridoxine (Vitamin B6) is an important co-factor for transamination of glyoxylate to glycine in the liver. This pathway is shunted to oxalate production in vitamin B6 deficiency. Treatment with pyridoxine is shown to reduce urinary oxalate in patients with type 1 primary hyperoxaluria [14]. Data in bariatric patients are limited and further studies are necessary to establish role of vitamin B6 in bariatric surgery patients.

Permeability of the GI tract to oxalate is increased by unconjugated bile salt. The bile acid sequestrant cholestyramine can bind with bile acids that can limit intestinal exposure to bile acid and reduce absorption of oxalate.

Summary

The prevalence of obesity continues to increase in the United States and bariatric surgery has emerged as the most effective therapy for durable weight loss. As a result, increasing numbers of post-bariatric surgery patients are being seen by all providers. Roux-en-Y gastric bypass has been found to be associated with a two- to threefold increase in the risk of kidney stone formation. Sleeve gastrectomy

and the LAGB do not confer an increased risk from baseline in patients with obesity. Patients at the highest risk for stone formation are those who have a personal history of kidney stones and undergo RYGB.

The increased risk of kidney stone formation in post-bariatric surgery patients appears to be secondary to hyperoxaluria, hypocitraturia, and low urine volume. Dietary management to prevent kidney stone formation in bariatric patients includes oxalate and sodium limitation. Calcium supplementation with meals for oxalate binding and low-fat diets to prevent oxalate absorption are both helpful in reducing urinary oxalate levels. Fluid intake should be increased to at least 2.5 liters per day to ensure adequate urine output. Medical therapy with potassium citrate is recommended in patients with recurrent kidney stones who continue to have hypocitraturia and high CaOx SS. Probiotics and colonization with *O. formigenes* represent as potential new therapeutic approaches.

Patient Case

- *HPI:* 80-year-old man, former marine and retired airline pilot who presents to the clinic with complaints of 6/10 lower back pain that radiates to his right side and lower abdomen and one episode of vomiting with persistent nausea for the last 24 hours. He has been drinking mostly liquids since yesterday and took ibuprofen to relieve his pain however found that it continued.
- *Medical history*: Hypertension, hyperlipidemia, obesity, single kidney stone in 2014 s/p lithotripsy, depression, migraine headaches, vitamin D deficiency.
- *Surgical history*: RYGB.
- *Medications*: Lisinopril, simvastatin, bupropion, sumatriptan, ibuprofen prn, complete multivitamin with iron once a day, vitamin B12 500 mcg a day, vitamin D 2000 units a day, calcium carbonate 400 mg a day.

Ht: 68” *Wt:* 206 lbs *BMI:* 31.4

24-hour dietary recall

- Take medications regularly in morning and evening.
- One cup regular coffee with cream, three cups decaf coffee w/cream.
- 8–10 oz. water.
- 5–6 saltine crackers.
- Slice of toast with butter.

Eating habits

- Eating frequency: three meals/day with occasional snack in the afternoon
- Protein choices: poultry, beef, pork, eggs, and cheese. No longer using protein supplements
- Eating out: 4–6×/week; pizza and salad, chicken parmesan with pasta and marinara sauce, 6 oz. steak with mashed potatoes and spinach, eggs with bacon, potatoes, and toast
- Fluid intake: regular and decaf coffee with cream, occasional water, or juice. No alcohol or milk

The patient was sent for a CT scan after initial visit and was found to have a kidney stone. He underwent lithotripsy, and stone analysis showed calcium oxalate.

Looking back at CM’s history, what were some of his risk factors for stone development?

- Hx RYGB with previous kidney stone.
- Low fluid intake – Perhaps learned this as a pilot; drinking mostly coffee
- Frequent meal out with likely high sodium and fat content, potential fat malabsorption
- Inadequate calcium supplementation – 400 mg calcium carbonate vs 1200–1500 mg calcium citrate recommended

What lifestyle recommendations will you discuss with the patient?

- Increase fluid intake to at least 2.5 liters a day, and devise a consistent hydration routine.
- Reduce sodium intake to <2300 mg/day, more cooking at home.
- Monitor oxalate content in foods and limit concentrated sources.
- Consider decrease in animal protein sources and increase calcium-containing foods such as yogurt or whey protein supplement.
- Change calcium carbonate to calcium citrate, and increase to 1200 mg a day; take with meals.

What medical evaluation and treatment recommendations will you discuss with the patient?

- Obtain 24-hour urinary chemistry profile before dietary modification and 6 weeks after.
- His baseline 24-hour urinary chemistry profile showed high urinary oxalate, low urinary citrate, high CaOx SS, and low urine volume.
- Start potassium citrate 20 mEq three times a day if the patient continues to have low urinary citrate and high CaOx SS after initial dietary and lifestyle modification.
- Repeat 24 urinary chemistry profile 4–8 weeks after initiating potassium citrate.

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Chapter 16
Nephrolithiasis in Patients with Gastrointestinal Disorders

Gebran Abboud

Keywords Malabsorption · Inflammatory bowel disease · Crohn's disease · Ulcerative colitis Ileostomy · Celiac disease · Bacterial overgrowth · Chronic pancreatitis · Hyperoxaluria

Introduction

Patients with malabsorptive gastrointestinal disorders are more prone to kidney stone formation than those without gastrointestinal ailments. The decrease in the absorption of water, potassium, magnesium, citrate, or bicarbonate results in the urinary supersaturation of stone salts.

This chapter provides an overview of the pathophysiology of nephrolithiasis in the context of the following conditions:

- Total colectomy with ileostomy
- Ulcerative colitis
- Ulcerative colitis with ileal pouch-anal anastomosis
- Crohn's disease and small bowel resection
- Chronic pancreatitis
- Celiac disease

There are no controlled trials assessing disease-specific therapies to treat or prevent stone formation in patients with these conditions. Therapies are directed at treating factors leading to stone formation as with non-gastrointestinal conditions and as detailed elsewhere in this book. This chapter will discuss factors related to ileostomy diarrhea as it can be addressed by providers not specialized in gastrointestinal disorders. The treatments of inflammatory bowel disease, chronic pancreatitis, and celiac disease are beyond the scope of this chapter.

Total Colectomy with Ileostomy

Pathophysiology

A total colectomy may be pursued in patients with severe inflammatory or infectious colitis, colonic inertia, and synchronous left- and right-sided colon cancer or prophylactically in those at high risk of

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colon cancer such as familial adenomatous polyposis. Those who have undergone a total colectomy with end ileostomy are at risk of forming both uric acid and calcium oxalate stones.

Uric Acid Stones

Uric acid stones comprise two-thirds of all stones in patients with an ileostomy [1]. There are two main factors that promote the precipitation of uric acid: urinary acidification and uric acid supersaturation.

Urinary Acidification

The urinary pH of ileostomy patients is usually less than 5.5 compared to a pH of about 6 in controls [2–4]. The acidification of the urine occurs because of a loss of alkaline ileostomy fluid as well as increased hydrogen ion excretion likely from renal conservation of sodium [3, 4].

Insoluble uric acid exists in equilibrium with the relatively soluble urate salt at a pKa of 5.5. As the pH drops below 5.5, the concentration of undissociated uric acid will greatly exceed that of urate as the following reaction is driven to the right:

$$H_{+} + \text{urate}_{-} \leftrightarrow \text{uric acid}$$

Below a pH of 5.5 only about 100 mg/L of uric acid can be held in solution. Therefore, a normal daily uric acid excretion of 500 mg could not be kept in solution with a low urinary volume [3].

Uric Acid Supersaturation

In most studies, ileostomy patients excreted only about a liter of urine per day. They also excreted 45–100 mmol less sodium than controls [2–4]. Chronic loss of water and sodium via the ileostomy effluent leads to persistent volume contraction and low urine volume. Whereas normal fecal water loss is less than 150 ml/day, the volume of ileostomy drainage is about 500–700 ml per day. Also, normal loss of sodium in feces is less than 10 mmol per day, while ileostomy loss is about 50–85 mmol per day. In effect, patients with ileostomies have a decrease in both total body water and exchangeable sodium [5].

Daily urinary excretion of uric acid does not differ on average between patients with ileostomies and controls [2, 3]. However, it is the concentration rather than the total amount of crystallizing solutes that determines stone formation. Supersaturation will occur as a result of the lower urine volumes. In addition, oliguria will promote urinary stasis and augment crystallization.

Calcium Oxalate Stones

Calcium oxalate stones are the most common nephroliths in the general population, accounting for 60–65% of stones [6]. Any condition that results in decreased urinary volume will increase the saturation of all crystallizing solutes and raise the risk of stone formation of any kind including calcium stones.

There are at least two other factors beyond low urinary volume that will increase the risk of calcium oxalate stones in patients with ileostomies: (1) decreased urinary citrate and magnesium and (2) the formation of uric acid crystals that act as a nidus for calcium stones.

Urinary citrate and magnesium chelate calcium and oxalate, respectively, thereby decrease urinary calcium and oxalate saturation. In patients who have undergone colon resection, urinary excretion

of citrate is decreased by up to 35%, and urinary excretion of magnesium is decreased by 50% [7, 8]. The decreased urinary excretion of citrate and magnesium reflects increased fecal losses of these substances as well as systemic acidosis [9, 10].

Finally, the uric acid crystals that form in ileostomy patients may grow into pure uric acid stones or may lead to nucleation of calcium oxalate stones. It is not uncommon for patients with ileostomies to have stones consisting of mixtures of uric acid and calcium oxalate.

Ulcerative Colitis

As in patients who have undergone a total colectomy with ileostomy, patients with ulcerative colitis (UC) are at risk of calcium oxalate crystallization due to decreased urine volume as well as reduced urinary citrate and magnesium excretion [4]. Magnesium is lost in the stool due to chronic diarrhea, and low urinary citrate levels result from metabolic acidosis [9].

Another contributing factor for the formation of calcium oxalate stones in ulcerative colitis is the presence of hypercalciuria. Excretion of calcium is increased by prolonged bed rest and corticosteroid use which mobilize calcium from the bones and inhibit its tubular resorption [1].

The reported frequencies of nephrolithiasis ranged from 0.2% to 11% in nonsurgical UC patients and from 8.4% to 40% in those with total colectomy and end ileostomy [11–14].

Ulcerative Colitis with Ileal Pouch-Anal Anastomosis

Restorative proctocolectomy with ileal pouch-anal anastomosis (IPAA) is now the gold standard surgical treatment for ulcerative colitis. In one study, 37% of IPAA patients had nephrolithiasis [15]. A follow-up study by the same group demonstrated that IPAA patients developed supersaturation of calcium oxalate and calcium phosphate stones [16]. This contrasts with UC patients with ileostomy who more commonly develop uric acid stones as discussed above.

Underlying stone formation in IPAA patients is a process called enteric hyperoxaluria. Under normal circumstances within the gut, calcium binds oxalate to form calcium oxalate crystals which are not absorbed by the intestines and are excreted. Any process that results in fat malabsorption will result in calcium saponification and the loss of calcium via steatorrhea. Decreased intestinal calcium results in enteric hyperoxaluria, and the resultant excess free oxalate is more readily absorbed by the intestine. Because oxalate is predominantly eliminated by renal excretion, increased oxalate uptake leads to increased urinary oxalate and thus calcium oxalate stone formation [15].

Any interruption to the enterohepatic circulation will result in bile acid loss and fat malabsorption which in turn will cause depletion of intestinal luminal calcium and result in enteric hyperoxaluria. In the case of IPAA patients, the interruption to the enterohepatic circulation occurs as a result of bacterial overgrowth.

Bacterial overgrowth is nearly universal in the pouch and prepouch ileum [17, 18]. Such overgrowth results in deconjugation of bile acids [17]. The unconjugated bile acids are poorly reabsorbed, resulting in fecal loss of bile acid and gradual depletion of the bile acid pool. The bile acid depletion results in steatorrhea and enteric hyperoxaluria which increases the risk of oxalate kidney stones. The oxalate crystals then act as substrates over which subsequent deposition of calcium phosphate occurs, resulting in mixed calcium oxalate/calcium phosphate stones [19, 20]. Evidence that bacterial overgrowth contributes to stone formation includes data showing that the use of antibiotics reduces the risk of stone formation in IPAA patients [15].

Crohn's Disease and Small Bowel Resection

The reported frequency of nephrolithiasis in Crohn's disease (CD) ranges from 4% to 5.5% in patients without small bowel resection and from 15% to 30.5% in CD patients after small bowel surgery [4, 13]. The majority of these stones are calcium oxalate and form as a result of hypomagnesuria, hypocitraturia, and enteric hyperoxaluria.

Hypomagnesuria

Hypomagnesuria is found in patients with chronic diarrhea [9]. In patients with small bowel resection, the degree of hypomagnesuria correlates with the length of bowel resected [21], and serum magnesium may be normal [22]. Urinary magnesium is a chelator of oxalate, reducing oxalate saturation.

Hypocitraturia

Hypocitraturia is multifactorial. It is more prevalent in CD than UC patients [22], more common in men than women [22], and observed in patients who had small bowel surgery [23]. Urinary citrate excretion is dependent on the pH of the proximal tubule cells [24]. Intracellular acidification can be associated with conditions in which the extracellular pH is low such as metabolic acidosis. Proximal tubule cellular acidosis amplifies citrate transport and metabolism in this nephron segment, leading to hypocitraturia [25]. Hypomagnesuria also contributes to hypocitraturia. The formation of magnesium citrate in the renal tubule is thought to reduce reabsorption of citrate, thereby increasing urinary citrate excretion. In magnesium-deficient states, a greater proportion of citrate is available for reabsorption, resulting in lower urinary citrate levels [22].

Enteric Hyperoxaluria

Disorders that inhibit the function of the distal ileum (Crohn's disease, ileal resection, or ileal bypass) will result in an increase in enteric oxalate absorption and hence hyperoxaluria.

The association between small bowel resection and increased urinary excretion of oxalate has been well documented [26–28]. The extent of ileal resection [29, 30] and the degree of steatorrhea [31–35] correlate with the severity of the hyperoxaluria.

The increased enteric absorption of oxalate is driven by a rise in enteric oxalate concentration, decreased enteric oxalate degradation, and increased gut permeability to oxalate.

Rise in Enteric Oxalate Concentration

Dietary calcium combines with oxalate in the gut to form a complex that is poorly absorbable. A decrease in luminal calcium allows more oxalate to exist as the absorbable sodium salt. Fatty acids bind intestinal calcium, forming insoluble soaps, thereby increasing soluble oxalate that is available for absorption. Evidence of this concept has been shown in patients with steatorrhea following small bowel resection, in whom urinary oxalate excretion can be decreased with the infusion of calcium-containing solutions into the colon [34]. Dietary calcium has also been shown to decrease hyperoxaluria after ileal resection [35, 36].

Decreased Enteric Oxalate Degradation

Oxalobacter formigenes is a Gram-negative anaerobe that is part of the normal fecal flora. This bacterium metabolizes oxalate to carbon dioxide and formate, thereby decreasing the oxalate available for absorption. Compared with fecal bacterial populations from normal individuals, the fecal bacterial populations from jejunoileal bypass patients and CD patients had decreased to negligible oxalate-degrading ability [37, 38]. CD patients have decreased *Oxalobacter formigenes* colonization [38]. Also, it has been shown that the growth of *Oxalobacter formigenes* is inhibited by bile salts [39].

Increased Gut Permeability to Oxalate

Increased colonic permeability to oxalate is caused by the malabsorbed fatty acids and bile salts [40–44], perhaps enhanced by changes in colonic epithelial tight junctions caused by the decrease in intraluminal calcium [45].

Chronic Pancreatitis

Pancreatic insufficiency results in inadequate delivery of digestive enzymes to the duodenum, thereby causing maldigestion of fats and hence enteric hyperoxaluria.

An observational study demonstrated that a quarter of patients with chronic pancreatitis have hyperoxaluria, with greater levels of oxaluria associated with lower glomerular filtration rate [46]. Also shown was a correlation between hyperoxaluria and clinical and biological signs of intestinal malabsorption and exocrine pancreatic insufficiency. In a population-based cohort study, patients with chronic pancreatitis were more likely to have kidney stones compared with patients without chronic pancreatitis (HR of 2.81) [47].

Celiac Disease

Adult patients with untreated celiac disease are four times more likely to have nephrolithiasis compared with healthy controls. However, the incidence of nephrolithiasis in celiac disease patients treated with a gluten-free diet was no different compared with healthy controls. Untreated celiac disease patients had greater urinary oxalate compared with healthy controls, and a reduction in urinary oxalate was noted following 1 year of a gluten-free diet. The mechanism underlying the formation of the nephroliths is postulated to be enteric hyperoxaluria, though there was no evaluation for fat malabsorption or steatorrhea in this study [48].

Interestingly a study of pediatric patients with celiac disease showed neither hyperoxaluria nor an increased incidence of nephrolithiasis compared with healthy controls. The discrepant findings between the adult and the pediatric populations may be related to differences in dietary oxalate intake and disease latency and differences in *Oxalobacter formigenes* colonization. It was observed that the pediatric patients were paucisymptomatic which signified that the disease was most probably of recent onset. Also, theoretically, adult patients were more likely to have been exposed to antibiotics which can diminish colonization with *Oxalobacter formigenes* [49].

Treatment

The first step in nephrolithiasis prevention is identifying the contributing pathophysiological factors. Initial therapy is often dietary modification which is guided mainly by urinary chemistry. Attention is paid to the intake of fluid, sodium, animal protein, fruits, calcium, and oxalate. When dietary modification proves to be insufficient or ineffective, pharmacological agents can be considered.

For uric acid stones, management will be dependent on controlling uric acid supersaturation and urinary acidification.

Controlling Uric Acid Supersaturation

Uric acid supersaturation can be diminished by increasing urine volume through increasing fluid intake and decreasing gastrointestinal fluid losses. Patients are encouraged to increase fluid intake to greater than 3 liters per day. Increased water consumption does not appear to elevate ileostomy output above baseline [50].

Controlling gastrointestinal fluid losses is first addressed by identifying the specific cause of increased output. Ileostomy diarrhea is generally defined as passage of greater than 1 L/d of ileostomy output, with patients typically having to empty ostomy contents six or more times a day [51]. Causes of ileostomy diarrhea include partial small bowel obstruction, intra-abdominal infection, recurrence of Crohn's disease, bacterial overgrowth, short bowel syndrome, and processes that cause diarrhea in an intact gastrointestinal tract such as infectious enteritis or lactose intolerance. However, in the majority of cases no identifiable cause is found and empiric treatment is initiated. In patients with ileal resection and without other identifiable cause of diarrhea, assessment for steatorrhea should be undertaken. If fecal fat is greater than 7 g/d on a diet with adequate intake of fat (70–100 g/d), a diet moderately reduced in fat content (50–70 g/d) should be pursued [52] because there is evidence that it decreases enteric absorption of oxalate [41]. Further reductions in fat intake may be necessary in those with short bowel syndrome. Even if steatorrhea is not present, a diet high in fat should be discouraged, as it may increase ileostomy output [53–55].

Therapeutic interventions for ileostomy diarrhea include antimotility agents, corticosteroids, and antisecretory medicines.

First-line treatment is generally loperamide, an antimotility synthetic opioid agonist. Loperamide can reduce ileostomy output by 20–30% [56, 57]. It is prescribed at a dosage of 2–4 mg three to four times per day, usually before meals. Loperamide is generally better tolerated than other antimotility agents such as codeine phosphate and diphenoxylate. Codeine phosphate can also decrease fluid output by 30% but has been associated with greater loss of sodium and potassium compared with loperamide. Codeine phosphate is generally administered at 30–60 mg every 6–8 hours. Diphenoxylate can be given at a dose of 2.5–5 mg three times daily [57, 58].

Corticosteroids, beyond their anti-inflammatory effect, can increase ion transport in the normal intestinal mucosa [59–61]. Budesonide is a topically acting corticosteroid. In a double-blind placebo-controlled trial of patients with quiescent Crohn's disease, 60% of patients had a greater than 25% reduction in ileostomy output [62]. Budesonide is given at a dose of 9 mg daily.

Antisecretory agents include octreotide and clonidine. Octreotide is a somatostatin analogue that reduces salivary, gastric, pancreatic, and biliary secretions. It also slows small bowel transit. It has been shown to be effective in both ileostomy diarrhea and jejunostomy patients with short bowel syndrome [63–65]. Octreotide is initially given subcutaneously at 50 ug one to three times daily with a range of 100–600 ug/d in two to four divided doses. After patients are stabilized for at least

2 weeks, depot injections can be given intragluteally at 20 mg every 4 weeks for 2–3 months with dose modification based on response. Clonidine stimulates alpha-2 adrenergic receptors on enterocytes, promoting fluid and electrolyte absorption and inhibiting ion secretion [66]. Clonidine can be used either alone or in combination with octreotide in refractory cases. It is given at a dose of 0.1 mg twice daily and increased up to 2.4 mg per day [67, 68].

Controlling Urinary Acidification

As detailed above, acidic urine contributes to increased uric acid nucleation and stone formation. Because of sodium deficits, sodium bicarbonate is preferred to potassium citrate, but both can be used in ileostomy patients [69, 70]. Sodium bicarbonate can be initiated at 0.5–1 meq/kg in four divided doses, with a target urine pH of 6.5.

Conclusion

Patients with malabsorptive gastrointestinal disorders are at higher risk of kidney stone formation through multiple mechanisms. The malabsorption of water, sodium, oxalate, bicarbonate, and fat leads to increased urinary concentration of stone-forming factors. Calcium oxalate and uric acid stones are most common. Treatment starts with dietary modification and is aimed at altering urinary chemistry. Addressing the underlying gastrointestinal disease is important, and pharmacotherapy may be appropriate in some circumstances. Kidney stones cause significant morbidity in these patients, and taking appropriate measures to prevent stone formation leads to improved quality of life and decreased hospitalizations.

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Chapter 17
Gastrointestinal Disease and Stone Risk: Nutritional Management

Desiree de Waal

Keywords Digestion · Gastrointestinal health · Probiotics · Prebiotics · Microbiome · Hyperoxaluria Bowel disease

Key Points

- The "Western" diet and lifestyle plus the overuse of antibiotics have been linked to changes in the microbiota community of the human gut.
- Alterations in the gut microbiota lead to increased intestinal permeability and mucosal immune response which can contribute to multiple chronic diseases including kidney stones.
- Many kidney stone formers are missing the bacterium *Oxalobacter formigenes*, the primary bacterium that degrades oxalate in the colon.
- Absorption of oxalate from the gut is thought to be partially dependent on transporters.
- Under normal condition, calcium binds to dietary oxalate in the intestine forming a complex that is expelled in the stool.
- In fat malabsorption syndromes, increased oxalate is absorbed when calcium binds to malabsorbed fats rather than oxalate.
- Inflammation in the gut increases permeability of intestinal mucosa causing excess free oxalate absorption.
- A heart-healthy diet (less meat, salt, and processed foods) plus high in fruits, vegetables, and whole grains is recommended.

Introduction

The microbiota of the gut plays a fundamental role in health. These gut bacteria aid in digestion, produce enzymes to breakdown foods, make vitamins (B12 and K), make compounds like serotonin, help in maintaining the integrity of intestinal lining plus regulate metabolism, boost immunity, and fight pathogens [1]. The "Western" diet and lifestyle plus the overuse of antibiotics have been linked to a dramatic change in the microbiota community of the human gut. An unfavorable alteration in the gut microbiota (dysbiosis) leads to increased intestinal permeability and mucosal immune response which can contribute to the development of multiple chronic diseases including kidney stones [2, 3].

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The Microbiota of the GI Tract

The GI tract contains more than 500 different species of bacteria, many of which are pathogenic. They live in coexistence with the host and are referred to as the microbiota, microflora, or normal flora [4]. The GI tract is the most heavily colonized organ with the colon alone estimated to contain over 70% of all the microbes, making it a preferred site for colonization [4]. Four bacterial phyla are found in the body, namely, *Firmicutes* (e.g., *Streptococcus*, *Lactobacillus*, *Clostridia)*, *Actinobacteria* (e.g., *Propionibacterium*, *Bifidobacteriales*), *Proteobacteria* (e.g., *Haemophilus*, *Escherichia coli*, *Salmonella*, *Oxalobacter*), and *Bacteroidetes* (e.g., *Prevotella*, *Bacteroides*). These bacteria carry out reactions that gut enzymes cannot perform such as fermentation, denitrification, sulfate reduction, aromatic fission, and hydrolysis/deconjugation [5]. The National Institute of Health (NIH) has initiated the Human Microbiome Project (HMP) to learn more about the ecology of host-associated microbial communities. The metabolic interaction between the host and its gut microbiota is directly affected by diet and an area of new research for health [6].

There are two main types of bacterial fermentation in the gut, saccharolytic and proteolytic. Saccharolytic is carbohydrate based and is the more favorable type of fermentation which includes the beneficial metabolites short-chain fatty acids (SCFA), propionate, and acetate. SCFA are integral to the health of the colonic epithelium and have a myriad of other benefits including anti-inflammatory properties. Proteolytic bacterial fermentation is protein based and a source of a number of toxic metabolites, particularly uremic toxins (indoxyl sulfate and *p*-cresyl sulfate) [7].

Nutrients in the diet have been found to influence the microbiome and different microbiomes were found in people eating low fiber diets as compared to those eating a high fiber diet [8]. The gut microbiota will shift depending on the type of diet consumed [9].

Current research for kidney stones is focusing on *Oxalobacter formigenes* (*O. formigenes*), the primary bacterium that degrades oxalate in the colon [10]. Many kidney stone formers do not have this oxalate-breaking bacterium in their gut. Antibiotics seemed to have a major effect on *O. formigenes* with a reduced recolonization rate after antibiotic therapy. In patients lacking this bacterium it is hypothesized that more oxalate is absorbed due to the lack of oxalate degradation in the gut [11]. A few other species of intestinal bacteria, including strains of *Lactobacillus* and *Bifidobacterium*, are also capable of consuming oxalate and have recently been shown to carry the same *oxc* and *frc* genes as *O. formigenes* that are thought to code for the oxalate-degrading enzymes [12].

The microbiome co-evolves with the host and influences the metabolism, physiology, nutrition, and immune function. It is thought to be fairly stable throughout a person's life once established but antibiotics dramatically affect the microbiome. Diets seem to influence the types of bacteria in the microbiome with new research focusing on a connection between the microbiome and health.

Gut-Related Mechanisms for Kidney Stones

Kidney stones are formed due to excess urinary concentration of stone-forming substances (calcium, oxalate, urate, cysteine, phosphate), concentrated urine, and decreased amounts of inhibitory substances (i.e., citrate, magnesium). Calcium oxalate and calcium phosphate make up the most common type with the next most prevalent being uric acid, struvite, and cysteine stones [13].

Low urine volume causes concentrated urine, thereby raising the risk of any type of stone. This can be due to inadequate intake or excessive loss of fluid via sweating or through gastrointestinal losses as in diarrhea. Increased fluid intake is the hallmark of recommendations for reducing recurrence of kidney stones by inducing a diluted state that is incompatible to crystallization [13–15]. Urinary oxalate comes from either exogenous or endogenous sources. Hyperoxaluria can also be

divided into two categories, primary and secondary hyperoxaluria. Primary hyperoxaluria (PH) is due to genetic hepatic enzyme deficiencies leading to increased endogenous oxalate formation. Secondary hyperoxaluria is caused by increased oxalate absorption which may be due to high dietary oxalate, fat malabsorption, alterations in the gut microbiome, and/or genetic variations in oxalate transporters in the gut.

Movement of oxalate across membranes is regulated by transporters. Epithelial oxalates, also called solute-linked carrier 26 (SLC26) anion exchangers/transporters, were identified in the kidney, liver, and gastrointestinal tract. These transporters differ in location of tissue with small differences in the substrates (sulfate, chloride, bicarbonate, formate, and oxalate). Additional anion exchangers may also be involved in oxalate transport exhibiting chloride /oxalate exchange. Oxalate transport is both paracellular and transcellular. Paracellular transport is passive whereas transcellular transport is coupled with other processes independent of the electrochemical gradient [14].

Absorption of oxalate from the gut is partially dependent upon such transporters but the exact mechanisms are unknown. The stomach is a site of oxalate uptake despite its acidic environment and is presumed to be via transcellular transport. Increased oxalate absorption is observed when transit time through the stomach is slow [14]. Under normal conditions, calcium binds to dietary oxalate in the distal intestine forming a complex that is expelled in the stool. Other dietary factors (magnesium, fatty acids, and bile salts) may also affect the absorption of oxalates. Calcium oxalate stone formers seem to have a greater transient increase in the absorption of oxalate as compared to normal individuals after an oxalate-rich meal [14]. In fat malabsorption syndromes, increased oxalate is absorbed when calcium binds to malabsorbed fats rather than oxalate which increases the amount of unbound oxalate. Inflammation increases permeability of the intestinal mucosa causing excess free oxalate absorption [16]. It is hypothesized that restriction of oxalates in the diet may also reduce the presence of *O. formigenes* when it is deprived of its food source [17].

GI-Related Medical Conditions and Risk for Kidney Stones

Inflammatory Bowel Disease

Inflammatory bowel disease (IBD) is associated with an increased risk of nephrolithiasis [18]. Altered intestinal permeability may promote the metabolic risk factors (urinary volume, pH, Ox and Ca excretion, citrate, and magnesium) [19]. Fat malabsorption diseases (i.e., Crohn's, celiac sprue, ulcerative colitis, and chronic pancreatitis by diseases such as cystic fibrosis) are caused with an increased risk for calcium oxalate stones possibly due to calcium binding to malabsorbed fats allowing excess-free oxalate to be absorbed by the colonic mucosa [20]. Antibiotics used in the treatment of IBD may reduce the concentration of beneficial bacteria in the gut [19]. IBD patients have low levels of *Bifidobacterium* so therapeutic interventions include methods to improve the amount of this bacteria in the gut [21, 22]. It remains unknown if the changes in the gut microbiota are the cause or consequence of IBD [4].

Short Bowel Syndrome

Short bowel syndrome (SBS) occurs when part of the intestine is missing or removed during surgery. Nutrients are not properly absorbed. In patients with an intact colon and SBS, the risk for kidney stones occurs due to increased absorption of oxalate in the colon. In the setting of fat malabsorption

(steatorrhea) increased intraluminal free fatty acids prefer to bind to calcium resulting in increased oxalate absorption [16]. Low urine volumes are also found among patients with colon surgery which increases risk for supersaturation of uric acid and oxalates. Chronic diarrhea causes increased losses of magnesium and a low urine citrate level [18, 23]. Small bowel bacterial overgrowth (SBBO) and D-lactic acidosis are also complications with SBS. SBBO produces inflammatory changes in the intestinal mucosa causing fluid losses, fat malabsorption, and fat-soluble vitamin deficiency.

Gastric Bypass Surgery

Malabsorption of fat as well as macronutrients, essential vitamins, and minerals may occur with substantial weight loss [24]. An increased incidence of kidney stones related to bariatric surgery has been observed similar to risk listed above for SBS with associated increased incidence of oxalate nephropathy [25]. Fat malabsorption which may accompany some forms of bariatric surgery decreases calcium and leaves less to bind to oxalate. A low fat diet has been shown to lower urinary oxalate levels [26]. Vitamin deficiencies due to malabsorption include pyridoxine (vitamin B6, a cofactor in liver metabolism of glyoxalate) which could also lead to increased urinary levels of oxalate. Specific alterations in the microbiome after bariatric surgery are not well characterized; however, a decrease in oxalate-degrading bacteria in patients after gastric bypass was observed [27].

Dietary Factors: Prebiotics and Probiotics

Prebiotics

Prebiotics was first defined as "a non-digestible food ingredient that beneficially affects the host by selectively stimulating the growth and/or activity of one or a limited number of bacteria in the colon, and thus improves host health" [1, 28]. Generally speaking prebiotics often contain fiber and/or carbohydrates. However, not all dietary fiber and carbohydrates are prebiotics, and clear criteria to identify a food ingredient as a prebiotic are currently lacking. For a food ingredient to be considered as a prebiotic it must at least meet the following requirements: (1) resistance to gastric acidity, to hydrolysis by mammalian enzymes, and to gastrointestinal absorption; (2) fermentation by intestinal microflora; and (3) selective stimulation of the growth and/or activity of those intestinal bacteria that contribute to health and well-being [1].

The intestinal flora in the colon ferments carbohydrates not digested in the upper gut to generate energy. Dietary carbohydrates include fermentable fiber (wheat dextrin, pectin, β-glucans, guar gum, inulin), resistant starch, non-starch polysaccharides (e.g., cellulose, hemicellulose, pectin, and gums), nondigestible oligosaccharides, and sugar alcohols. These colonic bacteria produce hydrogen, methane, carbon dioxide, SCFA (mainly acetate, propionate, and butyrate), and lactate. Fermentable fibers increase the growth of *bifidobacteria* and *lactobacilli* which are considered beneficial for human health and are also capable of consuming oxalate [1, 12]. Foods with the highest prebiotic content include leeks, asparagus, chicory root, Jerusalem artichokes (sunchokes), garlic, onions, wheat, oats, raw dandelion greens, whole grains, beans, banana, and psyllium husk [1, 29]. While there is no broad consensus on an ideal daily serving of prebiotics, a diet with more plant foods (vegetables, beans, fruit, whole grains) may improve the gut microbiota.

Probiotics

Probiotics are microorganisms, naturally found in the GI tract of humans, that are believed to provide health benefits when consumed [30]. Probiotics appear to reduce inflammation due to intestinal permeability [31]. Current research on *O. formigenes* is promising, but there is much to learn about how to acquire this organism and what factors will help keep this population intact in the gut [3]. *Lactobacillus* and *Bifidobacterium* seem to have similar qualities as *O. formigenes* [12].

Foods high in probiotics include fermented foods with added active live cultures like yogurts, miso, cheese, kefir, kimchi, and sauerkraut. However, in response to consumer demands, some probiotic foods' nutrition quality has declined. The use of probiotic supplements is increasing despite a paucity of reliable data showing clinical benefit and lack of FDA regulation. There is moderate evidence supporting the use of probiotics to prevent *Clostridium difficile* (*C. diff*) in patients receiving antibiotics [31]. At a minimum validation of probiotic contents in commercial products is needed. Concerns on quality of probiotic products have been raised when some products have been found to contain smaller numbers of live microorganisms and some contain bacterial strains not listed on the ingredients [32]. The concept of improving the gut microflora by adding "good bacteria" is an exciting concept in theory, but at this time, very little evidence supports claims that probiotic dietary supplements reduce incidence of kidney stones. Improved health through gut flora modulation appears to be directly related to long-term dietary changes.

Nutritional Management for Kidney Stones and GI Disorders

Generally a diet high in fruits, vegetables, and whole grains is recommended. Although firm evidence is lacking, this strategy may provide prebiotics and may improve the microflora of the gut as a way to prevent kidney stones.

Summary table of medial nutrition therapy (MNT) for kidney stone management and GI disorders

GI disorder	Nutrition risk factors	Nutrition recommendations
Inflammatory bowel disease	Altered intestinal permeability Fat malabsorption Use of antibiotics	Fluid intake of 2–3 quarts per day Increase citrate in diet Adequate calcium intake with meals Adequate intake of fruits, vegetables, and whole grains Reduced animal protein Probiotics when antibiotics have been used Reduced simple sugar intake Reduced sodium intake
Irritable bowel syndrome and diverticular disease	Luminal stasis and constipation Bacterial overgrowth Bowel surgery Use of antibiotics	High-fiber diet Fluid intake of 2–3 quarts per day Increase citrate in diet Adequate calcium intake with meals Adequate intake of fruits, vegetables, and whole grains Reduced animal protein Probiotics when antibiotics have been used Reduced simple sugar intake Reduced sodium intake

GI disorder	Nutrition risk factors	Nutrition recommendations
Short bowel syndrome	Nutrient malabsorption Fat malabsorption Diarrhea Low urine volume Bacterial overgrowth Fat-soluble vitamin deficiency	Fluid intake of 2–3 quarts per day Increase citrate in diet Adequate calcium intake with meals Adequate intake of fruits, vegetables, and whole grains Reduced animal protein Reduced simple sugar intake Reduced sodium intake
Gastric bypass surgery	Nutrient malabsorption Fat malabsorption Diarrhea Low urine volume Bacterial overgrowth Fat-soluble vitamin deficiency	Fluid intake of 2–3 quarts per day Increase citrate in diet Adequate calcium intake with meals Adequate intake of fruits, vegetables, and whole grains Reduced animal protein Reduced simple sugar intake Reduced sodium intake

Summary

The digestive system is a complex assembly of organs responsible for providing most of the calories and nutrients we need to survive. The GI system also modulates immune function and produces several essential vitamins and nutrients not readily available from exogenous sources. Some of the process in the gut including calcium and oxalate metabolism may contribute to the risk of forming kidney stones. The bacteria in the intestinal tract perform a number of crucial functions, including digesting otherwise indigestible carbohydrates, stimulating the immune system, fending off colonization of pathogens, and directing the body to store fats. The composition of the diet that passes through the gut changes the microbiome which can affect health of the host. Inflammatory diseases of the digestive system or surgical changes to the length of the gastrointestinal system have been shown to increase the risk for kidney stones. The identification of oxalate transport carriers throughout the digestive system is an area of new research. Current evidence is limited, but a heart-healthy diet (less meat, salt, and processed foods plus more fruits, vegetables, and whole grains) promotes an improved microflora and may prevent kidney stones. The digestive system is an area of continuing and future research for kidney stones.

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Chapter 18
Nephrolithiasis in Chronic Kidney Disease

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Keywords Nephrolithiasis · Kidney stones · Chronic kidney disease (CKD) · End-stage renal disease (ESRD) · Glomerular filtration rate (GFR) · Inherited tubulopathies · Dent disease · Hypercalciuria Hyperoxalurias · Cystinuria · Inborn errors of purine metabolism · Adenine phosphoribosyltransferase (APRT) deficiency · Familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) Lithotripsy

Key Points

- Nephrolithiasis, a condition linked to both heritable and environmental traits, is becoming more prevalent (likely due to changes in our dietary habits and a growing obesity epidemic) and has associated annual expenditures in the billions of dollars.
- While there is data to suggest that nephrolithiasis and/or its surgical management may raise the risk of future chronic kidney disease, prospective randomized trials are necessary to fully assess this relationship.
- Chronic kidney disease does result in alterations in urine chemistry, but whether these changes increase the risk of nephrolithiasis remains unclear and in need of additional study.
- There are a number of rare, inherited diseases that result in both nephrolithiasis and chronic kidney disease.

Introduction

Nephrolithiasis in the United States is an expanding problem associated with major economic and health consequences [1–3]. Since the 1970s, the overall prevalence of this condition has risen. According to NHANES data from last decade of the twentieth century, 6.3% of males and 4.1% of females reported a history of nephrolithiasis; estimates in 2016 were 16% and 8% in males and females, respectively [1–4]. This rise has been attributed in part to the population's dietary habits (high sodium, low potassium, high sugar, and high protein) and the obesity epidemic, both of which are associated with metabolic syndrome, a condition closely associated with calcium-based and uric

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acid calculi [5]. Early twenty-first-century analyses estimate annual expenditures of over $2 billion to manage nephrolithiasis; however, these estimates do not account for the economic losses associated with this disease [1–3].

Concordant with nephrolithiasis, the prevalence and cost of chronic kidney disease (CKD)/end-stage renal disease (ESRD) have also climbed over the last 40 years. The prevalence of CKD/ESRD currently rests at ~16% and ~14% for males and females, respectively, with just over $80 billion in expenditures in 2013 [6]. With close to 10% of the Medicare budget dedicated to CKD/ESRD, there is a clear need to identify risk factors for CKD/ESRD and implement risk-reduction strategies to curtail expenditures [6]. In part one of this chapter, we aim to discuss the impact nephrolithiasis may have on the risk of future CKD/ESRD, while in part two we will touch on those diseases that share both as complications.

Part One A: The Relationship Between Nephrolithiasis and CKD/ESRD

Numerous studies over the last 30 years have suggested an increased risk of kidney disease due to nephrolithiasis and/or its management (see Tables 18.1, 18.2, and 18.3); however, the heterogeneity in study design and the varying definitions of kidney injury among these publications have made it difficult to draw any distinct conclusions. An early 1980s study of hospitalized patients in North Carolina demonstrated that a history of (self-reported) stone disease (more than 5 years prior to study entry) nearly doubled the risk of having CKD [7]. Mayo Clinic investigators, examining patients retrospectively from the same decade, identified the following risk factors for future CKD in stone formers: hypertension (OR 3.57 1.49–8.55), diabetes (OR 4.27, 1.77–10.29), six or more UTIs (OR 5.81, 1.75–19.33), struvite stones (OR 15.61, 1.83–∞), and allopurinol use (OR 10.38, 3.02–35.62) [8]. Outside of its retrospective design, a significant limitation of this study was its small sample size (160 patients) [8]. Another study, also limited because of its small size, identified higher rates of hypertension, diabetes, and CKD in recurrent stone formers from Iceland [9]. Rule et al.'s retrospective chart review of Olmsted County, Minnesota, residents over an 18-year period demonstrated that first-time stone formers (4066 patients) had just under a twofold increase in CKD risk compared to controls (10,150 patients) [10]. Of note, stone formers in this study also had higher rates of the following comorbid conditions: diabetes, hypertension, dyslipidemia, cardiovascular disease, alcohol intake, and gout [10]. A second study of Olmsted County residents conducted by El-Zoghby et al. over a similar time period showed a similar pattern between nephrolithiasis and ESRD (rather than CKD), and this relationship persisted even after adjusting for comorbid conditions (diabetes, obesity, hypertension, dyslipidemia, gout, and CKD) [11]. These studies, however, all suffered from population homogeneity (predominantly Caucasian from the same area), lack of information regarding stone characteristics (i.e., type, size, location, etc.) and stone therapy, and their retrospective approaches.

The Mayo Clinic study, mentioned above, did identify struvite stones, compared to those with calcareous composition, as being associated with future CKD [8]. Other retrospective analyses attempted to define whether stone composition was important in assessing CKD risk. A Taiwanese study suggested that both struvite and uric acid stones were associated with a lower MDRD-calculated eGFR as compared to calcium-containing stones, but this study included patients with pre-existing CKD [12]. Another study concluded that radiographically identified radiolucent stones (presumably uric acid) carried a higher risk of CKD than their radiopaque counterparts (presumably calcium-containing) [9]. With a paucity of studies and no prospective evaluations, it is unclear what role, if any, stone type plays in future renal disease.

A prospective Canadian study from the mid-1990s through the first decade of the twenty-first century, in which over 1 million patients with creatinine measurements but without renal disease or pyelonephritis were followed for development of CKD/ESRD, identified stone-forming patients as

Table 18.1 Retrospective studies on the effects of nephrolithiasis on renal function

Study authors (year, country)	Study design	Sample size	Inclusion and exclusion criteria	Results	Limitations
Ozden et al. (2012, Turkey)	Retrospectivecohort	67 total	*Inclusion* Patients who underwent PNL at Ondokuz Mayıs University in Samson, Turkey, between 1/2002 and 7/2010 and had an eGFR <60 mL/min/1.73m^2 (CKD3 or more) *Exclusion* Patients with unknown eGFR before or after surgery, those with less than 12 months of follow-up or those with a solitary kidney	Mean eGFR preoperatively was 37.9 ± 14.05 mL/min/1.73m^2, which significantly increased postoperatively and persisted during each of the annual assessments for the 5 years of follow-up There was not a statistically significant increase in eGFR annually between these measurements Only one of the 67 patients studied progressed to end-stage renal disease requiring hemodialysis 32 patients experienced down-staging of their CKD, and only two had upstaging of their disease Interestingly, the study found that risk factors for deterioration of renal function in their patient population were: A. Diabetes mellitus (OR 15.82, 1.489–243.621) B. Urinary tract infections (OR 10.6, 1.036–94.714)	Retrospective Small sample size Single center Lack of demographic information Loss of follow-up
Shoag et al. (2014, USA)	Retrospectivecohort	12,110 total 1081 stone formers	*Inclusion* 20 years or older enrolled in NHANES Study between 2007 and 2010 *Exclusion* Prevalent CKD	Increased risk of CKD (OR 1.76, 1.13–2.76) and treatment with dialysis (ESRD) (OR 3.26, 1.48–7.16) among women with kidney stones compared with controls, once adjusted for comorbidities, age, BMI, and lifestyle factors	Retrospective Did not report type of stone, number or location of stones Self-reported stones (survey) Many people were excluded from final analysis due to the absence of serologic markers
Denburg et al. (2016, United Kingdom)	Retrospectivecohort	11,570 w/ calculi 127,464 w/o calculi	*Inclusion* 18 years or older with eGFR >60 mL/min/1.73m^2 at start of observation period Diagnosis of urolithiasis *Exclusion* Age > 90 years Hypertension Proteinuria eGFR <60 mL/min/1.73m^2	Urolithiasis associated with increased risk of developing CKD (HR 1.82, 1.67–1.98) *SWL*: No increased risk of CKD (HR 1.01, 0.79–1.29), no effect of stone location *URS*: Borderline increased risk of CKD (HR 0.70, 0.49–1.00)	Retrospective No information on ethnicity

(continued)

Table 18.1 (continued)

Study authors (year, country)	Study design	Sample size	Inclusion and exclusion criteria	Results	Limitations
D'Costa et al. (2016)	Retrospectivecohort	1340 total	*Inclusion* Patients with nephrolithiasis in the MESA database between 1/1991 and 5/2007 *Exclusion* Patients with clinical CKD or ESRD before index date or within 90 days after the index date or elevated mean SCr during the 3 years to 1 month before the index date Patients without follow-up clinic visit within 90 days after the index date Patients without incident CKD censored at their last clinic visit or death or on 12/31/2011 (whichever came first)	After controlling for potential confounders, those who underwent urologic interventions were found to have an increased risk of elevated serum creatinine without CKD (OR 1.49, 1.19–1.85) There was no significant increase in risk of mortality or CKD among these same 446 patients who underwent interventions	Retrospective Stone disease defined by either asymptomatic disease (potential detection bias) or by imaging Homogenous population (mainly Caucasian individuals) Did not adjust for diseases which may increase risk of stone disease Limited number of procedures other than cystoscopy Liver disease not included in initial analysis
Vupputuri et al. (2004, USA)	Retrospective 1:1 case-control	1062 total 548 stone formers	*Inclusion* Hospitalized patients and community controls between ages 30 and 79 years old residing in North Carolina between 1980 and 1982 *Exclusion* Age under 30 years Residence outside North Carolina Pre-existing kidney disease or evidence of prior creatinine measurements greater than 1.5 mg/dL (from medical histories and chart review) and evidence of normal kidney function (despite the diagnosis of chronic kidney disease) History of systemic lupus erythematosus History of polycystic kidney disease	Overall increased risk for CKD (OR 1.9, 1.1–3.4) among stone formers Among non-hypertensives with long-standing stone disease (first stone 5 years or more prior to study), there was a significantly increased risk of CKD, as it related to both diabetic nephropathy (OR 6.0, 1.4–25.9) and interstitial nephritis (OR 9.0, 2.7–29.5) This difference was not found among the treated hypertensive group	Hospitalized patients and community controls Self-reported kidney stones Small geographic area

Rule et al. (2009, USA)	Retrospective 1:3 case-control	17,749 total 4774 stone formers	*Inclusion* Adult residents of Olmsted County with new diagnosis of kidney stone by ICD code *Exclusion* eGFR <60 mL/min/1.73 m^2 at time of first stone or within 3 months (MDRD)	Higher rates of comorbidities in stone formers (HTN, DM, obesity, DLD, gout, alcohol dependence, CAD) Any CKD (HR 1.67, 1.48–1.88) No significant increase in mortality, ESRD, or death with CKD Clinical CKD when controlling for age, gender, and all comorbidities (HR 1.56, 1.39–1.77) Sustained elevated SCr when controlling for age, gender, and all comorbidities (HR 1.36, 1.13–1.62) Similar findings when controlling for obesity, diabetes, and hypertension individually Similar findings for reduced eGFR as elevated SCr	Retrospective High rate of patients lost to follow-up Emphasis on diagnosis by diagnostic codes Homogenous population Limited lab data Lack of information about interventions, stone type, or stone burden
Saucier et al. (2010, USA)	Retrospective 1:2 case-control	159 total	*Inclusion* All Olmsted County residents who had a kidney stone diagnosis (by diagnosis codes) at the Mayo Clinic between 1980 and 1994 *Exclusion* Those who denied access to medical records	Additional risk factors for development of CKD in those with history of kidney stones were: Hypertension (OR 3.57 1.49–8.55) Diabetes mellitus (OR 4.27, 1.77–10.29) Six or more UTIs when compared with those who had none (OR 5.81, 1.75–19.33) Struvite stones compared with calcium-based stones (OR 15.61, 1.83–∞) and allopurinol use (OR 10.38, 3.02–35.62) Neither a particular surgical intervention nor the absolute number of surgical interventions showed an association with increased risk of development of CKD Symptomatic stone disease or number of kidney stone events were also not associated with increased risk of CKD	Single center study Retrospective design Small sample size Lack of stone information Homogenous patient population
El-Zoghby et al. (2012, USA)	Retrospective 1:4 case-control	31,546 total 6926 stone formers	*Inclusion* Adult residents of Olmsted County with new diagnosis of kidney stone by ICD code *Exclusion* Prevalent ESRD	Significantly higher rates of CKD, HTN, DM, obesity, DLD, and gout in stone formers than controls ($p < 0.001$, except gout $p < 0.02$) Stone formers (by diagnostic codes alone) had higher risk of developing ESRD than controls (HR 2.36, 1.65–3.37) that persisted when symptomatic stones were validated (HR 1.98, 1.13–3.45) Increased risk persisted when controlling for each and all comorbidities (HR 2.09, 1.45–3.01) as well as excluding those with baseline CKD (HR 2.25, 1.42–3.56)	Retrospective Small number of people who developed ESRD (34 cases, 75 controls) Emphasis on diagnosis by diagnostic codes Homogenous population Limited lab data Lack of information about interventions, stone type, or stone burden Limited statistical power

(continued)

Table 18.1 (continued)

Study authors (year, country)	Study design	Sample size	Inclusion and exclusion criteria	Results	Limitations
Keller et al. (2012, Taiwan)	Retrospective 1:1 case-control	42,948 total 7802 stone formers	*Inclusion* Aged ≥18 years who had received their first-time diagnosis of CKD (by diagnosis codes) during ambulatory care visits between 1/2001 and 12/2009 *Exclusion* None listed	Those with CKD were more likely to have had UC than controls (OR 1.91, 1.81–2.01) after adjusting for potential confounders Those with CKD were more likely to have been previously diagnosed with kidney calculus (OR 2.10, 1.95–2.27), ureteral calculus (OR 1.68, 1.51–1.85), bladder calculus (OR 1.49, 1.13–1.98), and unspecified UC (OR 1.89, 1.74–2.06) than controls Among patients with ureteral calculi, both cases and controls, those with CKD were more likely to have received endoscopic intervention (OR 2.43, 1.68–3.51) and percutaneous nephrolithotomy (OR 1.42, 1.06–1.92) than controls, after adjusting for demographics and medical comorbidities The association with CKD was not found in those who received extracorporeal shockwave lithotripsy (OR 0.99, 0.88–1.11) No significant differences in the rates of CKD based on stone location when comparing kidney, ureteral, or bladder stones, as well as unspecified stone locations and multiple stone locations	Homogeneity of population Incomplete lifestyle information Diagnoses attained by documented discharge diagnosis, not standardized criteria
Chou et al. (2011, Taiwan)	Retrospective	1918 total	*Inclusion* All patients hospitalized from 2/2004 to 3/2009 in the Department of Urology, Kaohsiung Medical University Hospital with radiologic evidence of upper urinary tract stones *Exclusion* Pre-existing CKD, chronic ureteral obstruction in both kidneys or in a solitary kidney, congenital renal anomalies, and ADPKD	Patients with struvite or uric stones had a significantly lower eGFR, calculated by MDRD, than those with any calcium-containing stone[a] There was no statistically significant difference in eGFR between struvite and uric acid stone formers All patients in the study had CKD stages 2–3 (mild disease)	Retrospective Homogenous population Post hoc analysis Did not consider treatment methods used Did not consider the association of stone disease duration with patient's renal function Lacking key demographic information (BMI)

ADPKD autosomal dominant polycystic kidney disease, *BMI* body mass index, *CHD* coronary heart disease, *CI* confidence interval, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *CT* computerized tomography, *DLD* dyslipidemia, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *ESWL* extracorporeal shockwave lithotripsy, *FPG* fasting plasma glucose, *HDL* hyperlipidemia, *HR* hazard ratio, *hsCRP* high-sensitivity C-reactive protein, *HTN* hypertension, *MESA* Marshfield (Wisconsin) Epidemiologic Study Area, *ICD* International Classification of Diseases, *MDRD* Modification of Diet in Renal Disease, *OR* odds ratio, *PNL* percutaneous nephrolithotomy, *RR* risk ratio, *RRT* renal replacement therapy, *SCr* serum creatinine, *SIR* standardized incidence ratio, *SWL* shockwave lithotripsy, *TSH* thyroid-stimulating hormone, *UC* ureteral calculus, *URS* ureteroscopy, *US* ultrasound, *UTI* urinary tract infection

[a]$p < 0.001$

Table 18.2 Prospective studies on the effects of nephrolithiasis on renal function

Study authors (year, country)	Study design	Sample size	Inclusion and exclusion criteria	Results	Limitations
Hippisley-Cox and Coupland (2010, United Kingdom)	Prospective cohort	775,091 females 799,658 males	*Inclusion* Adults age 35–74 years old in primary care practices in England and Wales that had been using EMIS computer system for at least a year (part of the QResearch database), without recorded evidence of CKD at study entry between 1/1/2002 and 12/31/2008 *Exclusion* Prevalent CKD	Women were at increased risk of developing both moderate to severe CKD (HR 1.27, 1.11–1.46) and ESRD (HR 2.07, 1.34–3.19) The same was not found for men in the study	Observational No information on stone type or burden
Alexander et al. (2012, Canada)	Prospectivecohort	3,089,194 total 23,706 w/ symptomatic calculus	*Inclusion* Adults aged ≥18 years who resided in Alberta, Canada, between 4/1997 and 3/2009 *Exclusion* Prevalent ESRD (documented eGFR <15 mL/min/1.73 m^2, chronic dialysis, or prior kidney transplant) at baseline History of pyelonephritis before or during follow-up	One or more stone episodes during follow-up was associated with: Increased risk of ESRD (HR 2.16, 1.79–2.62) New stage 3b–5 CKD (HR 1.74, 1.61–1.88) Doubling of SCr (HR 1.94, 1.56–2.43) when compared with those without kidney stones during follow-up Significantly higher increased risk of ESRD ($p = 0.003$) and doubling SCr ($p = 0.03$) in women more than men Significantly higher increased risk of CKD ($p < 0.001$) and doubling of SCr ($p = 0.01$) in people aged <50 years than in those aged ≥50	No information on stone composition Only identified people who presented for health-care services Obtained data by hospitalization data, claims, and diagnostic codes

(continued)

Table 18.2 (continued)

Study authors (year, country)	Study design	Sample size	Inclusion and exclusion criteria	Results	Limitations
Kummer et al. (2015, US)	Prospectivecohort	10,678 total	*Inclusion* 45–64 years old in four communities throughout the United States and conducted visits beginning between 1996 and 1998 with follow-up until December 31, 2010 *Exclusion* Prevalent CKD or ESRD (needing RRT) at initiation of study	Association between incident CKD and a history of stone disease that was present after adjusting for age, sex, race, and study center (HR 1.29, 1.07–1.54), reverted to the null when adjusting for all other demographic factors (HDL, hypertension, urine albumin-to-creatinine ratio, eGFR, diuretic use, smoking status, BMI, DM, uric acid levels, history of CHD, hsCRP) (HR 1.09, 0.90–1.32) Lower uric acid levels were associated with higher risk of incident CKD among stone formers, in both adjusted models noted above (HR 1.65, 1.31–2.08, 1.34, 1.05–1.72)	Use of diagnostic codes to capture CKD, which may miss milder disease Stone history being captured by self-report only, which may lead to exposure misclassification

ADPKD autosomal dominant polycystic kidney disease, *BMI* body mass index, *CHD* coronary heart disease, *CI* confidence interval, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *CT* computerized tomography, *DLD* dyslipidemia, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *ESWL* extracorporeal shockwave lithotripsy, *FPG* fasting plasma glucose, *HDL* hyperlipidemia, *HR* hazard ratio, *hsCRP* high-sensitivity C-reactive protein, *HTN* hypertension, *MESA* Marshfield (Wisconsin) Epidemiologic Study Area, *ICD* International Classification of Diseases, *MDRD* Modification of Diet in Renal Disease, *OR* odds ratio, *PNL* percutaneous nephrolithotomy, *RR* risk ratio, *RRT* renal replacement therapy, *SCr* serum creatinine, *SIR* standardized incidence ratio, *SWL* shockwave lithotripsy, *TSH* thyroid-stimulating hormone, *UC* ureteral calculus, *URS* ureteroscopy, *US* ultrasound, *UTI* urinary tract infection

$p < 0.001$

Table 18.3 Other studies on the effects of nephrolithiasis on renal function

Study authors (year, country)	Study design	Sample size	Inclusion and exclusion criteria	Results	Limitations
Ahmadi et al. (2015, Iran)	Cross-sectional	97 total	*Inclusion* Patients who were referred to a teaching hospital urology clinic for ESWL in Tehran, Iran, between 3/2012 and 3/2013, who were at least 18 years old *Exclusion* Elevated SCr >1.3 mg/dL at presentation, presence of signs/symptoms indicative of UTI, previous intake of corticosteroids, history for DM or abnormal FPG, history of HTN or elevated systolic/diastolic blood pressures at visit and abnormal serum TSH	Significant rise in the risk of CKD with each 1 mm rise in renal stone size until 20 mm (OR 1.24, 1.02–1.52) No significant rise in the risk of CKD for stones over 20 mm (OR 0.95, 0.74–1.21)	Small sample size Study population had a high burden of disease compared with epidemiological studies and high intervention rates Lack of generalizability Excluded ureteral stone US, not CT used to detect stones
Sigurjonsdottir et al. (2015, Iceland)	Cross-sectional 1:2 case-control	585 total 195 recurrent stone formers	*Inclusion* Adults age 18–70 years old in Iceland Recurrent stone formers (2 episodes of documented clinical stone events >6 months apart) *Exclusion* Self-reported or diagnosis code showing the presence of renal disorders other than kidney stone disease	Reduced eGFR in stone formers vs. controls[a] Reduced SCr in stone formers vs. controls[a] Number of stone events did not impact renal function Increased prevalence of CKD3 or greater overall[a] Higher prevalence of CKD3 or greater in radiolucent stone formers compared with calcium-containing stone formers[a] Higher SCr and BMI in Ca-containing stone formers than controls[a] Higher prevalence of CKD3 or greater among both radiolucent and Ca-containing stone formers than controls[a] Higher prevalence of HTN in Ca-containing stone formers than controls ($p = 0.02$) No difference in prevalence of DM or CVD in Ca-containing stone formers than controls	Homogenous population (Caucasian, non-Hispanic) Small sample size Low number of radiolucent stones (16)

(continued)

Table 18.3 (continued)

Study authors (year, country)	Study design	Sample size	Inclusion and exclusion criteria	Results	Limitations
Zhe et al. (2016, Multiple)	Meta-analysis	8 cohorts 9 total studies 4,790,691 total patients	*Inclusion* Studies that adhered to ALL of the following: *Population*: General adults w/o history of CKD *Exposure*: Kidney, ureter, and bladder stones *Comparison*: Patients w/o any type of urinary tract stones *Outcome*: Primary: "Any stage of CKD or deterioration of kidney function at least 3 months" Secondary-ESRD or dialysis *Study designs*: Cohort, case-cohort, or nested case-control *Exclusion* Not discussed	Increased risk of developing CKD in stone formers (RR 1.52, 1.24–1.68) Increased risk of ESRD among stone formers (RR 2.16, 1.83–2.54)	Included retrospective studies Majority of patients from two studies Lack of information on stone type Significant heterogeneity Low sample size for subgroup analyses The absence of some entire ethnic groups and populations
Shang et al. (2017, Multiple)	Meta-analysis	7 observational studies 2,810,233 total patients	*Inclusion* Studies that adhered to *all* of the following: Case-control or cohort studies of 18 years or older participants Provided multivariate-adjusted OR, RR, HR, or SIR with 95% CI or sufficient information to calculate these Had a comparison group of participants w/o a history of kidney stones *Exclusion* Nonhuman studies, reviews, comments, editorials, case reports, cross-sectional studies	Increased risk of CKD in patients with nephrolithiasis (RR 1.47, 1.23–1.76) Six of the seven studies included were characterized as having a "good" quality of evidence after review by two independent investigators, using the Newcastle-Ottawa Scale as their assessment tool for study quality The populations exhibited significant heterogeneity[a] Significantly higher risk of CKD (RR 1.98, 1.85–2.11) among individuals with kidney stones in case-control studies compared to their counterparts in cohort studies. This significantly increased relative risk of CKD persisted whether small or large sample studies, Asian and "Western" populations, mean age less than 50 years, and in studies with follow-up of both less and more than 7.5 years and in females Males and age greater than or equal to 50 years showed similar trends, but their RR of CKD did not reach statistical significance	Included retrospective studies Lack of randomized controlled trials available for review Inclusion of studies in which diagnosis was based on ICD codes and telephone interviews alone Significant heterogeneity of study populations Lack of information on stone type Significant heterogeneity, except in case-control studies Low sample size for subgroup analyses

ADPKD autosomal dominant polycystic kidney disease, *BMI* body mass index, *CHD* coronary heart disease, *CI* confidence interval, *CKD* chronic kidney disease, *CVD* cardiovascular disease, *CT* computerized tomography, *DLD* dyslipidemia, *DM* diabetes mellitus, *eGFR* estimated glomerular filtration rate, *ESRD* end-stage renal disease, *ESWL* extracorporeal shockwave lithotripsy, *FPG* fasting plasma glucose, *HDL* hyperlipidemia, *HR* hazard ratio, *hsCRP* high-sensitivity C-reactive protein, *HTN* hypertension, *MESA* Marshfield (Wisconsin) Epidemiologic Study Area, *ICD* International Classification of Diseases, *MDRD* Modification of Diet in Renal Disease, *OR* odds ratio, *PNL* percutaneous nephrolithotomy, *RR* risk ratio, *RRT* renal replacement therapy, *SCr* serum creatinine, *SIR* standardized incidence ratio, *SWL* shockwave lithotripsy, *TSH* thyroid-stimulating hormone, *UC* ureteral calculus, *URS* ureteroscopy, *US* ultrasound, *UTI* urinary tract infection

[a]$p < 0.001$

having a near doubling of risk of CKD/ESRD compared to non-stone formers [13]. A second prospective study, with an effort to develop a CKD/ESRD 5-year risk prediction score in a Northern European population, identified stone-forming females as having upward of a twofold higher risk of developing progressive renal disease; interestingly, this was not found in males [14]. These studies, while prospective in their design, suffered from similar shortcomings as their aforementioned retrospective counterparts. Another potential design flaw of all of the previously mentioned investigations was that the populations studied resided within latitudes not generally associated with high stone rates (as compared to those populations residing in more equatorially based geographic areas where arid conditions generally prevail) [15–21]. However, Shoag et al. surveyed NHANES participants evaluating (self-reported) stone history and its relationship with CKD/ESRD; this was a US study and thus would likely include those from the southern "stone belt" [22]. With just under a 10% response rate, the results mirrored that of the Northern European study with a higher risk of CKD and ESRD (odds ratio of 1.8 and 3.3, respectively) in stone-forming females, not males [22]. Another prospective investigation, spanning four communities in the United States and including over 10,000 Atherosclerotic Risk in Communities (ARIC) participants that were CKD-free (at entry), demonstrated a relationship between nephrolithiasis and CKD after correcting for age, gender, race, and study center (HR 1.29, 1.07–1.54) [23]. However, the association was lost after adjusting for additional variables including HDL, hypertension, urine albumin-to-creatinine ratio, eGFR, diuretic use, smoking status, BMI, diabetes, uric acid levels, history of CHD, and hsCRP [23]. These prospective studies, similar to their retrospective counterparts, have their shortcomings and do not definitively define nephrolithiasis as a risk factor for CKD/ESRD. One additional pitfall of survey-based studies is the tendency of women to respond at higher rates than men, which is particularly important in a disease such as nephrolithiasis, which has higher prevalence among men (potentially excluding a high proportion of individuals with disease) [24, 25]. Furthermore, they do not specifically assess whether urologic intervention for stones may pose risk for future renal disease.

A Taiwanese study assessed the relationship between stone location and stone intervention in CKD and non-CKD groups [26]. The CKD group had a near twofold higher rate of stone disease (regardless of anatomic location) in addition to having more percutaneous or endourologic procedures when compared to the non-CKD group (which underwent more lithotripsy) [26]. A more recent publication by Denburg et al. evaluated CKD (and hypertension) risk in stone-forming English patients undergoing urologic intervention and found a near twofold higher risk of CKD when compared to non-stone formers [27]. Both studies suffer from lack of population heterogeneity as well as offer only the suggestion of association without the ability to assess causation.

Two recent meta-analyses (published in 2016 and 2017) suggest nephrolithiasis nearly doubles the risk of developing CKD/ESRD, but, unfortunately, the weaknesses of the individual studies hinder the strength of their conclusions [28, 29]. Prospective trials with large CKD-free heterogeneous populations comparing urologically intervened nephrolithiasis (with secondary analyses for each type of intervention), non-urologically intervened nephrolithiasis, and nephrolithiasis-free groups are needed to fully assess the relationship between stones and future renal disease.

Part One B: The Relationship Between CKD/ESRD and Nephrolithiasis

While the above-reviewed studies have attempted to address the role of nephrolithiasis (or its management) on future renal disease risk, data on the obverse (the role of renal disease on future nephrolithiasis risk) is less abundant and inconclusive. Worcester et al. demonstrated in a stone-forming population (over 3000 patients) there was no worsening of stone disease in 151 patients following loss of a kidney (by either medical disease or nephrectomy). Additionally, females with only one functioning kidney had reduced urinary levels of calcium and citrate, as well as reduced supersaturations of calcium

oxalate, calcium phosphate, and uric acid; the male subjects had only reduced urinary calcium levels and reduced supersaturations of calcium oxalate and calcium citrate [30]. The generalizability of these results is unclear given the small sample size and the homogeneity of the population (nearly all were Caucasian) [30]. Kadlec et al. retrospectively examined 158 stone formers based on eGFR and analyzed stone type and 24-hour urine chemistries; they found that while supersaturation measurements were no different, uric acid stones and calcium phosphate stones were more common in lower eGFR and higher eGFR groups, respectively [31]. The small sample size, the lack of knowledge for possible confounders, and the limited number of patients with eGFRs < 30 mL/min were substantial limitations of the study [31]. Hung et al. found that stone-free rates 3 months post-lithotripsy were lower in patients with lower eGFRs, but patients with eGFRs < 30 mL/min were excluded, and comorbid conditions such as diabetes and hypertension tended to occur with greater frequency in the lower eGFR group [32]. Finally, Gershman et al. demonstrated that a declining GFR was associated with reduced supersaturations for calcium oxalate and calcium phosphate and urine citrate levels, while supersaturation for uric acid was not changed. The study, however, didn't specifically address the development of nephrolithiasis, didn't adjust for medications used in the study population, and didn't have adequate representation from those with eGFRs < 30 mL/min [33].

Several potential explanations have been considered to describe this association between nephrolithiasis and CKD/ESRD [34–36]. As both CKD and nephrolithiasis have been associated with several other conditions, such as metabolic syndrome, diabetes mellitus, obesity, hypertension, and cardiovascular disease, it would appear that these conditions may share a common origin [37–39]. While one such theory involves the impact of these conditions on urinary supersaturation or pH, the most compelling pathophysiologic descriptions are that of a vascular abnormality origin, linking the initial condition with the downstream complications of these various diseases [40–44]. The renal papilla has been found to be the primary site of calcification (Randall's plaques), and its vascular bed is fraught with areas of turbulent vascular flow, similar to bifurcating coronary and peripheral arteries, also making them vulnerable to cholesterol deposition [40, 45]. Cholesterol may be found within the pathology of many stones. This deposition coupled with the intricate interplay and proximity of vasa recta and collecting tubules creates a nidus for calculus formation [40, 45]. Despite the limited body of evidence, there are epidemiological, clinical, physiologic, anatomic, and molecular findings that support this vascular injury theory as the primary source for stone development.

Part Two: Diseases Associated with Both Nephrolithiasis and Kidney Disease

Diseases associated with both nephrolithiasis and CKD are most often inherited and have various phenotypic patterns (see Table 18.4) leading to them being un-/under-recognized. In this section, we highlight some of the hereditary syndromes associated with kidney stones and renal disease as well as touch on some acquired entities associated with both conditions.

Dent Disease

In 1964, Dent and Friedman reported on two unrelated English boys who on evaluation for childhood rickets were found to have tubular proteinuria, aminoaciduria, phosphate wasting, and hypercalciuria, but with a normal ability to acidify the urine [46]. While not initially described, subsequent evaluation (over a 30-year period) of these and other patients by Wrong and colleagues established nephrolithiasis and renal disease as features of this X-linked recessive syndrome [47]. Dent disease is rare (about

Table 18.4 Inherited disorders associated with nephrolithiasis and CKD

Disease	Gene involved	Location of defect	Type of stone	Nephrolithiasis Age of onset	CKD Age of onset	Other clinical manifestations	Mode of inheritance
Dent 1	*CLCN5*	Proximal tubules	Calcium phosphate, calcium oxalate	Childhood	Adulthood	Hypercalciuria, nephrocalcinosis, hematuria, hypophosphatemia, LMW proteinuria	X-linked recessive
Dent 2	*OCRL1*	Proximal tubules	Calcium phosphate, calcium oxalate	Childhood	Adulthood	Hypercalciuria, nephrocalcinosis, hematuria, hypophosphatemia, LMW proteinuria	X-linked recessive
Primary hyperoxaluria type 1	*AGXT*	Hepatocytes	Calcium oxalate	Childhood	Childhood	Nephrocalcinosis	Autosomal recessive
Primary hyperoxaluria type 2	*GRHPR*	Various cells	Calcium oxalate	Childhood	No known progression	Nephrocalcinosis	Autosomal recessive
Primary hyperoxaluria type 3	*HOGA1*	Various cells	Calcium oxalate	Childhood	No known progression	Nephrocalcinosis	Autosomal recessive
Cystinuria type A	*SLC3A1*	Proximal tubules	Cystine	Childhood	Adulthood	Absent	Autosomal recessive
Cystinuria type B	*SLC7A9*	Proximal tubules	Cystine	Childhood	Adulthood	Absent	Autosomal dominant with incomplete penetrance
APRT deficiency	*APRT*	Hepatocytes	2,8-DHA	Childhood	Childhood	Urinary tract infections, hematuria	Autosomal recessive
FHHNC	*CLDN16/ CLDN19*	Thick ascending loop of Henle	Calcium phosphate, calcium oxalate	Childhood	Childhood/late adolescence	Magnesium wasting, hypercalciuria, nephrocalcinosis	Autosomal recessive
Lesch-Nyhan	*HPRT1*	Hepatocytes	Uric acid	Childhood	Adulthood	Hyperuricemia, gout, dystonia, choreoathetosis, cognitive deficits, and self-destructive behaviors	X-linked recessive
PRPP synthetase superactivity	*PRPS1*	Hepatocytes	Uric acid	Childhood	Adulthood	Hyperuricemia, gout, sensorineural deafness, hypotonia, motor delay, autistic features	X-linked recessive

APRT adenine phosphoribosyltransferase, *FHHNC* familial hypomagnesemia with hypercalciuria and nephrocalcinosis, *PRPP* phosphoribosyl pyrophosphate, *CLCN5* chloride voltage-gated channel 5, *OCRL1* oculocerebrorenal syndrome of Lowe, *AGXT* alanine-glyoxylate aminotransferase, *GRHPR* glyoxylate and hydroxypyruvate reductase, *HOGA1* 4-hydroxy-2-oxoglutarate aldolase 1, *LMW* low-molecular-weight, *SLC3A1* solute carrier family 3 member 1, *SLC7A9* solute carrier family 7 member 9, *CLDN16* claudin 16, *CLDN19* claudin 19, *HPRT1* hypoxanthine phosphoribosyltransferase 1, *PRPS1* phosphoribosyl pyrophosphate synthetase 1, 2,8-*DHA* 2,8-dihydroxyadenine

250 reported families worldwide as of 2010) and is defined by the presence of both low-molecular-weight proteinuria and hypercalciuria along with at least one of the following: nephrolithiasis, CKD, nephrocalcinosis, hematuria, or hypophosphatemia [48, 49]. Kidney stones develop in about half of affected males, while kidney disease typically evolves in the third to fourth decades of life in about two-thirds of patients [47, 50, 51].

Dysfunctional recycling of low-molecular-weight proteins (normally filtered at the glomerulus and reabsorbed in the proximal tubule) due to impaired acidification of endosomes causes Dent disease. Inactivating mutations of either CLCN-5 (encoding the chloride-proton exchanger CLC-5 and found in 60% of affected families; this is termed Dent 1) or OCRL1 (encoding phosphatidylinositol 4,5-bisphosphate 5-phosphatase and found in 15% of families; this is termed Dent 2) have been identified as culprit genes in this disorder. However, 25% of those with the clinical phenotype have no mutations present in either gene [52, 53].

Hypercalciuria, a risk factor for calcareous stone formation, appears to be mediated by 1,25 hypervitaminosis D which, while not fully elucidated, could be the result of impaired reabsorption of the normally filtered low-molecular-weight parathyroid hormone resulting in increased PTH activity in the late proximal tubule. This may also explain the hyperphosphaturia seen in this disease and the finding of nephrocalcinosis (perhaps the result of increased calcium phosphate supersaturation) which is seen in about 75% of patients [54]. Kidney disease appears to be mediated by tubulointerstitial nephritis with glomerular sclerosis, but the mechanisms behind this pathology are incompletely understood; the prevailing hypothesis is that calcium deposition activates an inflammatory cascade resulting in fibrosis [55].

There is no treatment specific to Dent disease with dietary and pharmacologic maneuvers utilized in an attempt to reduce hypercalciuria. As for all stone formers, fluid intake to achieve 2–3 liters of urine output daily is important to reduce calcium supersaturations. Restricting sodium intake to <2 g daily is recommended as excess sodium promotes increased calcium excretion. Alkali-rich diets have been shown to reduce bone demineralization and calcium supersaturations; thus, they may have a role as well [55]. Thiazide diuretics, if hemodynamically tolerated, can be considered owing to their anti-calciuretic effect in the distal tubule (direct action) and increased calcium reabsorption in the proximal tubule (by enhancing proximal tubule sodium reabsorption) [56]. While one would expect the management of proteinuric renal disease to include inhibitors of the renin-angiotensin-aldosterone system (RAAS inhibitors), these medications have not been studied in the Dent population and, given that proteinuria is tubular more than glomerular, may not have a role.

Hyperoxalurias

Oxalate is a metabolic end product that must be excreted from the human body. Hyperoxaluria is excessive urinary oxalate excretion (generally more than 45 mg daily) which may occur via excessive production of oxalate due to various inherited hepatic enzyme deficiencies (termed primary hyperoxalurias (PH)) or because of increased gastrointestinal absorption due to excessive oxalate ingestion or malabsorptive disorders (termed secondary hyperoxalurias) [57].

Primary hyperoxaluria (PH) is a rare autosomal recessive disease that has three known subtypes owing to three different enzyme abnormalities currently identified: PH 1 (found in 80% of cases and due to defective hepatic pyridoxine-dependent alanine-glyoxylate aminotransferase), PH 2 (found in 10% of cases and due to defective non-hepatic glyoxylate reductase/hydroxypyruvate reductase), and PH 3 (found in about 5% of cases and due to defective hepatic mitochondrial 4-hydroxy-2-oxoglutarate aldolase) [58–62]. The defective metabolism of substrate results in various degrees of oxalemia, but all result in hyperoxaluria and oxalate deposition in the kidney (via formation of either calcium oxalate stones or “nephro-oxalosis”) [63]. PH 1, the most common subtype, unfortunately, carries the most significant phenotype with deposited oxalate in the kidney believed to launch an inflammatory

cascade resulting in renal injury [64]. By the fourth decade, patients generally develop ESRD in addition to systemic oxalosis (the impaired urinary excretion of oxalate results in oxalate deposition in various tissues resulting in dysfunction/failure of the heart, vasculature, nervous system, bones, and eyes) [65]. While stones and oxalosis are also seen in PH 2 and PH 3, both are less common as are the end-organ manifestations in the kidney and other tissues [65, 66].

There is no specific treatment for primary hyperoxalurias. Dietary maneuvers aimed at reducing calcium excretion and supersaturation are applied in this condition, but even higher urine volumes are recommended given the high calcium oxalate supersaturations. Pyridoxine may have value in PH 1 [67]. Because systemic oxalate deposition is indirectly related to renal function, a reduction in GFR <30 mL/min requires that renal replacement therapy be initiated (in most other situations, renal replacement therapy begins at much lower GFRs) with preference given to a preemptive kidney transplant (this would also include liver transplant in the PH 1 subtype; there is no value to liver transplant in PH 2). If preemptive transplantation is not an option, extended and/or more frequent dialysis regimens are generally necessary to reduce risk of systemic oxalate deposition [68, 69].

Secondary hyperoxalurias result from increased absorption of oxalate from the gastrointestinal tract. While it would seem logical a diet rich in oxalate would result in enhanced urinary excretion, the bioavailability of oxalate in foods muddies this conclusion. Malabsorptive gastrointestinal processes are important risk factors and serve to paradoxically increase oxalate absorption due to bile and/or fat saponification of calcium, thereby resulting in greater amounts of free oxalate (with no calcium to form salts with) available to be absorbed and, thus, eventually excreted in the urine. Chronic pancreatitis and celiac disease are examples, but perhaps of greater concern is the increased use of bariatric surgery to manage the obesity epidemic [57]. Malabsorptive, as opposed to restrictive, weight loss surgical techniques have demonstrated higher oxalate excretion rates with greater risk of nephrolithiasis and nephro-oxalosis [70].

Cystinuria

Cystinuria, a rare disorder affecting 1 in 7000 patients and accounting for ~1% of all kidney stones in adults (~25% in children), is the result of a defective dibasic amino acid transporter in the proximal tubule leading to increased excretion of the COLA amino acids: cystine, ornithine, lysine, arginine [49]. To date, mutations in two genes whose products make up the heterodimer complex, SCLC3A1 (encoding the glycoprotein, rBAT, which anchors the transporter to the brush border) and SLC7A9 (encoding $b^{0,+}$AT which functions as the transporting component), have been identified as culprits for the defective reabsorption of COLA [71, 72]. Autosomal recessive inheritance is seen with defects in the former gene (termed type A cystinuria), while it has been recently demonstrated that mutations in SLC7A9 result in autosomal dominant disease with incomplete penetrance (termed type B cystinuria) [73]. Should there be a mutation in SLC3A1 and the contiguous PREPL gene (encoding prolyl endopeptidase-like protein), cystinuria-hypotonia syndrome results in which affected individuals are developmentally delayed, hypotonic, hyperphagic, and heavier and suffer from cystine stones [74]. While all four amino acids are expelled in the urine, the latter three amino acids have high solubility characteristics; cystine, however, does not, such that the enhanced excretion leads to augmented supersaturations favoring crystallization [75].

Preventive measures again include dietary recommendations as previously outlined, but because of the high supersaturations often seen in this condition, greater urine volumes are needed as is urinary alkalinization (cystine solubility is directly related to urine pH) [72]. If these measures fail to control the disease, thiol-containing medications (such as penicillamine and tiopronin) which interfere with cysteine-cysteine disulfide bonding can be tried; however, systemic side effects (viz., hepatic dysfunction, blood cell dyscrasias, and proteinuria) may limit their use [76].

Kidney disease can develop in patients with cystinuria, although the mechanisms underlying the dysfunction have not been elucidated. Prevailing theories include the multiple urologic procedures generally needed and often starting at a young age, repeated obstructive insults, calcium phosphate deposition (perhaps the result of urine alkalinizing therapy), and the glomerular dysfunction that may develop with the use of thiol-containing drugs [77]. Should ESRD develop, renal transplantation can be considered as the donor kidney should likely have normal handling of the dibasic amino acids.

Adenine Phosphoribosyltransferase (APRT) Deficiency

APRT deficiency, a rare autosomal recessive disease affecting 1 in 50,000–100,000 individuals, is characterized by abnormal activity of the APRT enzyme that impairs the conversion of adenine to adenosine monophosphate, thereby leading to increased production of 2,8-dihydroxyadenine (DHA) by xanthine dehydrogenase [78, 79]. 2,8-dihydroxyadenine is excreted in urine where it is poorly soluble. The excretion of this poorly soluble substance can result in nephrolithiasis, while interstitial deposition and intratubular plugging has been associated with kidney disease. While an inherited condition, many affected individuals will not present until adulthood with chronic kidney disease developing insidiously [66, 80].

In addition to recommending high urine volumes, treatment requires the lifelong use of a xanthine oxidase inhibitor such as allopurinol or febuxostat. Restriction of dietary purines may also provide some benefit, but urine alkalinization does not appear to have a role in this condition [79, 81].

Familial Hypomagnesemia with Hypercalciuria and Nephrocalcinosis (FHHNC)

Originally named Michelis-Castillo syndrome, familial hypomagnesemia with hypercalciuria and nephrocalcinosis (FHHNC) is a rare autosomal recessive disorder characterized by renal magnesium wasting, hypercalciuria, nephrocalcinosis, and kidney failure [82, 83]. Defects in either of the tight junction proteins claudin-16 and claudin-19, which normally allow for the paracellular reabsorption of divalent cations driven by the potassium recycling in the loop of Henle, result in calcium and magnesium wasting [84]. The resulting hypoelectrolytemias can result in abdominal pain, tetany, and seizures, while the hypercalciuria may increase the risk of kidney stones, nephrocalcinosis, and renal failure. Claudin-19 is also found in the eye such that various retinal pathologies can be seen in individuals afflicted with this defective protein. While the mechanisms behind the development of kidney disease remain unclear, claudin-19 disease seems associated with a higher risk of CKD when compared to those with claudin-16 disease, and ESRD can often manifest in late adolescence [33, 85].

No treatment to date, outside of renal transplantation, has demonstrated benefit in this disease [82, 85].

Inborn Errors of Purine Metabolism

Inborn errors of purine and pyrimidine metabolism may be associated with nephrolithiasis. They represent 1–3% of renal stones in children in France [86]. They are characterized by hyperuricemic hyperuricosuria, which increases the risk of uric acid stones.

Lesch-Nyhan syndrome is an X-linked recessive disorder due to deficiency of hypoxanthine-guanine phosphoribosyltransferase (HGPRT) activity, which leads to excessive uric acid production. Uric acid overproduction is associated with nephrolithiasis and gout. Its prevalence is estimated at 1 in 380,000 live births in Canada [87]. Additional symptoms include dystonia, choreoathetosis, cognitive deficits, and self-destructive behaviors, all of which can present in varying degrees [88]. In the absence of appropriate treatment, patients develop recurrent uric acid nephrolithiasis and are at increased risk of obstruction and chronic renal failure.

Phosphoribosyl pyrophosphate (PRPP) synthetase superactivity, another X-linked recessive disorder, is characterized by enhanced production of PRPP (a precursor of uric acid) from sugars and manifests as gouty arthritis and uric acid nephrolithiasis [88]. It usually begins early in a young male's life with some progressing to ESRD later on in adulthood. Other clinical manifestations involve sensorineural deafness, hypotonia, motor delay, and autistic features [89].

Treatment of both of these disorders involves the use of xanthine oxidase inhibitors, thereby decreasing the production of uric acid. Doses of these agents need to be adjusted to reach a target concentration of plasma uric acid of 0.4 mmol/L while avoiding the risk of oxypurinol crystallization [90]. Additional measures include a low purine diet and high fluid intake.

Part Three: Therapeutic Considerations in CKD Patients with Nephrolithiasis

A decrease in GFR will reduce clearance of all measured substances while tubular dysfunction can further alter solute excretory rates. Thus, the presence of CKD is unlikely to allow for reliable metabolic risk patterns in nephrolithiasis patients with 24-hour urine studies. Confirmatory literature in this area is scant such that no guidelines or recommendations currently exist for use of urine chemistries in CKD patients with nephrolithiasis [91].

Management of nephrolithiasis in patients with CKD/ESRD lacks significant evidence to support decision making and is largely focused on balancing potential risks associated with both diseases. For instance, caution must be made with volume of intake to not exacerbate fluid retention or other comorbid conditions [92]. While thiazides may be helpful in the treatment of calcium oxalate stones in the general population, their efficacy may wane in those with advanced CKD, particularly as eGFR falls below 30 mL/min [93, 94]. For treatment of uric acid stone disease, alkalinizing agents are the staple of therapy, with potassium citrate serving as the predominant medication of choice. However, in patients with concurrent CKD, which may also warrant the use of ACE inhibitors or ARBs to preserve renal function, hyperkalemia becomes a significant concern. An alternative, sodium bicarbonate, may be associated with worsening of hypertension and increased calcium secretion (both owing to the sodium load), potentially leading to increased risk of calcium-based stones [95]. Allopurinol for hyperuricosuria must be dosed appropriately and used cautiously in those with CKD [96].

Summary

CKD and nephrolithiasis are two common entities that are increasing in prevalence and are associated with high costs. While there is some evidence to suggest each has an impact on the development of the other, the strength of evidence is weak. If, indeed, there is a relationship, causality has not yet been elucidated nor has the question of how management of one condition may reduce the risk of the other.

However, health-care providers must recognize that nephrolithiasis in a young patient may very well indicate an inherited condition that could result in future kidney disease. As such, these patients require very close monitoring.

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Chapter 19
Nephrolithiasis in Kidney Transplant

Nitender Goyal

Keywords Kidney transplant · Kidney stones · Nephrolithiasis

Abbreviations

AKI	Acute kidney injury
ESRD	End-stage renal disease
ESWL	Extracorporeal shock wave lithotripsy
PCNL	Percutaneous nephrolithotomy
RTA	Renal tubular acidosis

Key Points
- Nephrolithiasis is uncommon after kidney transplant but can lead to significant morbidity because of isolated functioning kidney and immunocompromised state.
- Risk factors for nephrolithiasis in kidney transplant recipients are metabolic derangements, recurrent urinary tract infections, and mechanical predisposition.
- Presentation is often asymptomatic because of renal denervation in allograft. Occasionally, patient can present with hematuria, acute kidney injury, or urosepsis.
- Management is often multimodal and is associated with good outcomes.

Introduction

Urologic complications are common in kidney transplant recipients and include hydronephrosis, urinary leak, ureteral stricture, nephrolithiasis, and vesicoureteral reflux. These complications can lead to significant morbidity and loss of allograft function [1]. Incidence of nephrolithiasis is low after kidney transplantation. Different studies have reported different frequencies of kidney stones in kidney transplant recipients. Rhee et al. reported an incidence of 0.4% after a mean follow-up of 68.6 months

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[2]. Mamarelias et al. and Ferreira Cassini et al. reported an incidence of 0.44% and 1.29% among 2045 and 1313 kidney transplant recipients respectively [3, 4]. An analysis of New York Statewide Database suggested an incidence of 2.8% [1]. Rezaee-Zavareh et al. in an Iranian study reported an incidence of as high as 4.4% [5]. However, there is significant heterogeneity among these studies with different diagnostic methodology and follow-up duration. A recent meta-analysis showed an incidence of 1% and a mean duration of 28 ± 22 months to diagnosis of a kidney stone after transplantation [6]. As in the general population, the majority of kidney stones (67%) in kidney transplant recipients are calcium-based stones (30% mixed calcium oxalate/calcium phosphate, 27% calcium oxalate, and 10% calcium phosphate), but the percentage of struvite stones (20%) is higher than in the general population [6]. Increased incidence of struvite stone is likely because of higher risk of urinary tract infection in kidney transplant recipients. Verrier et al. reported a decrease in incidence of kidney stones over time (2.1–0.6% during the three decades) in a single center and attributed it to use of double J stent and early treatment of ureteral obstruction [7].

Risk Factors

Kidney stones in the transplanted kidney can be of donor origin or newly formed in the graft after transplantation. Although living donors with recurrent or symptomatic kidney stones are not accepted, many centers allow donation from patients with a small incidental kidney stone noted on imaging. The presence of renal calculi in deceased donor kidney is not a reason to refuse the organ for transplantation [8]. There are multiple predisposing factors for de novo stone formation in the transplanted kidney. Although there is limited data on urinary supersaturation in kidney transplant recipients, many studies have reported increased risk of kidney stones with hyperparathyroidism, hypercalcemia, hypercalciuria, hypocitraturia, hyperuricosuria, hypophosphatemia, and recurrent urinary tract infection [6, 7, 9–12]. Calcineurin inhibitors are the most commonly used immunosuppressive drugs posttransplant and may cause renal tubular acidosis (RTA) by decreasing urinary ammonium excretion. RTA leads to hypocitraturia by increasing proximal tubular reabsorption of citrate [13]. Uncommonly, urinary outflow obstruction mainly due to ureteral stenosis and the presence of foreign body like ureteral stent and suture material are associated with increased risk of kidney stone formation [6, 7, 9]. Urinary anastomosis type is significantly associated with risk of bladder stones. Anastomosis in an enterocystoplasty or an ileal conduit is associated with a higher risk of bladder stones [7, 10].

Most studies and systematic review did not show increase in the incidence of uric acid stone despite increased incidence of hyperuricemia and gout in transplant recipients. This may be explained by high urinary pH from partial RTA.

Clinical Presentation

Nephrolithiasis in kidney transplant recipients is often asymptomatic due to renal denervation and is diagnosed incidentally on imaging. Some patients may present with hematuria, oliguria, anuria from urinary outflow obstruction, and elevated serum creatinine [10, 12]. Urinary tract infection and sepsis in some may indicate nephrolithiasis. Single functioning kidney and immunocompromised state put transplant patients at risk for serious complications. Therefore a high index of clinical suspicion is required, and any patient with unexplained fever should undergo imaging (renal ultrasound or computed tomography (CT)) to rule out renal calculi. Occasionally nephrolithiasis is noted at the time of ureteral stent removal or inability to remove stent because of stone encrustation [10, 12].

Management

Diagnosis and management are similar to general population and is often multimodal. Ultrasound is the most important diagnostic tool. Other investigations may include plain abdominal X-ray, computed tomography, intravenous urography, and nephrostogram [10]. For non-obstructing stones < 1.5 cm in size, treatment with extracorporeal shock wave lithotripsy (ESWL) is usually sufficient [10]. Multiple ESWL sessions are sometimes required. ESWL should be performed with the patient in prone position due to potential difficulty in locating transplant calculi because of overlying bony pelvis [10]. Obstructing stones require nephrostomy tube insertion or double J ureteric stent placement to relieve obstruction followed by one or more session of ESWL. Flexible ureteroscopy with basket extraction or in situ lithotripsy is needed in cases of unsuccessful ESWL. Percutaneous nephrolithotomy (PCNL) provides the best success for stones > 1.5 cm [10]. Bladder stones can be successfully treated with instrumental fragmentation during cystoscopy with endolithotripsy [7]. Occasionally, open pyelolithotomy for staghorn calculi after an unsuccessful PCNL and open cystolithotomy for multiple bladder stones is needed [10]. Smaller non-obstructing stones can be managed with surveillance [7].

There is very little data about medical management of nephrolithiasis prevention in transplant recipients. Patients with hypercalcemia due to tertiary hyperparathyroidism may warrant parathyroidectomy to prevent recurrence of kidney stones [9]. Cinacalcet is used sometimes in treating hyperparathyroidism. However, there are some studies showing that cinacalcet may increase hypercalciuria but there was no increase in calcium deposits on kidney biopsies of patients who received cinacalcet after 18 months of treatment. There are no clinical recommendations on not using cinacalcet in kidney stone patients with hyperparathyroidism and hypercalciuria, but parathyroidectomy would be the treatment of choice in that case. Thiazide diuretics are usually avoided as standard practice in transplant recipients because of concern in the rise in creatinine and probably better avoided for hypercalciuria in nephrolithiasis patients.

Allopurinol and febuxostat are contraindicated in patients who are on azathioprine as it is metabolized by xanthine oxidase [14]. Hyperkalemia is not uncommon in kidney transplant recipients who are on CNI, and one has to be cautious with potassium citrate.

Outcomes

Urinary stones in kidney transplant recipients can be a potential threat due to risk of obstruction in single functioning kidney, sepsis in immunocompromised host, and potential loss of allograft function. Rezaee-Zavareh et al. reported no significant association between kidney stones and allograft survival [5]. With timely management, Kim et al. found no significant changes in renal allograft function at diagnosis and after stone removal [9].

Summary

Nephrolithiasis is uncommon in kidney transplant recipients. However, the risk of complications is greater in this population. Metabolic risk factors for kidney stone formation like hypercalcemia, hypercalciuria, hyperparathyroidism, hypocitraturia, and hyperuricosuria are present in the majority. Other predisposing factors may include recurrent UTI, ureteral obstruction, and the presence of postsurgical foreign body. Stones in kidney transplant recipients are often asymptomatic because of

renal denervation at the time of organ procurement and transplantation, but patients may present with hematuria, oliguria, anuria, elevated serum creatinine, and sepsis. Management is multimodal and is similar to general population. Outcomes are good with timely management of nephrolithiasis.

Patient Case

HPI

A 61-year-old female with end-stage renal disease (ESRD) secondary to lupus nephritis received a deceased donor kidney transplant after being on dialysis for 8 years. She had immediate allograft function with a nadir creatinine of 0.84 mg/dL/1.73 m^2. Basiliximab was used for induction and tacrolimus, mycophenolate mofetil, and prednisone for maintenance of immunosuppression.

Medical History

ESRD from lupus nephritis, obesity, hypertension. hyperlipidemia, tertiary hyperparathyroidism, and anemia of chronic kidney disease

Surgical History

Deceased donor kidney transplant

Medications

Mycophenolate mofetil, tacrolimus. prednisone, simvastatin, omeprazole, cinacalcet, trazodone, citalopram, magnesium oxide, potassium and sodium phosphate, sulfamethoxazole/trimethoprim, valganciclovir

Posttransplant Course

Patient developed hypercalcemia and hypophosphatemia early posttransplant in the setting of tertiary hyperparathyroidism and was initiated on cinacalcet and phosphorus supplement. Parathyroid hormone remained elevated at greater than 1000 pg/mL despite titrating up the cinacalcet dose, and the patient had multiple hospitalizations for acute kidney injury (AKI) in the setting of hypercalcemia. Patient underwent 3.5 parathyroidectomy 4 months posttransplant. Post-op course was complicated by AKI, and renal ultrasound revealed moderate hydronephrosis. Computed tomography (CT) scan showed hydronephrosis with hydroureter and obstructing calculus in distal ureter. Patient had percutaneous nephrostomy tube placement to relieve obstruction and underwent cystoscopy and ureteroscopy of transplant ureter with basket stone extraction of multiple transplant ureteral stones. Follow-up CT

scan showed interval placement of nephrostomy tube in right pelvis and resolution of the hydronephrosis. Persistent allograft hydroureter and multiple ureteral stones were again noted. She underwent successful PCNL without evidence of stone recurrent after 6 months of follow-up. Stone analysis revealed mixed calcium oxalate and calcium phosphate stones.

Conclusion

Persistent hypercalcemia in the setting of tertiary hyperparathyroidism can increase risk of nephrolithiasis in kidney transplant recipients. Early parathyroidectomy in patients with persistently high PTH levels and hypercalcemia might prevent this complication.

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Chapter 20
Nutritional Management of Nephrolithiasis in Chronic Kidney Disease

Haewook Han, Pamela S. Kent, and Judith A. Beto

Keywords Chronic kidney disease (CKD) · Nephrolithiasis · 24-hour urine test · Nutrition assessment Nutrition recommendations · Renin-angiotensin-aldosterone system (RAAS) inhibitors · Calcium stones · Uric acid stones · Cystine stones

Key Points

- Some risk factors for kidney stones (nephrolithiasis) are similar to those leading to chronic kidney disease (CKD) such as diabetes, hypertension, and obesity.
- The primary goal of nutritional management for CKD is to maintain or improve the nutritional status by slowing the progression of kidney disease, and the goal of kidney stone management is to prevent recurrence.
- Nutrition assessments of both CKD and kidney stones include anthropometric, biochemical indices including blood tests and urinalysis (24-hour urinalysis for stone), clinical indices, diet history to identify meal patterns, and drug-nutrient interactions.
- Nutrition recommendations for stone patients with CKD should be based on the type of stones and patients' medical conditions. A combination of American Urology Association (AUA) guidelines and Kidney Disease Outcome Quality Initiative (KDOQI) recommendation is appropriate for development of diet plan for patients with CKD and kidney stone prevention.
- Overall nutrition recommendations are increase of fluid intake >3 L/day, low sodium (2000–2300 mg/day), adequate amount of dietary calcium, moderate amount of protein (especially low in animal protein), and healthy eating pattern such as Dietary Approaches to Stop Hypertension (DASH) diet with close monitoring of blood test and urinalysis.

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Introduction

Prevalence of chronic kidney disease (CKD) in the United States continues to increase over the past few decades. Causes of CKD include diabetes, hypertension, polycystic kidney disease (PKD), obesity, and other known/unknown medical conditions [1]. Risk factors for kidney stones (nephrolithiasis) are similar with selected CKD causes such as diabetes, hypertension, and obesity. Dietary intervention is important to control or reduce disease progression. In addition, risk factors for kidney stones include genetic, disease-related, environmental, and dietary factors [2–5]. Table 20.1 summarizes the risk factors for stone formation in CKD.

The published studies to investigate the relationship between CKD and nephrolithiasis have not been conclusive. The detailed summary is addressed in the medical management section of this chapter.

Reduced filtration in CKD can lower excretion of renal solutes such as calcium, oxalate, citrate, sodium, potassium, magnesium, and phosphate [2, 3]. Table 20.2 shows the possible risks of stone formation by the standardized stages of CKD. The most common stone type in the general population is calcium stones (calcium oxalate mixed with calcium phosphate) followed by uric acid stones. Low urine pH promotes both calcium oxalate and uric acid stone risks. For these stone formers, alkalization of urine is critical to lower stone risks especially patients with low citrate levels. However, low level of urinary citrate in patients with CKD may not be as important as patients with normal kidney function [2–5].

Nutritional intervention for kidney stone prevention in CKD is similar to all other stone management interventions. Nevertheless, additional dietary restrictions are required for stone formers with CKD. Nutritional management of CKD and stones is based on CKD status and type of stones to prevent recurrence of stone formation [2–5]. This section provides practical guidelines for stone and CKD management.

Table 20.1 Risk factors for stone formation in chronic kidney disease

Hereditary and other disease states		Environmental	
Category	Risk factors	category	Risk factors
Genetic	Idiopathic hypercalciuria Primary hyperoxalosis Cystinuria Dent's disease APRT deficiency FHHNC Inborn errors of purine metabolism (uric acid stone)	Climate	Heat water loss, sweating
Kidney disease related	Medullary sponge kidney PKD (10% develop stones) Horseshoe kidney Metabolic causes: hypercalcemia, secondary hyperparathyroidism, DM, and obesity	Dietary	Na Oxalate Protein (animal) Acid/alkaline ash diet Fluid Potassium and citrate Fluid Vitamins (C, D) Ca supplement Low Ca diet High-protein weight-loss diet
Systemic disease	GI, inflammatory bowel diseases (Ox and UA stones)		
Hyperparathyroidism	CaP stone		
Renal tubular acidosis (RTA)	hypercalcemic states, Ca phosphate		
Sarcoid	Hypercalciuria, CaOx stone		
Gout	Uric acid stone		

References: [2–5]

ARPT adenine phosphoribosyltransferase, *Ca* calcium, *CaOx* calcium oxalate, *CaP* calcium phosphate, *DM* diabetes mellitus, *FHHNC* familial hypomagnesemia with hypercalciuria and nephrocalcinosis, *GI* gastrointestinal, *Na* sodium, *Ox* oxalate, *PKD* polycystic kidney disease, *UA* uric acid

Table 20.2 Risk for stone formation by stage of chronic kidney disease

CKD stage	eGFR	Risk for stone formation	Comment
Stage 1	>90 ml/min/1.73m^2	↑↑↑	Normal kidney function with good filtration rate
Stage 2	60–89 ml/min/1.73m^2	↑↑	Slightly decreased filtration but still close to normal
Stage 3a Stage 3b	45–59 ml/min/1.73m^2 30–44 ml/min/1.73m^2	↑	Decreased filtration rate so less solutes in the urine
Stage 4	15–29 ml/min/1.73m^2	↓	Further decrease of filtration so risk goes down
Stage 5	<15 ml/min/1.73m^2	↓↓	Risk continues to decrease with GFR
Stage 5D ESRD on dialysis		No risk	No risk of stone formation without kidney function

References: [2, 3, 6]
CKD chronic kidney disease, *eGFR* estimated glomerular filtration rate, *ESRD* end stage renal disease

Nutritional Management of CKD and Nephrolithiasis

The primary goal of nutritional management for CKD is to maintain or improve the nutritional status by slowing the progression of kidney disease through control of diabetes, hypertension, electrolyte balance, mineral bone disease management, and other risk factors of CKD [2, 7–9].

Nutrition assessments for CKD include anthropometric measurement, evaluation of biochemical indices, clinical assessment, and dietary analysis [9–11]. In nephrolithiasis, the overall nutritional assessments are similar to those of CKD. However, biochemical indications especially urinalysis and specific dietary analysis have more weight to evaluate stone risk factors [2, 4, 12]. These analyses can guide nutritional interventions for the prevention of recurrence of stones.

Nutrition Assessment

Dietary Intakes and Eating Pattern

Nutrition assessment is very important in both CKD and stone risk. Dietary intake data should be used in treating and preventing stone formation. The dietitian should evaluate dietary intakes of calcium, oxalate, sodium, protein (both animal and plant), dietary supplements, and fluid intake since these can either promote or inhibit stone formation. The therapeutic diet is based on this nutrition assessment information [9–11].

There are several dietary assessment methods: the 24-hour recall, food record, usual diet history, and food frequency questionnaire. These are commonly used to evaluate dietary assessments for both CKD and stone patients. In nephrolithiasis, the dietary intakes should be reflected from the urinalysis as an effective way to evaluate the causes of kidney stones and to prevent recurrence [13]. Food records compared with 24-hour recall and food frequency questionnaires provide more accurate information on specific intake of foods, beverages, and dietary supplements such as over-the-counter vitamins, minerals, and herbal supplement. Food frequency questionnaires are not commonly used for among CKD or nephrolithiasis patients although it can provide a better dietary pattern. The most appropriate diet assessment for kidney stones is the food record prior to 24-hour

urine collection, which reflects the urinalysis. The food record should be analyzed to evaluate intakes of protein, sodium, potassium, calcium, phosphorus, magnesium, uric acid, oxalate, and fluid [7, 9–14].

Fluid intake is particularly important to quantify. Some elderly CKD patients develop hyponatremia with a large quantity of free water; therefore, patients with CKD with stone risks should be more careful to consume free water [15, 16]. Based on the food intake and urinalysis, the clinicians can provide adequate medical and dietary treatments.

Anthropometric Measurement

Anthropometric measurement is an important tool to assess nutritional status, but it is more valuable for patients with CKD to evaluate patient's nutritional risks with progression of CKD. High body mass index (BMI) is positively correlated to risk of nephrolithiasis with increased risk of metabolic disease such as diabetes and hypertension. Different methods and calculations of body weight are used in nutritional assessments [10, 17–24].

Standard Body Weight The standard body weight is the median body weight of a normalized sample of adults of the same height, gender, skeletal frame size, and age range from National Health and Nutrition Survey (NHANES) data. This is based on a randomized sample of adults during the survey. There are two age groups: younger adults and older adults [17, 24].

Desirable Body Weight The desirable body weight is based on published Metropolitan Life Insurance Height and Weight Tables for Adults.

Gender Differences Male and female ideal body weight can be calculated by following formula, but this method is not population based.

Male: 106 lbs. for 5 feet, and then add 6 lbs. for each additional inch

Female: 100 lbs. for 5 feet, and then add 5 lbs. for each additional inch [17, 18, 23]

In the practice of CKD management, dietitians use adjusted body weight (ABW) for the obese and underweight patients [9–11]. The following is the Kidney Disease Outcome Quality Initiative (KDOQI) guidelines to calculate ABW [23].

ABW ABW weight is used for obese or lean patients who are <95% or >115% standard body weight.

$$\text{Adjusted body weight}\left(\text{ABW}\right) = \text{edema free BW} + \left[\left(\text{standard BW} - \text{edema free BW}\right) \times 0.25\right]$$

This weight adjustment is important for stone patients to provide an adequate amount of dietary protein. The general protein recommendation of 0.8–1.2 gm/d/kg is used as a guideline. Daily protein intake as well as the source of protein (animal, plant, biological value) needs to be individualized. For example, proteinuria may focus on a moderate level of protein to potentially slow the progression of CKD. High-protein intake for nephrolithiasis patients increases stone risks by increasing calcium in the urine with lower urine pH, especially with high animal protein diet [7, 9–12, 22, 25–27].

Biochemical Indices: Blood and Urine Tests

Both blood and urine tests are necessary to evaluate risk factors of nephrolithiasis. If a patient had a stone analysis, the dietary and medical interventions will be based on the stone type. However, many stone patients do not know the type of stones. Blood and urine tests are therefore important to identify risk factors for various types of stone prevention. Blood creatinine, electrolytes, albumin, mineral bone disease panel (calcium, phosphorus, parathyroid hormone, and 25[OH]D3), and both urine microalbumin and protein levels are usually routinely monitored for CKD patients. For patients with kidney stones, stone panels may be similar to regular CKD monitoring with the addition of uric acid and magnesium levels. If a patient consumes a high-purine diet such as high animal protein, this can lower urine pH which can increase uric acid stone risks [28–30]. Table 20.3 summarizes acceptable ranges of the blood tests for both CKD and nephrolithiasis.

Urine tests are the major tests to evaluate risks of types of stones. Urinalysis is more important if there is no stone analysis available. A 24-hour urine collection should be performed to measure urine volume, urinary calcium, oxalate, uric acid, pH, creatinine, and citrate. Some laboratories calculate supersaturation values for calcium oxalate, calcium phosphate, and uric acid. These specific parameters are particularly helpful for treatment interventions [13, 15, 16].

The best way to evaluate stone risk is a 24-hour urine collection and analysis [15, 16]. Two 24-hour urine collections are recommended for the initial evaluation for an accurate analysis and to determine variability. The 24-hour urine collection should be done 6–8 weeks after stone removal procedures such as lithotripsy in order to minimize the risk of result being influenced by infection or the presence of blood due to these causes. Infection can change the pH and citrate levels. It is very important that patients continue with their usual diet and activities during the collection period. The 24-hour urine creatinine excretion can give information about the adequacy of the urine collection [13]. In general, adult males produce 18–24 mg creatinine/kg/d and females 15–20 mg/kg/d. The accuracy of a 24-hour urine collection can be assessed by urinary creatinine levels which will be higher than normal for over-collection and lower than normal for under-collection [13, 15, 16].

The 24-hour urine sample should include volume and the individual solutes (calcium, phosphorus, oxalate, citrate, pH, and uric acid) to provide an estimate of supersaturation and the risk of stone formation. Creatinine is tested to ensure full collection and to normalize solute excretion to the more constant amount of creatinine. Dietary factors include sulfates which are mostly from animal protein and sodium since they are related to calcium, potassium, and magnesium excretion. Urea nitrogen is used to estimate protein catabolic rate (PCR). The PCR is usually indicative of dietary protein intake in an individual who is not in a catabolic state. The relationship between urinary nitrogen appearance rate and estimated dietary protein intake is then calculated. The value of the 24-hour urine is to evaluate dietary nutrients and fluid intakes and to provide guidance for the patient's management [13, 16]. For example, normal urinary calcium levels are <250 mg/d for men and <200 mg/d for women. High urinary calcium may be caused by idiopathic hypercalciuria, or diets high in sodium or protein. Low urinary calcium is often due to malabsorption or underlying bone disease. High urine oxalate levels may be due to a high-oxalate diet, increased endogenous production, high vitamin C consumption, and/or inflammatory bowel disease. High animal protein diets and renal tubular acidosis (RTA) can lower urine pH with low urinary citrate by increasing proximal tubule reabsorption of citrate [2, 30–32].

Table 20.3 Serum laboratory parameters with variations for chronic kidney disease and nephrolithiasis

	Normal range	CKD comment	Nephrolithiasis comment
Creatinine	0.5–1.1 mg/dL female 0.6–1.2 mg/dL male	2–15 mg/dL: varies by stages	Higher in CKD, obstructive uropathy
eGFR	>90 ml/min/1.73 m2	Varies among 5 stages of CKD: decreases with CKD progression	Lower with CKD Usually in the normal range
Albumin	3.5–5.0 g/dL	Lower: malnutrition or urinary protein loss, fluid retention, infection Higher: dehydration	Normal range
Calcium	8.5–10.2 mg/dL	Lower: advanced CKD due to low active vitamin D, post-parathyroidectomy Higher: Secondary hyperparathyroidism ??? or too much Ca supplement, lithium nephropathy	Lower: bowel disease with malabsorption, hypoparathyroidism Higher: hyperparathyroidism (primary), thiazide medication, sarcoidosis
Phosphorus	2.5–4.5 mg/dL	CKD range: 3.5–5.5 mg/dL Lower: vitamin D deficiency, excess phosphorus binding in late stage of CKD, diuretic treatment, alcoholism Refeeding syndrome (posttransplant), Malabsorption Higher: advanced CKD	Lower: idiopathic hypercalciuria with primary hyperparathyroidism, excess active vitamin D with sarcoidosis
Parathyroid hormone	10–65 pg/ml	Acceptable range varies with advanced stage of CKD Lower: hypoparathyroidism, hypercalcemia, sarcoidosis, hypomagnesemia Higher: hyperparathyroidism, hypercalcemia, malabsorption, vitamin D deficiency, lithium use	Lower: vitamin D excess, sarcoidosis Higher: primary hyperparathyroidism, vitamin D deficiency
Total vitamin D (25-OH-D2 and 25-OH D3)	30–100 pg/ml	Lower: vitamin D deficiency, sarcoidosis Higher: vitamin D toxicity	Lower: vitamin D deficiency, sarcoidosis Higher: vitamin D toxicity
1,25 (OH)2 D3	18–64 pg/ml male 18–78 pg/ml female	Lower: vitamin D deficiency	Higher with sarcoidosis
Uric acid	1.7–7.5 mg/dL	Usually normal Higher with diuretics, gout	Lower: pregnancy, renal hypouricemia Higher: gout, diuretics
Magnesium	1.5–2.5 mg/dL	Lower: posttransplant Higher: advanced CKD	Lower: bowel disease, thiazide use
Potassium	3.5–5.0 mEq/dL	Lower: diuretics, alcohol abuse, diarrhea/emesis, malabsorption, correction of diabetic acidosis Higher: CKD, acidosis, dehydration, hyperglycemia, ACEI/ARB use, K sparing diuretics, excess dietary K intake	Lower: thiazide use Higher: K-citrate with ACEI/ARB use in CKD, acidosis
CO_2	23–30 mEq/L	Lower: metabolic acidosis Higher: metabolic alkalosis	Lower: renal tubular acidosis Higher: diuretics, chronic pulmonary disease

References: [2, 7–11]

ACE angiotensin-converting enzyme inhibitors, *ARB* angiotensin II receptor blockers, *CKD* chronic kidney disease, *eGFR* estimated glomerular filtration rate, *K* potassium

Table 20.4 Normal ranges of 24-hour urine collection with probable causes of abnormal values

	Normal value	Probable cause of abnormal value
Calcium (Ca)	<250 mg/d for males <200 mg/d for females	↑ idiopathic hypercalciuria, high Na diet (high urine Na) High-protein diet ↓ with bone disease
Phosphorus (P)	0.6–1.2 g/d	↓ with bowel disease, malnutrition, with large amounts of food intake
Magnesium (Mg)	30–120 mg/d	↓ with some laxatives, malnutrition, malabsorption
Oxalate (Ox)	20–40 mg/d	↑ with high-oxalate diet, high vitamin C consumption if >80, intestinal (Inflammatory bowel disease) or oxalosis
Citrate	>450 mg/d males >550 mg/d females	↓ RTA, hypokalemia, high animal protein diet, acidosis, diarrhea
Uric acid (UA)	<0.8 g/d males <0.75 g/d females	↑ with high animal protein diet (high purine), alcoholic beverages, overproduction
Volume	>2000 ml/d	↓ with low fluid intake
pH	5.8–6.2	↓ RTA, urea-splitting infection, acidosis, high animal protein intake (high-purine content) ↑ vegetarian diet, high citrus consumption, soft drink
Sodium (Na)	50–150 mEq/d (1150–3450 mg)	↑ with high Na diet ↓ with low volume
Potassium (K)	20–100 mEq/d	<20 mEq bowel disease, diuretics, laxatives
Chloride (Cl)	70–250 mEq/d	
Urea nitrogen	6–14 g/kg/d	↑ with high-protein diet
PCR	0.8–1.4 g/d	↑ with high-protein diet
Sulfate	20–80 mEq/d	↑ with high-protein diet
Ammonium	15–60 mM/d	↑ pH > 7 urea-splitting infection ↓ pH < 5.5 CKD, UA stones, gout
Creatinine	18–24 mg/kg for males 15–20 mg/kg for females	↑ with more than 24-hour collection ↓ with under-collection

References: [2, 16, 31, 32]
Range: Courtesy from Litholink Corporation, Chicago, IL [30]
RTA renal tubular acidosis, *CKD* chronic renal kidney disease, *PCR* protein catabolic rate

Clinical Information and Other Conditions Related to Stones

There are a few clinical conditions that may increase kidney stone risks. Primary hyperparathyroidism, diabetes, obesity, Crohn's disease, gastric bypass surgery, gout, medullary sponge kidney disease, horseshoe kidney, and autosomal dominant polycystic kidney disease (ADPKD) have high risks of CKD and stones [2, 33]. Nutritional assessments should include special nutritional consideration of these comorbidities and risks of stones. Table 20.4 includes medical conditions that may increase stone risks.

Drug-Nutrient Interactions: Selected Common Medications

There are drug-nutrient interactions for selected medications used for CKD, complications of CKD, and mineral bone disorder management. Dietitians should evaluate drug-nutrient interactions for the stone patients who take these medications to provide appropriate diet plans. Table 20.5 shows possible effects of medications on blood, urine tests, and diet recommendations.

Table 20.5 Effects of selective common medications prescribed in chronic kidney disease on laboratory parameters, stone risk, and nutrition recommendations

Medication	Laboratory parameters		Stone risk effects	Nutrition recommendations
Medication category	Serum	Urine		
Antihypertensive ACEI /ARB	Increased K	Decreased K	Low urine citrate (?)	Low Na (2 gm/d) Moderate K (3–4 gm/d)
Diuretics Lasix/torsemide Spironolactone HCTZ/chlorthalidone	Decreased K Increased K Decreased K Increased Ca	Increased Ca Increased Ca Decreased Ca	Increased CaOx or CaP stone risk Prevention for Ca stones	Higher K Low K Higher K
Secondary hyperparathyroidism Calcitriol Vitamin D Ca supplement (or Ca-based binders)	Increased Ca Possible increased Ca Increased Ca	Increased Ca Increased Ca	Increased Ca stone risks	Dietary Ca 1,000–1,200 mg per day (3 servings of dairy/d) unless P restriction
CKD with gout Allopurinol	Low uric acid	No effect	Increased uric acid stone risk with low urine pH	Low-purine/low animal protein diet

References: [7–11, 32, 34–38]
ACEI angiotensin converting enzyme inhibitor, *ARB* angiotensin receptor blocker, *Ca* calcium, *CKD* chronic kidney disease, *HCTZ* hydrochlorothiazide, *K* potassium, *Mg* Magnesium, *Na* sodium, *Ox* oxalate, *P* phosphorus

Renin-Angiotensin-Aldosterone System Inhibitors and Other Medications Affecting Kidney Stone Risks

Renin-angiotensin-aldosterone (RAAS) inhibitors are widely used for blood pressure control among CKD patients, especially patients with proteinuria. The most common side effect of RAAS is hyperkalemia. After initiation of these medications, laboratory values are usually monitored for creatinine and potassium levels [7, 8]. If patients have stone risks with low urine citrate and low pH, potassium citrate is usually initiated to reduce stone risks from calcium oxalate or uric acid. It is important for dietitians to understand the effects of medications especially for hyperkalemia. Lemon juice can be used to help improve serum citrate and alkalization of urine, but it is not as effective as oral potassium citrate. If patients have uric acid stones with low citrate, potassium citrate is the best choice [34, 35, 39]. Dietitians can instruct on a reduced potassium diet if necessary and monitor labs closely.

Mineral Bone Disease (MBD) and Idiopathic Hypercalciuria

Calcium (Ca) absorption is controlled by the gastrointestinal tract, bone, and kidney. The kidney activates vitamin D 25 (OH) D3 to 1,25 (OH)2 D3 (calcitriol). This conversion will enhance gastrointestinal absorption of calcium, maintain normal serum Ca level, and provide sufficient Ca to the bones. When calcitriol conversion level decreases with the progression of kidney disease, the serum Ca level may decline. A low serum Ca level triggers the activation of the calcium-sensing receptors in the parathyroid glands. This, in turn, increases parathyroid hormone (PTH) synthesis and secretion to maintain normal Ca level [3, 7–11]. Calcium supplementation is often recommended for patients with advanced CKD. Calcium supplements can increase stone risks, especially in patient with history of calcium stones with CKD. Rather than supplementation, dietary sources of calcium (i.e., dairy products) will be more appropriate with stone patients with CKD [32, 36, 37]. Patients should be monitored for elevated phosphorus levels that may occur in advancing stages of CKD [7–11].

Gout and Xanthine Oxidase Inhibitor

The use of drugs (xanthine oxidase inhibitors) to prevent or treat gout symptoms temporarily increases urinary uric acid excretion to decrease serum uric acids until a new steady status of uric acid production and excretion is achieved. Xanthine oxidase inhibitors are commonly used for long-term prevention of gout, but not as a prevention of recurrent uric acid stones. The medication can help in lowering urinary uric acid excretion. Therefore, monitoring of blood and urine uric acid levels is important [16, 38].

Nutrition Recommendations

Macro- and Micronutrient Recommendations for CKD

Individualized nutrition assessment and management is required on an ongoing basis to maintain kidney function and prevent and/or control progression. Medical nutrition therapy provides a balance between necessary nutrients and the ability of the kidneys to filter and eliminate metabolic waste products. The Council on Renal Nutrition of the National Kidney Foundation in conjunction with the Renal Dietetic Practice Group of the Academy of Nutrition and Dietetics has published extensive guidelines for CKD nutritional management. The Center for Medicare Services (CMS) provides reimbursement for dietitian counseling for specified levels of kidney function [9–11]. Table 20.6 provides a comparison of nutrition recommendations for CKD and nephrolithiasis by selected professional organizations.

Table 20.6 Comparison of nutrition recommendations in CKD and nephrolithiasis by selected professional organizations

	CKD stage 4–5 eGFR (15–30 ml/min/1.73 m): Kidney disease outcome quality initiative	Nephrolithiasis guidelines (American Urological Association)	Nephrolithiasis CKD in typical clinical practice
Calories	23–35 kcal/kg	NA	Maintain healthy weight or weight reduction diet if obese
Protein	0.8–1.3 g/kg	Limit intake of nondairy protein and high-purine foods (animal protein)	0.8–1.3 g/kg
Sodium	<2000 mg	<2300 mg	<2000 mg
Potassium	Unrestricted unless serum level is elevated or above normal range	Increase high K fruits/ vegetables to reduce acid load	Unrestricted unless serum level is high
Calcium	Maintain serum calcium in normal range 1000–1200 mg	1000–1200 mg elemental calcium, consume meal time	1000–1200 mg, limit dairy products if phosphorus level is high. Use Ca supplement during meal time to bind oxalate and phosphorus if phosphorus restriction is indicated
Phosphorus	800–1000 mg, maintain serum P and PTH in acceptable range		800–1000 mg, maintain blood phosphorus and PTH in acceptable range
Vitamin D	Note: Decide what you are doing with calcium, then do the same for vitamin D		Maintain normal level D3 1000–2000 IU daily for insufficiency D2 50000 IU weekly with deficiency
Oxalate	NA (except in diagnosis of primary hyperoxaluria)	Avoid high-oxalate foods	NA (except in diagnosis of primary hyperoxaluria)
Fluid	Usually unlimited if urine output sufficient; then adjusted accordingly	Fluid >3 L to achieve urine volume >2.5 L	Recommend 2–2.5 L/day for patients who are at the risk of hyponatremia

References: [5, 9–11, 28]
K potassium, *NA* not applicable, *P* phosphorous, *PTH* parathyroid hormone

Overall Recommendation for Stones

General nutrition recommendations and guidelines have been published by selected organizations. The Agency for Healthcare Research and Quality (AHRQ) conducted a systematic review on recurrent nephrolithiasis in adults [40]. The American Urological Association (AUA) provided evidence-based guidelines for clinical practice in stone management in 2014 [41]. The guidelines for stone prevention are not specific for patients with CKD which necessitates the individualization by a registered dietitian.

Dietary guidelines of the AUA include fluid, calcium, sodium, oxalate, and protein intakes. Fluid intake is the most important to prevent recurrence of stones [41]. Patients with CKD usually do not follow a fluid restriction unless the patient has low serum sodium level. The goal of fluid intake is to produce at least 2.5 L of urine volume per day for all types of stones. The type of fluid intake also affects stone formation. Alcoholic beverages, coffee, tea, wine, and orange juice have been correlated with lower risk of stone formation. Sweetened beverages including soda have increased risks [42–45]. CKD patients taking potassium-sparing medications or RAAS inhibitors should be aware of the potassium content of fluid choices (i.e., higher potassium found in orange juice, prune juice, selected sports beverages). Dietitians should consider patients' comorbidities with stones to deliver a more individualized recommendation.

Dietary sodium intake is associated with urinary calcium excretion [46]. The AUA recommends sodium intake ≤100 mEq (2300 mg) per day. [41] CKD patients are usually instructed to follow a low-sodium diet (<2000 mg/d) which can help manage hypercalciuria [9–11, 36]. Low-sodium diet is also recommended (<100 mEq or 2300 mg/d) for cysteine stone formers to reduce cysteine excretion [47].

Dietary calcium recommendation by AUA is 1000–1200 mg per day. A randomized controlled clinical trial conducted by Borghi to monitor recurrence of calcium oxalate stones among men compared a low dietary calcium intake (400 mg/day) with normal calcium diet (1200 mg/day). The normal calcium diet showed 51% less stone recurrence rate than low-calcium group [48]. In contrast supplemental calcium can elevate stone risks by 20% among women [37]. Patients with CKD often restrict dairy products due to high phosphorus content and take calcium supplements in advanced stages. An individualized nutrition assessment and management plan designed by dietitians should consider adequate recommendation of nondairy calcium-rich foods for stone formers if patients have an elevated phosphorus level.

High-oxalate foods are usually restricted for calcium stone formers. However, urinary oxalate excretion is dependent on dairy consumption with high-oxalate foods. Calcium-rich foods can lower oxalate absorption which decrease urinary oxalate excretion. Consumption of dairy products or nondairy calcium-rich foods with meal will help prevent recurrence of calcium oxalate stones [49–51].

Gastric bypass surgery or malabsorption conditions such as inflammatory bowel disease can increase risks of calcium oxalate stones due to less available calcium in the gastrointestinal tract to bind oxalate [33]. The time of calcium supplement is very important for patients with gastric problems to lower the calcium oxalate stones. Vitamin C is metabolized to oxalate in the body; therefore, high dose of vitamin C should be avoided for patients with calcium oxalate stones [52].

Dietary protein, especially nondairy animal protein, can increase acid load, which enhances citrate reabsorption in the kidney. Therefore, this will lead to low urine citrate (hypocitraturia), which affects urine pH acidic which is favorable for calcium oxalate and uric acid stones. Renal tubular acidosis, chronic diarrhea, and carbonic anhydrase inhibitors can cause hypocitraturia. Fruits and vegetables (alkaline foods) are recommended to improve urine pH [35, 53]. Patients with a history of uric acid stones are recommended to reduce the intake of high-purine foods and increase intake of alkaline foods to raise urine pH. Alkaline urine can resolve uric acids.

High fluid intakes (>4 L/day) in conjunction with low-sodium and moderate animal protein diet are recommended for patients with cystinuria. Animal protein is high in methionine, which is the precursor of cysteine [47].

Vitamin, Mineral, and Herbal Supplements

Multivitamin and mineral supplementation is based on patients' nutritional need and CKD stage. The majority of early stage CKD (stages 1–3) patients do not need extra vitamin or mineral supplements. Often CKD patients will want to take multivitamin supplements for security of inadequate dietary intakes [11]. In the United States, over-the-counter dietary and herbal supplements are very popular. Many patients believe the claims of these products which usually do not have scientific proof of efficacy. Nephrolithiasis patients with CKD should be more careful about starting multivitamin, mineral, and herbal supplements [2, 52].

Calcium supplements can increase stone risks especially in older women with concurrent osteoporosis risks. Gambaro et al conducted a study on Ca with vitamin D supplement and these supplements increased the risk of calcium nephrolithiasis [54]. Regular multivitamins with low dose of calcium <200 mg is usually acceptable for patient with CKD and nephrolithiasis. If a patient has low vitamin D status without sarcoidosis, low dose of vitamin D (D3 of 1000–2000 IU) is recommended without increasing stone risks [54].

Megadoses of vitamin C are often used for common cold symptoms. However, vitamin C supplement >1000 mg per day can increase endogenous oxalate production. Large doses of vitamin C are not recommended for CKD patients with stone risk [2, 52].

Herbal supplements and complementary and alternative medicine (CAM) are also very popular among the general population to improve the overall quality of life and prevent diseases via naturalistic practice. The safety of herbal supplement for CKD and nephrolithiasis is unknown. Therefore, the use of specific herbal supplements should be discussed with a nephrologist and dietitian. More detailed information is discussed in the chapter on "Kidney Stone Myth, Reality, Dietary and Herbal Supplement."

Nutrition Recommendations for Different Types of Stones

A recurrent stone former should undergo an evaluation for a treatable metabolic cause of kidney stones. This is guided by the results of the 24-hour urinalysis and blood tests. Table 20.7 outlines nutrition recommendations for different types of stones.

Calcium Stones

For calcium stones, dietary sodium restriction is important as it is associated with a reduction in urine calcium excretion. Sodium restriction is common with CKD patients and <2 gm sodium diet is recommended, which is also appropriate for stone patients [2, 9–11].

Thiazide diuretics lead to increased serum calcium levels and reduced urine calcium levels and are therefore used in therapy for patients with hypercalciuria. Oxalate absorption is reduced by the formation of insoluble calcium oxalate. This is very important in therapy because low dietary calcium results in less calcium being available in the intestinal lumen to bind oxalate. This leads to increased oxalate absorption and therefore increased urinary oxalate excretion [26, 37, 49, 55]. A list of high-oxalate foods is found in the appendix.

High-oxalate foods are considered to be healthy with high fiber and nutrient density of vitamins and minerals. Patients who have diabetes, hypertension, and high blood cholesterol are often instructed to consume high-oxalate foods such as fruits and vegetables. When patients develop kidney stones, they are instructed to change the diet to lower oxalate contents, and therefore most patients are

Table 20.7 Nutrition recommendations for different types of kidney stones

Nutrient	Ca stones	Uric acid stones	Unknown stones	Cystine stones	Struvite stone
Fluid	>3 L (total) Urine output >2.5 L	>3 L (total) Urine output >2.5 L	>3 L (total) Urine output >2.5 L	>3 L (total) Urine output >2.5 L	>3 L (total) Urine output >2.5 L
Dietary Ca	3 servings of dairy with meal time DRI (1000–1200 mg)	N/A	3 servings of dairy with meal time DRI 1000–1200 mg)	N/A	N/A
Ca Supplement	Only if pt. has malabsorption with CaOx stones	N/A		N/A	N/A
Oxalate	55 mg per day	N/A		N/A	N/A
Protein	0.8–1.3 g/kg total	Low animal protein, low-purine diet Lower acid load	0.8–1.3 g/kg total	Low animal protein to lower methionine	N/A
Sodium	2000–2400 mg/d	N/A	2000–2400 mg/d	2000–2400 mg/d	N/A
Vitamin C	<1000 mg	N/A	<1000 mg	N/A	N/A

References: [2–5, 16, 40, 41]
Ca calcium, *K* potassium, *Mg* magnesium, *P* phosphorus

confused [48–50, 56, 57]. The dietitian should individualize advice for each patient to prevent kidney stone but balance intake to reflect a healthy diet.

Uric Acid Stones

As uric acid is more soluble in an alkaline urine, awareness of urine alkalization is an important part of the treatment of uric acid stones. Patients should decrease their intake of animal proteins, which helps decrease uric acid generation. Allopurinol, a xanthine oxidase inhibitor, is used to decrease the formation of uric acid among patients with gout [26, 36, 38, 41].

A low-purine diet is recommended if the patient has an elevated blood uric acid level. A high-protein diet (>2.0 g/kg) can cause a decrease in urine pH, which can increase the risk of uric acid stone [2, 4, 31]. A moderate amount of protein (0.8–1.2 g/kg/day) is recommended. This intake is very acceptable for CKD protein recommendation [9, 11].

Cystine Stones

There are no specific diet recommendations for cysteine stones except increasing fluid intake. Cystine solubility can be increased by alkalization of the urine, although solubility only increases when the pH reaches 7–7.5. Low animal protein diet can lower the stone risk by lowering methionine, which is a precursor of cysteine [12], as well as high fluid intake (>4 L/day) and low-sodium diet help [47, 53, 58, 59].

Struvite Stones

The preferred treatment of struvite stones is surgical removal because they are large. Antibiotic therapy is important and may slow down stone growth. It is important to culture stone material to help direct antibiotic therapy. However, low-sodium diet can help prevent struvite stone as well as high fluid intake [2, 12].

Stones of Unknown Composition

The challenge of an unknown stone type is very common. Patients often cannot catch the stone while passing or a stone analysis was not done. Clinicians evaluate stone risks via blood and urine tests. Nutritional management of unknown stone composition includes parameters for the prevention of all stone types.

Nutrition Recommendations for Stone Risk Post-Kidney Transplant

End-stage kidney failure patients undergoing dialysis treatment do not develop kidney stones due to lack of urine production. However, patients who have successful kidney transplants are prescribed multiple immunosuppressive medications which can increase the risk of kidney stones. Table 20.8 outlines some of the most common prescribed medications for post-kidney transplant patients.

Most common immunosuppressive medications are calcineurin inhibitors (tacrolimus and cyclosporine) and prednisone. Calcineurin inhibitors can cause renal tubular acidosis which leads to lower citrate in the urine [2, 16]. In addition, post-kidney transplant patients have pre-existing medical condition such as diabetes and PKD. The incidence of obesity can increase posttransplant. The first consideration of diet for post-kidney transplant patients is heightened awareness of food safety for at least the first year. The use of the Dietary Approaches to Stop Hypertension (DASH)

Table 20.8 Effects of selective common immunosuppressive medications prescribed in post-kidney transplant on laboratory parameters, stone risk, and nutrition recommendations

Medication	Laboratory parameters		Stone risk effects	Nutrition recommendations
	Serum	Urine		
Prednisone	Increased K	No effect	Unknown	Healthy diet to prevent weight gain; Ca, vitamin D supplement
Cyclosporine	Increased K Decreased Mg Decreased P	Increased Mg Increased P	Unknown	Moderate K High Mg diet
Tacrolimus (Prograf)	Increased K Decreased Mg Decreased P	Increase Mg Increase P	Unknown	Moderate K High Mg diet High P

References: [2, 8, 16]
Unless prior history of kidney stones in CKD 1–5
Ca calcium, *K* potassium, *Mg* magnesium, *P* phosphorus

diet is a common recommendation for these patients. The DASH diet is high in potassium, magnesium, and phytate but also high in oxalate [60]. However, high phytate and fiber can lower the absorption of oxalate.

Other common dietary recommendations for post-kidney transplant include adequate amount of calcium, magnesium, and phosphorus and healthy eating to prevent weight gain, steroid induced diabetes, and bone disease. At least three servings of dairy products provide an adequate amount of calcium from the diet as well as phosphorus. The high-fiber, magnesium-rich DASH diet along with dairy products can lower calcium oxalate stone risks. The perceived mechanism is the binding of calcium with oxalate in the gastrointestinal tract as well as less absorption of Ox due to high phytate from the fiber [2, 60]. Individualized diet recommendation is necessary for post-kidney transplant patient to prevent further stone risks.

Summary

Patients with CKD at risk for stones need ongoing individualized nutritional management. Nutrition assessment involves comprehensive dietary intake analysis, anthropometric measurement, and biochemical indices serial tracking. Drug-nutrient interactions should be considered. General nutrition recommendations include macro- and micronutrient parameters that need to balance healthy diet intake with the reduction of selected stone risk. Patients in kidney failure undergoing dialysis treatments are not at risk for stone formation. However, post-kidney transplant patients often resume stone risk particularly with the use of immunosuppressive medications.

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Chapter 21
Kidney Stone: Diet, Myth, and Realty

Lisa Vosatka and Haewook Han

Keywords Nephrolithiasis · Calcium oxalate · Uric acid stone · Hypercalciuria · Hyperoxaluria
High-purine foods · High oxalate foods · Vitamin and mineral supplement

Key Points
- There are many available dietary recommendations to prevent kidney stones; however, many of them are unsubstantiated and not based on evidence.
- Dietary recommendation of stone prevention should be individualized for different stone types and should follow general guidelines developed by American Urology Association (AUA).
- Most common dietary recommendations entail increasing fluid intake and consuming adequate amount of calcium-rich foods, moderate amount of protein intake, lower sodium, and more fruits and vegetables.
- Vitamin or mineral supplements should be used carefully after completion of metabolic and nutritional evaluation.

Introduction

Nephrolithiasis is the process of kidney stone formation that is caused by a disruption in the balance between solubility and precipitation of salts within the urinary tract.

The incidence is at peak among white males aged 20–30 years. The National Health and Nutrition Examination Survey (NHANES) III (1988–1994) reported that there was a 5% prevalence of stone formation among adults in the United States and it was increased to 8.8% in 2007–2010 [1, 2]. The lifetime incidence of kidney stone is 13% for men and 7% for women [1]. Nephrolithiasis is considered to be a disease of affluence like obesity, hypertension, and type 2 diabetes because it is prevalent in wealthy countries [3, 4]. Urologic intervention is required in as many as 20% of patients with renal

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Table 21.1 Common types of kidney stones and risk factors associated with them

Stone type	Frequency (%)	Gender	Risk factors
Calcium oxalate/mix	75	M	Idiopathic hypercalciuria, high protein diet, high sodium intake, acidic urine, high oxalate diet, high vitamin C intake, diseases of small bowel, gastric bypass surgery, hyperoxalosis (genetic), sarcoidosis, low urine volume
Calcium phosphate (brushite)	5	F > M	Recurrent urinary tract infections, alkaline urine, excessive citrate supplementation, hyperparathyroidism
Uric acid	5 – 15	M = F	Obesity, acidic urine, DM, high protein/purine intake, low urine volume
Struvite	10–20	F	Recurrent urinary tract infections, alkaline urine
Cystine	1	M = F	Dent disease

Reference: Courtesy from Dr. J. Seifter, Harvard Medical School, Renal Division Brigham and Women's Hospital, Boston

colic [3], and more than $5.3 billion is spent on treatment annually in the United States [5]. Kidney stones develop when urine becomes "supersaturated" with insoluble compounds containing calcium oxalate (CaOx) and calcium phosphate (CaP), resulting from dehydration or a genetic predisposition to over-excrete these substances in the urine.

The most prevalent stones in the Western Hemisphere are calcium oxalate (75–85%), uric acid (5–10%), and struvite (5%). Stones may also contain mixtures of these compounds (Table 21.1). Some stones are more prevalent in men than women because of the complicated male urinary tract, their larger muscle mass, and consequent increased metabolic waste. Acidic urine is a risk factor for most types of kidney stones. There are significant hereditary components in kidney stone causation and its high recurrence rate. Twenty-four hour urinalysis is used to determine kidney stone risks [6]. Table 21.2 shows the normal range of urine composition and causes of abnormal values: urine volume, 24-hour urinary concentrations of calcium, oxalate, magnesium, phosphorus, citrate, pH, uric acids, sodium, potassium, magnesium, protein catabolic rates, and supersaturations of calcium oxalate, calcium citrate, and uric acid [7]. There are many myths regarding the relationship between dietary factors such as the intakes of various vitamins and minerals, fluids, and animal proteins and risk of kidney stones. The purpose of this chapter is to address these myths and to promote a better understanding of the relationship between diet and kidney stone development.

Myths and Realities

Myth: A High Calcium Diet Causes Kidney Stones

– *Reality: Avoid total intakes of calcium that are very high (>2500 mg/day) or very low (<500 mg/day) and aim for calcium 1000–1200 mg/day.*

Calcium-based kidney stones represent over 75% of all stones in the Western world. In some stone formers, a genetic predisposition for hypercalciuria increases the likelihood of calcium ions binding with oxalate and/or phosphate in the urinary tract. Therefore, some assume that dietary calcium is directly related to stone development [3].

Calcium intake over the upper level of 2500 mg/day (based on Dietary Reference Intake; DRI) increases risk of hypercalciuria, especially when combined with excessive vitamin D supplementation [8]. Interestingly, a cohort study of 49,976 adult men showed no association between supplemental

Table 21.2 Normal values of urinalysis and causes of abnormal values

	Normal value	Cause of abnormal values
Ca	<250 mg/day for males <200 mg/day for females	↑ idiopathic hypercalciuria, high Na diet (high urine Na) high protein diet ↓ with bone disease
Phosphorus	0.6–1.2 g/day	↓ with bowel disease, malnutrition, with high food intake
Mg	30–120 mg/day	↓ with some laxatives, malnutrition, malabsorption
Oxalate	20–40 mg/day	↑ with high oxalate diet, high vitamin C consumption If >80, intestinal (inflammatory bowel disease) or oxalosis
SSCaOx	6–10	↑ with low urine vol, high Ca and Ox ↓ with high urine vol, low Ca and Ox
SSCaP	0.5–2.0	↑ urine pH, idiopathic hypercalciuria
Citrate	>450 mg/day males >550 mg/day females	↓ RTA, hypokalemia, high animal protein diet, acidosis, diarrhea
Uric acid	<0.8 g/day males <0.75 g/day females	↑ with high animal protein diet (high purine), alcoholic beverages, overproduction
SSUA	0–1.0	↑ urine pH <5.8, high uric acid with animal protein
Volume	>2000 ml/day	↓ with low fluid intake
pH	5.8–6.2	↓ RTA, urea-splitting infection, acidosis, high animal protein intake (high-purine content) ↑ vegetarian diet, high citrus consumption, soft drink
Na	50–150 mEq/day (1150–3450 mg)	↑ with high Na diet ↓ with low volume
K	20–100 mEq/day	<20 bowel disease, diuretics, laxatives
Cl	70–250 mEq/day	
Urea nitrogen	6–14 g/kg/day	↑ with high protein diet
PCR	0.8 – 1.4 g/day	↑ with high protein diet
Sulfate	20–80 mEq/day	↑ with high protein diet
Ammonium	15–60 mM/day	↑ pH > 7 urea-splitting infection, ↓ pH <5.5 CRI, UA stones, gout
Cr/kg	18–24 mg/kg for males 15–20 mg/kg for females	↑ with more than 24 hour collection ↓ with under collection

Range: Courtesy from [7]
SSCaOx supersaturation of calcium oxalate, *SSCaP* supersaturation of calcium phosphate
SSUA supersaturation of uric acid, *PCR* protein catabolic rate

calcium intakes and risk of stone formation in men of all ages, when the highest quintile of total intake was a mean of 1218 mg calcium/day (versus the DRI of 800 mg/day and the UL of 2500 mg/day) [9, 10]. These results were confirmed in a twin study based on reports from the Vietnam Era Twin (VET) Registry [11].

Findings are similar among women. A randomized study of 53 postmenopausal women found that kidney stone risk did not increase with 750 mg/day dietary supplements, with (n = 28) or without additional 0.5 mcg vitamin D supplementation (n = 25); both $p > 0.05$ [12]. Increased dietary and supplemental calcium intake was also not associated with stone risk in the Nurses' Health Study II of women ages 27–44 (n = 96,245). The median of the highest quintile of dietary intake was 1300 mg calcium/day versus 540 mg/day in the lowest quintile (RR 0.73, 95% CI 0.59–0.90, NS). The highest quintile of supplemental calcium was >500 mg/day versus the lowest quintile of 0 mg/day (RR 1.13, p = 0.60) [13]. This is important because middle-aged women are often encouraged to take calcium supplements to reduce the risk of osteoporosis. Conversely, restricting calcium intake to 400 mg/day reduces intestinal chelation of dietary oxalate by calcium, causing the intestine to absorb more oxalate

and increasing oxalate stone risk. Severely restricting calcium also decreases urinary calcium, leading to secondary hyperparathyroidism and bone demineralization [8]. A 5-year randomized controlled trial (RCT) of 60 stone-forming men illustrated this effect: a diet low in protein and salt but high-normal in calcium content (1200 mg/day) provided greater protection from stones than a low calcium (400 mg/day) diet with the same levels of protein and salt (adjusted RR of stone recurrence 0.37, 95% CI 0.18–0.78, $p = 0.04$). The study concluded that a protective effect did not exist for a low animal protein and low salt diet [14]. Another fact is that serum active vitamin (calcitriol) increases during calcium restriction, [15]. The American Urology Association (AUA) recommends the consumption of calcium between 1000 and 1200 mg/day [16].

Myth: Water Is the Only Beverage That Can Help Prevent Kidney Stones

– *Reality: Stone formers should drink 3 L (96 oz) of fluids such as water, coffee, lemonade, juice, and milk daily to produce at least 2500 mL of urine/day and decrease stone risk* [16].

Increased fluid intake (3000 mL/day) dilutes urine and significantly reduces urinary calcium oxalate and calcium phosphate saturation [17]. Drinking more water is additionally beneficial for stone formers whose stones are not calcium-based. For example, risks of uric acid stones also decrease with increased fluid intake. Uric acid stones represent only 5–10% of kidney stones in the US population and result from the acidic urine and low urine volume that are associated with metabolic syndrome and gout [3]. Uric acid is soluble in alkaline urine. Addition of lemon juice in water can help increase urine volume and urine pH [18]. Higher pH of urine with large urine volume will lower supersaturation of uric acid stone formation therefore lower uric acid stone risks.

A large 5-year RCT concluded that a "large" intake of water was the best initial therapy to prevent stone recurrence. In this trial, stone formers' urine volume was significantly lower and their urinary supersaturations of calcium oxalate and uric acid were significantly greater than controls. It was assumed that water consumption was directly proportional to urine volume, but unfortunately, the investigators did not quantify the optimal water intake [19]. The finding that a high water intake decreases risk was corroborated by two other large observational studies of men and women [10, 13]. The National Kidney Foundation (NKF) and AUA also recommend that stone formers drink enough fluids to produce at least 2500 mL of urine daily [16, 20].

Also, there are protective effects of kidney stones consuming other beverages. Coffee drinking was protective in the VET twin study: those who drank ≥1200 mL (more than five cups) of coffee daily were 60% less likely to develop stones than non-coffee drinkers (OR 0.4, $p = 0.03$) [11]. Another cohort study reported similar findings [21]. The benefit was likely due to increased urine output after drinking a large volume of coffee, which has a diuretic effect.

In contrast, the VET study found that tea had no effect on stone risk, possibly because it is richer in oxalate than coffee (7.5 mg/100 g serving versus 0.9 mg/100 g serving, respectively) [11]. However, when black tea was consumed regularly with 25 mL of low-fat milk in a small double crossover study, 35% less oxalate was absorbed from the tea over 24 hours ($p < 0.01$) [22]. Presumably, the calcium in the milk bound the tea's oxalate and this non-absorbable complex passed in the stool, reducing gut oxalate absorption [3].

Likewise, drinking at least 240 mL of milk daily prevented stone development in the VET study (OR 0.5, 95% CI 0.3–0.8, $p < 0.05$) [11], probably because milk consumption raised urinary volume and may have chelated oxalate in foods and beverages. Milk or other dairy consumptions three servings per day with meals also assist in meeting the calcium DRI.

Individuals should still exercise caution with alcohol, large volumes of cola, and some fruit juices. Some recent studies have examined the effects of different alcoholic beverages on stone risk, but

evidence is insufficient to make a safe recommendation for alcohol consumption. Cola is high in phosphoric acid, which reduces urinary citrate. Citrate is beneficial because of its buffering properties and ability to bind oxalate [23]. In a study of 45 adults, an acute load (2000 mL) of cola raised oxalate excretion by a mean of 0.7 mg daily ($p < 0.05$). Urinary pH also decreased significantly in females, which may have promoted oxalate crystallization [24]. In contrast, sodas like Diet Sunkist Orange, Diet 7Up, Sprite Zero, and Diet Canada Dry Ginger Ale contain at least 6.3 mEq/L of citrate, which is the protective dose against kidney stones. The researchers who discovered this did not investigate the citrate contents of the sweetened soda counterparts, so their effectiveness cannot be determined at this time [25].

Fruit juice in moderate to large amounts may also cause problems. For each daily 240 mL serving in a large observational study, the risk of stone formation in healthy men increased by a mean of 35% ($p = 0.02$) with apple juice and 37% ($p = 0.03$) with grapefruit juice [21], perhaps because apple juice is rich in fructose, which is positively associated with oxalate excretion [26, 27]. More research is needed to confirm these associations.

Myth: Kidney Stone Formers Should Limit Intake of Vitamin C

– *Reality: Aim for the DRI for vitamin C (75 mg/day for women, 90 mg/d for men). Those prone to oxalate stones should avoid dietary supplements providing >1000 mg ascorbic acid/day.*

In alkaline conditions, vitamin C is metabolized to oxalate (Fig. 21.1).

In fact, ascorbate accounts for approximately 40% of all oxalate excretion [28]. Vitamin C intakes near the DRI of 90 mg/day for men and 75 mg/day for women has not been shown to increase kidney stone risk, according to the NKF [20]. However, there may be some risk associated with very large amounts of ascorbic acid in stone formers [29].

One small RCT ($n = 24$) found that ingesting 2000 mg ascorbic acid/day (about 25 times the DRI) significantly raised urinary oxalate in non-stone formers (20% increase) and stone formers (33% increase). A larger RCT ($n = 48$) reported similar findings [30].

When reports of actual stone formation were studied versus simply urinary oxalate excretion in large cohort studies, women reporting vitamin C intakes in the highest quintile (>1500 mg/day) had a stone RR of 1.06 (95% CI 0.69–1.63, $p = 0.43$) [31], and men consuming >1000 mg/day had a RR of 1.41 (95% CI 1.11–1.80, $p = 0.01$). Since the results were not significant for women, Curhan et al. [31] concluded that routine vitamin C restriction to prevent stones was warranted in men, but not women.

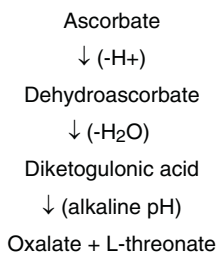

Fig. 21.1 Metabolism of ascorbate to oxalate [28]

Myth: Eating Meat Causes Kidney Stones

– *Reality: Eating amounts of protein near the DRI (0.8–1.0 g/kg/day) does not increase risk of stone recurrence, even if protein is from animal sources, but intake >2 g/kg/day may increase risk. Stone formers are advised by the NKF to meet the DRI for protein* [20]. *Evidence is insufficient to recommend animal fat restriction in stone formers.*

Some believe that consuming meat increases renal acid load and may cause supersaturation of calcium, phosphate, and uric acid in the urine. There is some research on optimal protein intake, the effects of reducing meat intake, and the effects of different dietary fats on stone development that is relevant when considering this assertion.

In a crossover study of 10 healthy individuals who followed their "usual" diet for 2 weeks, then spent 6 weeks on a low carbohydrate, high protein (about 2 g/kg/day) diet consisting mainly of animal protein, net acid excretion increased and urinary pH decreased (mean initial 6.09 to mean final 5.56, $p < 0.01$) [6].

In contrast, low protein diets did not seem to lower stone risk. A 4-year RCT ($n = 175$) found that a moderately low animal protein diet (about 0.8 g/kg/day) did not reduce stone recurrence in calcium stone formers compared to controls; however, compliance was poor in the intervention group and the control group ate more protein but also drank more water [32].

An intervention with the same moderate protein restriction (0.8 g/kg/day) in 18 stone formers noted a decline in calcium excretion ($p < 0.001$) from reduced bone resorption (likely due to a smaller exogenous acid load) and lower urinary oxalate ($p < 0.01$) [33]. Another trial found that one-third of calcium stone formers excreted less oxalate on diets lower in animal protein [34].

There is also interest in the role that animal fat plays regarding stone risk, particularly arachidonic acid because it is abundant in meats. Arachidonic acid intake was positively correlated (0.51, $p = 0.0012$) with oxalate excretion and intestinal oxalate absorption and clearance from the kidneys in 58 stone formers ($p = 0.003$), suggesting, but not proving higher risk for calcium oxalate stones [35]. More rigorous clinical research is needed on this topic.

Concerning the potential of reduced meat consumption to lessen stone risk, a study of ten healthy males showed that a lacto-ovo vegetarian diet reduced uric acid crystallization by 93% versus a typical "Western" diet [36]. Possibly during the vegetarian diet phase, less arachidonic acid and more fruits and vegetables were consumed, contributing a larger alkali load and averting a drop in urinary pH. However, it is difficult to discern if this was true or if results were simply due to differences in fluid consumption, which was significantly greater in the vegetarian group.

Myth: Fruits and Vegetables Cause Kidney Stones Because of Their High Oxalate Content

– *Reality: Not all fruits and vegetables are high in oxalate. Consumption of fruits and vegetables (at least five servings/day) may decrease risk for kidney stones. Stone formers should choose fruits and vegetables with <80 mg oxalate/serving or half portions of items with >100 mg/serving.*

The NKF recommends that stone formers limit oxalate intake less than 80 mg/day [20]. This is based on data revealing that about one-third of stone formers are "hyperabsorbers" who absorb over 10% of dietary oxalate, outside the normal range of 3–8% [30]. Typical oxalate intake in the US is 150–250 mg/day, so this would represent a considerable change in diet and should be accompanied by dietary counseling [37]. In observational studies, both stone formers and non-stone formers consuming the highest quartile of oxalate excreted 1.7 mg/day more urinary oxalate than lowest

Table 21.3 High-risk foods for stone formers

High oxalate (mg/serving) [39]		High purine (>100 mg/serving) [40]
Spinach, cooked	750	Bacon
Beets, cooked	675	Gravies
Swiss chard, cooked	660	Haddock
Sweet potatoes, cooked	141	Mussels
Kale, cooked	125	Scallops
Almonds (roasted) 1 oz	134	Anchovies

quartile ($p = 0.001$) [26]. The upper level for normal daily urinary oxalate excretion is 43 mg for men and 32 mg for women. This is key because small variations in urinary oxalate concentration can disrupt the delicate balance between urinary calcium and oxalate, leading to calcium oxalate supersaturation [37]. No trials have been performed to investigate the efficacy of a 40–50 mg/day oxalate restriction in stone formers or those with high oxalate intake.

Dietary oxalate is naturally occurring in all plants and some fruits and vegetables are highly concentrated in it. Dark leafy greens including kale, spinach, and collard greens are extremely high in oxalate (65–750 mg/serving). In one recent observational study, spinach accounted for >40% of total oxalate intake [38]. Apples, strawberries, and oranges have moderate amounts of oxalate (20–40 mg/serving) [38] (Table 21.3). Many other fruits and vegetables are lower in oxalate than these, such as bananas, avocado, melon, grapefruit, cabbage, plums, and broccoli [39]. In fact, adequate fruit and vegetable intake may decrease stone risk in stone formers and also healthy individuals, possibly because of their alkalinizing effect on the urine. In a study by Meschi et al., eliminating fruits and vegetables in healthy patients adversely altered stone risk profiles, raising calcium excretion by 49% ($p < 0.05$) and calcium oxalate saturation by 30% ($p = 0.03$). As a part of the same study, adding 100 g of fresh orange juice, 400 g of fresh fruit, and 300 g of fresh vegetables (none of which were high in oxalate) to the diets of stone formers whose consumption was originally low lowered calcium oxalate saturation by 50% ($p < 0.001$) and uric acid by 60% ($p = 0.003$) [41]. Finally, an observational study found that women with recurrent stones had diets that were suboptimal in fruit and vegetables (fewer than five servings/day) [42]. Most high oxalate foods are also very healthy. Consumption of dairy products with these high oxalate foods are recommended to lower calcium oxalate stone risk by lowering oxalate absorption in the gut.

Myth: Kidney Prevention Stone Medications Will Work Without Any Changes to Diet

– *Reality: It is important to follow the dietary recommendations that accompany kidney stone medications. Failure to do so may impair the efficacy of the medications.*

Some stone formers believe that anti-stone medications work on their own and that diet need not be changed while taking those medications. In reality, the most popular anti-stone medications *do* have dietary instructions that are crucial to their effectiveness.

For example, moderate sodium restriction to about 2000 mg/day (the adequate intake (AI) of sodium is 1500 mg/day) is essential during thiazide diuretic therapy (Diuril, hydrochlorothiazide [HCTZ], chlorthalidone), which is often prescribed to treat calcium stones. These diuretics lower urine calcium by approximately 50%, but increase sodium and potassium concentrations in the collecting ducts, which raises the risk for hypochloremic metabolic alkalosis. Observational studies show that individuals with hypercalciuria have exaggerated increases in urinary calcium per 100 mmol increase in sodium chloride intake (urinary calcium increase of 2 mmol versus the

normal 1 mmol increase) [43]. Sodium chloride inhibits tubular reabsorption of calcium, leaving it in the urine; this illustrates the increased risk of calcium stones when not adhering to the prescribed sodium restriction.

Allopurinol is a xanthine oxidase inhibitor that is used to treat gout and uric acid stones. It reduces uric acid production by an average of 60 mg/L of urine. While taking allopurinol, it is essential to drink at least 2 L fluids each day to dilute the excessive amounts of uric acid in the urine and facilitate its excretion [44]. Fluid recommendation for stone patients is 3 L; therefore this will dilute urine further and prevent stone formation. In addition, low-purine diet is important for the gout treatment; therefore low animal protein and increment of fluid intake will be necessary for uric acid stone prevention.

Myth: Minerals and Electrolytes Cannot Protect Against Kidney Stones

– *Reality: Magnesium and potassium appear to be protective against kidney stones. All individuals should strive for the DRIs for these micronutrients, but avoid exceeding the Upper Level of 350 mg/day of magnesium.*

Magnesium has the capacity to bind urinary oxalate as citrate does. Magnesium oxalate does not precipitate in the urine and therefore, it reduces the amount of free oxalate that is available to crystallize with calcium. The DRI for magnesium is 320 mg/day for women ≥30 years and 420 mg/day for men ≥30 years. The upper level for magnesium dietary supplementation is 350 mg/day for both men and women, not including foods and beverages [45].

Total magnesium intake was inversely associated with kidney stone risk in a cohort study of men: when compared with the lowest quintile of total magnesium intake (below 314 mg/day), the highest quintile of intake (>450 mg/day) had a RR of 0.71 for developing kidney stones (95% CI 0.56–0.89, $p = 0.01$) [10]. No similar effect has been documented in women yet; the Nurses' Health Study II cohort found no significant difference in relative risk for stones between the average of the highest quintile of total intake of 358 mg/day and the lowest quintile average intake of 271 mg/day, but these were estimates of intakes from an observational study [13]. Randomized controlled trials isolating magnesium supplementation and diet should be conducted to make more accurate conclusions about this potentially protective tendency.

Potassium citrate alkali supplements (Urocit-K) are also recommended frequently as a form of therapy for uric acid and calcium stone formers if patient has low citrate level with low urine pH. An RCT by Barcelo et al. ($n = 57$) observed that long-term potassium citrate therapy of 30–60 mEq/day caused a significant increase in 24-hour urinary citrate (from 268 to 460 mg/day, $p < 0.001$) and urinary pH (from 6.44 to 6.91, $p < 0.001$). Their most noteworthy finding was that after 3 years, the potassium citrate supplement effectively reduced new stone formation by 92%, from an initial average of 1.2 stones per patient year to a final mean of 0.1 stone. No benefit was observed in the placebo control group [46]. However, potassium citrate treatment should be used carefully with patients with history of hyperkalemia.

There has also been interest in the role that total potassium intake has on risk of initial stone formation. Potassium intake was inversely related to stone risk among men in the Taylor study discussed above, with the highest quintile of total intake of ≥3958 mg/day having a RR of 0.54 compared to the lowest quintile of <2914 mg/day (95% CI 0.42–0.68, $p < 0.001$)[8]. The AI for potassium is 4700 mg/day for men and women and there is no Upper Level for intake [47].

Myth: Low-Purine Diets Do No Good

– *Reality: Hyperuricosuric patients can reduce their uric acid excretion and increase their urinary pH by consuming <150 mg of purine daily.*

In actuality, it seems that low-purine diets (<150 mg/day versus the typical intake of 600–1000 mg/day) reduce urinary uric acid excretion. Purines are nitrogen-containing bases occurring naturally in protein-rich foods (Table 21.3). They are also produced endogenously through tissue catabolism and, when they are broken down, release uric acid [48]. As elevated uric acid raises stone risk, low-purine (≤150 mg/day) or purine-free diets are sometimes recommended for uric acid stone formers. Two early observational studies of hyperuricosuric patients discovered that the relationship between purine intake and uric acid excretion was linear and that acid excretion was normal when stone formers followed a purine-free diet [49, 50]. Another small crossover study (n = 8) fed stone formers a low-purine diet and then a high-purine diet (isoenergetic) and noted a 90% increase in uric acid excretion with a 0.9 unit drop in urinary pH after transitioning to the high-purine diet [51]. The ability to lessen uric acid excretion would undoubtedly represent a decrease in stone risk.

Summary

Although there are many myths about the relationship between diet and kidney stones, the reality is really quite simple once the composition of an individual's stones has been determined. Table 21.4 summarizes the best evidence-based recommendations that exist for stone formers. More individualized dietary instructions can and should be obtained by visiting a registered dietitian who specializes in nephrolithiasis prevention.

Table 21.4 Summary of National Kidney Foundation dietary recommendations and American Urology Association recommendation for stone formers [16, 20]

NKF guidelines	AUA recommendation
Drink 12–16 cups fluid daily to produce urine volume of >2.5 L	Fluid intake 3 L/day to produce urine volume >2.5 L
Normalize protein intake to 0.8–1.0 g/kg/day Limit intake of animal protein and high purine foods	Limit nondairy animal protein for uric acid and calcium stone patients (no specific level)
Normalize calcium intake to 1000 mg/day for men and 1200 mg/day for women; do not restrict intake and balance calcium intake throughout the day	Calcium recommendation: 1000–1200 mg/day
Limit oxalate intake to <80 mg/day	Limit very high oxalate foods but consume adequate dairy products
Limit sodium intake to 100 mg/day (2300 mg)	Limit sodium intake for calcium stone
Normalize vitamin C intake to 90 mg/day for men and 75 mg/day for women. Avoid excess vitamin C and other OTC supplements	

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Chapter 22
Herbal Use in the Nutrition Management of Kidney Stones

Judith A. Beto

Keywords Nephrolithiasis · Herbal supplements · Herbal formulas · Kidney stone treatment · Nutrition supplements

Key Points
- Nephrolithiasis evaluation should include discussion on the personal use of herbs and herbal preparations while encouraging communication on potential effects and symptoms.
- There is currently a lack of evidence-based literature for herbal therapy.
- Most commonly used herbs, herbal formulas, and commercial products are not linked to direct harm nor do they provide any known direct benefit.
- The strongest advice a health professional may offer to a consumer is to drink large quantities of water if they choose to ingest any of these preparations since scientific evidence is supportive of high fluid ingestion.

Introduction

The use of herbs in the treatment of kidney stones has a long and varied history. The use of natural remedies seldom claims to treat or dissolve the kidney stones themselves. They are more often prescribed by natural practitioners to relieve symptoms or promote body balance. Herbal preparations are often used in conjunction with other complementary and alternative medicine (CAM) supporting therapies such as meditation, cleansing, food systems, yoga, and acupuncture. Ayurvedic medicine derived from the Sanskrit word translated as "knowledge of the life span" is comprised of interrelated therapies including herbal formulas. These formulas have multiple spectrums of intended action including analgesic, anti-inflammatory, antimicrobial, anti-spasmodic, anti-calcifying, diuretic, or litholytic [1–3]. This chapter will review the literature available on the use of herbs in kidney stone treatment while recognizing there is currently a lack of evidence-based literature to support herbal therapy.

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Overall Literature Review of Herbal Use

A comprehensive literature review of herbal use in the management of kidney stones \found very few published studies of rigor and quality in humans. The epidemiology reports were typically qualitative surveys of natural practitioners regarding their use of herbal preparations in the treatment of a variety of symptoms [4–8]. These reports were specific to the cultural application of the predominantly native plants from a defined region or country. Other population-based studies tracked the use of herbal systems such as the Chinese herbal formula Wu-Ling-San [9]. Other studies described herbal preparations as part of multiple therapies within Ayurvedic medicine [9, 10] or traditional Chinese medicine management systems [1, 11]. One review attempted to create a formula for strength of evidence and/or practitioner consensus [6].

The majority of animal-based studies were completed primarily with rodents. There is no valid animal model for human kidney stones. These studies were excluded from this chapter as their direct application to humans was lacking.

Complementary Medicine Herbal Systems

Alternative medicine incorporating herbs has been used for centuries in many forms. Table 22.1 summarizes the major herbs and herbal mixtures that have published literature to describe their use in humans. The composition ratio, dosage parameters, and exact content of these preparations vary

Table 22.1 Selected herb/herb mixtures reported to be used in kidney stone treatment

Herb/herb mixture	Possible action	Comments
Aerva lanata [10]	Not stated	Amaranthaceae plant family Common name: Cheroola Decoction of leaves and juice for kidney stone inflammation
Alhagi camelorum [5]	Not stated	Papilionaceae plant family Common name: Kharshotor Decoction of aerial parts
Alhagi camelorum [5] *Alhagi maurorum* [5]	In rats, reduced kidney calcium oxalate deposits	Fabaceae plant family Decoction of aerial parts
Bontia daphnoides L. [5]	Not stated	Myoporaceae plant family
Chanca piedra [1, 2, 7] (also known as *Phyllanthus niruri*)	Disrupts calcium oxalate deposits/stone formation	Phyllanthaceae plant family
Cheilocostus speciosus [10]	Not stated	Zingiberaceae plant family Decoction of rhizome
Chorei-to extract preparation [1] Composition: Takusya (alismatis Rhizoma) Kagosou (Purunellae Spica)	Inhibit calcium oxalate Enhance calcium excretion	Commonly known as “Kampo”
Citrus X limon L. [7]	Urine acidification	Rutaceae plant family Juice has given with olive oil
Flemingia strobilifera L. [7]	Not stated	Leguminosae plant family
Gomphrena globosa L. [7]	Not stated	Amaranthaceae plant family
Jin Qian Cao (*Desmodium styracifolium* Merr) [1]	Urine acidification Inhibit crystal growth and aggregation	Used to reduce “heat and swelling”

Table 22.1 (continued)

Herb/herb mixture	Possible action	Comments
Mimosa pudica L. [7]	Not stated	Leguminosae plant family
Niao Shi Mixture (NSM) [1] Composition: Squama Mantis Spina Gleditsiae Resina Olibani Resin Myrrhae Radix Achyranthis Bidentatae Radix Angelicae Dahuricae Pericarpium Citri Reticulatae Viride Semen Colic Cortex Magnoliae Officinalis Fructus Aurantii Semen Persicae, Whizone Spargani Thizona Zedoariae Semen Plantaginis Radix Paeoniae Rubra Herba Lysimachiae	Combination of antiurolithiatic compounds to treat or prevent stone formation Decreases serum calcium	Traditional mixture with regional variations
Nigella sativa [5, 11, 12]	Thymoquinone, an active quinone, may have preventive and disruptive effects on calcium oxalate deposits Antioxidant	Ranunculaceae plant family
Orthosiphon stamineus [2] Orthosiphon grandiflorus [2]	Flavonoid composition enhances diuretic effect	Lamiaceae plant family Common name: Java tea
Paronychia argentea Lam [6]	Not stated	Caryophyllaceae plant family Common name: Chickweed, Algerian tea Decoction of entire plant
Plantago ovata Forssk [6]	Not stated	Plantaginaceae plant family Common name: Blonde Psyllium Dried and ground seed
Prunus avium [6] *Prunus cerasus* [5]	Not stated	Rosaceae plant family Wild cherry family; 100 ml juice 4×/day
Taraxacum syriacum [6]	Not stated	Compositae plant family Common name: Silkweed Decoction of roots
Tinospora cordifolia Merr [10].	Not stated	Menispermaceae plant family Plant juice has given 2×/day to “reduce urinary diseases”
Tribulus terrestris [2, 5]	Diuretic, analgesic, and litholytic Decreases urinary oxalate through hepatic enzymes	Zygophyllaceae plant family
WLS (Wullingsan) [1, 9] Composition: *Alisma orientalis* Alisma rhizome (Takusya) *Polyporus umbellatus* *Poria cocos* *Cinnamomum cassia*	Diuretic compound Decrease PO4 concentration Inhibit hydroxyapatite Inhibit calcium oxalate Enhance calcium excretion	First used in the third century Used to “drain dampness, strengthen spleen, warm the Yin (cold nature), promote QI transformation”

Note: References are provided for each herb/herb mixture; currently no evidence-based literature exists to support herb/herbal treatment

considerably. There is little or no oversight into their standardization, purity, or quality control. None are regulated in the United States by the Food and Drug Administration (FDA). The published literature has a wide array of singular or small case reports that may describe both success and more often adverse events with their use. Most of these reports lack the statistical methodology to support a cause-effect relationship. Natural practitioners and patients seldom use in isolation. Rather, the complexity of the conditions and other confounding variables associated with their use are neither controlled nor reported.

Many of these herbs have a scientific name but the actual plant species and variation of genus may be unknown or vary by region. As natural plants, the growing conditions may affect the actual content of the herbal component itself. The conditions under which the plants are harvested, dried, and stored are also unknown. Different plant components (i.e., bark, flowers, leaves, seeds, and stems) challenge comparisons.

The actual physiological mechanism for these herbs typically promote fluid intake or enhance a diuretic effect. The dilution factor of kidney stone formation particles has been shown to reduce risk in traditional medicine. Most doses are done by individual herbalists based on personal practice patterns, not by the weight of individual or other objective criteria. The preparation method, particularly "teas" or "infusions," produces an inconsistent dilution for comparison of effect. The method of administration can be orally or topically [2, 10–12].

Conversely, herbs may be present in weight loss supplements and other dietary supplements unrelated to kidney stone prevention. Their role in renal calculi may not be recognized [3].

Commercial Herbal Products

Numerous commercial products are marketed and many are sold only online. The search engine terms include kidney stone support, kidney stones, renal stones, kidney supplements, and kidney remedies. One website clearly posted an "advertorial disclaimer" stating the "reviews and ratings of our products on our website are for entertainment purposes only. Any buying decision should be researched by the consumer on their own first" [13].

Table 22.2 provides information on a few selected commercial herbal products with kidney health claims. The products are not reviewed or controlled by the FDA. Testimonials are often posted to describe the use and results by individuals. One website (kidneyremedyreviews.org) has a rating system based on stated criteria of ingredients, delivery method, commitment of brand to consumer, strength of money-back guarantee, and customer service. They state the information on their website is obtained from PubMed, WebMD, and the Prescribers' Digital References (PDR, pdr.net) [13]. A group of self-help websites also exists. One (top10homeremedies.com) includes a section on kidney stones and an ongoing blog of comments and replies. These websites label their footnotes to state they are informational only and do not provide medical advice [14]. Most of the websites advertise the commercial products in the margin.

Potential Herbal Nephrotoxicity

Limited information is available on herbal supplements and potential nephrotoxicity. The information is circumstantial, based on individual case reports. The herbal plant *Rumex crispus* (yellow dock) has been reported in conjunction with nephrolithiasis [3]. Nephrotoxicity of food plants such as rhubarb, cranberry, and sorrel has been discussed in other chapters.

Table 22.2 Selected commercial herbal-based products claiming to have an effect on kidney stones

Commercial product name (manufacturer)	Listed primary ingredient(s)	Listed treatment conditions
Cleanse Drops™ (Cleanse Drops LLC)	Chanca piedra extract	Kidney, gallbladder, and liver cleansing
Kidney Complete™ (Complete natural products)	Apple cider vinegar, beet extract, blueberry extract, and pomegranate extract	Kidney health
Kidney Stone Crusher™ (Blue Organics)	100% Chanca piedra extract	Kidney stones
Renavive® (Renavive)	Chanca piedra, *Tribulus terrestris*, parlsey seed extract, *Lawsonia inermis*, *Ficus racemosa*, *Boerhavia diffusa*, *Bergenia ligulata*, celery seed, *Crateva nurvala*, marshmallow root	Kidney support
Stone Breaker™ (Herb Pharm)	Chanca piedra, *Phyllanthus niruri*, *Hydrangea arborescens*, celery seed (*Apium graveolens*), and burdock seed (*Arctium lappa*)	System restoration, urinary, and gluten-free herbal supplement
Stone Free™ (Planetary Herbals)	Dandelion root, turmeric root, parsley root, ginger root	Kidney support
Uriflow™ (Uriflow)	Chanca piedra extract, turmeric, and *Boerhavia diffusa*	Natural dietary supplement

Information obtained from websites: top10homeremedies.com, kidneyremedyreviews.org, amazon.com (for individual drug manufacturers of products listed in table), Accessed April 2, 2019

Summary

Consumers often consider alternative therapies, such as herbal medicine, to treat a wide variety of chronic disease. Kidney stones are one of the largest areas of interest. Access to the internet provides a wide array of information that may or may not provide scientific evidence of efficacy or harm. Many consumers may be unable to effectively evaluate the safety and efficacy of suggested treatment. They hold a perception that "natural" products are a viable alternative or adjunct to traditional medicine. The majority of herbs, herbal formulas, and commercial products are not linked to direct harm. However, there is scant evidence that they provide direct benefit in most cases. The strongest advice a health professional may offer to a consumer is to drink large quantities of water if they choose to ingest any of these preparations since scientific evidence is supportive of high fluid ingestion and report any symptoms for professional evaluation.

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Chapter 23
Evaluation and Management of Pediatric Nephrolithiasis

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Keywords Pediatric · Nephrolithiasis · Primary hyperoxaluria · Dent disease · Cystinuria · Genetics

Key Points
- All children with nephrolithiasis should have a complete metabolic evaluation on initial presentation, as a metabolic risk factor may be found in the majority of children.
- Many rare genetic causes of kidney stones present in childhood and are associated with a lifetime of morbidities related to nephrolithiasis as well as the risk for development of chronic kidney disease. Hence, it is important to consider these diagnoses early.
- In the majority of children, metabolic risk factors can be found, resulting in tailored medical and dietary therapy and prevention of further stone formation.

Introduction

As in the adult population with nephrolithiasis, the incidence of pediatric nephrolithiasis has been increasing over the last 20 years in the United States. Recent population-based studies have suggested an increase in emergency room visits for pediatric nephrolithiasis from 1997 to 2012 in South Carolina with a particular increase in the adolescent female population [1, 2]. Furthermore, the Rochester Epidemiology Project also reported a 4% annual increase in incidence rate of stones from 1984 to 2008, completely represented by an increase in incidence in the adolescent population, with stability in the younger age groups [3]. The impact of kidney stones presenting in the pediatric age group is lifelong, and hence the long-term ramifications of nephrolithiasis in these children must be considered. Adult kidney stone disease has been associated with increased risk of heart disease, chronic kidney disease, hypertension, and decreased bone mineral density [4]. Lastly, stone recurrence rates in childhood are high, with approximately a 50% recurrence rate within 3 years of the first stone [5]. Metabolic risk factors for nephrolithiasis have been identified in 75–84% of children evaluated [6–8]. Lastly, early detection of genetic causes of nephrolithiasis is critical for prevention of stone recurrence, as well as potentially decreasing progression to end-stage renal disease [9–12]. This underscores the importance in children of metabolic evaluation and institution of early prevention and treatment measures upon initial presentation with nephrolithiasis.

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Clinical Presentation

Symptoms of pediatric urolithiasis are similar to adult urolithiasis—renal colic with flank pain, vomiting, gross hematuria, or stone passage. However, in younger children, symptoms may be much less specific: abdominal pain, similar to appendicitis, intussusception, or gastroenteritis; urinary tract infection; lower tract symptoms such as dysuria, difficulty voiding or lower abdominal pain, as well as in infants' unexplained colic [13, 14]. With acute stone presentation, flank tenderness, suprapubic tenderness, scrotal pain, or even a stone present in the urethra should be assessed.

Evaluation (Fig. 23.1)

A detailed medical history should start from birth history, gathering information on prematurity and complications in the neonatal intensive care unit (NICU), cardiopulmonary disorders, and potential medication exposures that may lead to increased stone risk in the NICU, such as furosemide, steroids, or excessive vitamin D [15]. History of urologic abnormalities, such as ureteropelvic junction obstruction, even after repair, may predispose to urinary stasis and stone formation [16]. Other urologic issues predisposing to stone formation include neurogenic bladder and bladder augmentation [17]. Anatomic

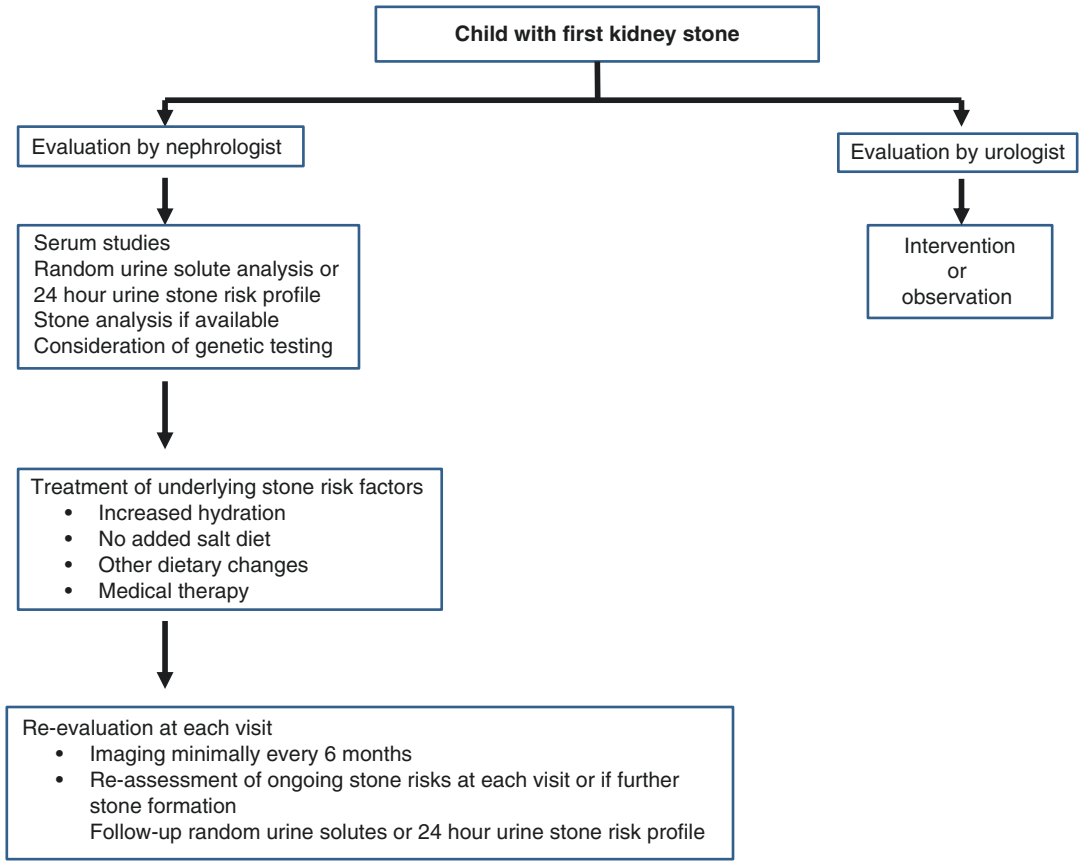

Fig. 23.1 Evaluation

abnormalities such as horseshoe kidney have been associated with a 20% incidence of nephrolithiasis, and hypercalciuria and hypocitraturia are the most common metabolic abnormalities found [18]. Inflammatory bowel disease, short gut syndrome, and cystic fibrosis are associated with secondary hyperoxaluria, hypercalciuria, and/or hypocitraturia, and these children may have decreased oral intake and increased gastrointestinal losses predisposing to nephrolithiasis as well [19–21]. Other systemic genetic disorders may carry risk of nephrolithiasis, such as Williams syndrome, which may result in hypercalcemia in the first year of life but hypercalciuria lifelong [22]. Similarly, glycogen storage disease type 1 is associated with hypercalciuria, hypocitraturia, and hyperuricemia [23, 24]. Lastly, prolonged immobilization due to the use of wheelchair or immobilization acutely after a surgical procedure or an injury may result in leaching of calcium from the bones and resultant hypercalciuria.

Further history should review all lifelong medication and dietary exposures. As mentioned, furosemide (loop diuretics) is associated with hypercalciuria and a common risk factor for nephrolithiasis and nephrocalcinosis. Children with seizure disorders treated with the ketogenic diet as well as medications such as zonisamide or topiramate (weak carbonic anhydrase inhibitors) have an increased risk of nephrolithiasis secondary to hypocitraturia and variable hypercalciuria [25, 26]. Excess vitamin supplements such as vitamin D or calcium (in the form of supplements or antacids) may result in hypercalciuria [27]. Excess vitamin C ingestion may result in increased oxalate production and urinary excretion [28]. Several protease inhibitors produce specific drug crystals in the urine and specific drug stone formation (indinavir, atazanavir, and darunavir) as well as may predispose to other stone formation due to concurrent urinary metabolic abnormalities [29–32]. Lastly, antibiotics such as ciprofloxacin, particularly with higher doses and prolonged course, have been reported to result in stone formation [33].

A detailed dietary history should include amount of fluid intake as well as type of fluid and how it is administered (oral or tube feeds). Given the increased risk of stones with a high salt diet, salt intake should be assessed, including added salt, and the use of prepared foods/frozen foods, "junk" foods, and fast foods. Individual diets should be reviewed, particularly given the increased oxalate in some foods in vegetarian or vegan diet and nonanimal protein sources such as nuts or beans and in nutritional substitutes such as nut-based milks or nut-based flours [34, 35].

Family history is very important, as more than 40% of children with stones have a family history of nephrolithiasis [7, 36]. Hypercalciuria is very common in first-degree relatives of calcium stone formers [37]. Furthermore, rare genetic disorders with variable inheritance patterns result in nephrolithiasis [10]. Dent disease, an X-linked disorder, may be elucidated by a history of stones, proteinuria, and renal failure in males. Other recessive disorders such as cystinuria or primary hyperoxaluria will not have a family history in the index case. However, genetic disorders should be considered if there is an early onset, familial prevalence, consanguinity of the parents, multiple or large recurrent stones, or nephrocalcinosis. The genetics of most kidney stone disorders is not well understood. Recent literature reported a cohort of pediatric patients with nearly 17% having a genetic diagnosis when screened for one of 30 known genes reported to result in nephrocalcinosis or nephrolithiasis [11]. Recessive disorders were found more commonly in children less than 1 year of age and dominant disorders more commonly in children over 1 year of age. In a further study in pediatric patients looking at whole exome sequencing, a causative mutation was found in a known nephrolithiasis/nephrocalcinosis gene in 29% of those screened [12]. Early identification of genetic disorders allows for tailored treatment to directly address the disease pathophysiology and potential other organ systems impacted and may also reduce the risk/progression of CKD [10]. Furthermore, once an index case has been identified, sibling screening is extremely important to diagnosis and treat early to prevent stone formation and other complications.

Physical exam in children should include assessment of growth parameters, as several disorders may present with growth delay, such as various causes of renal tubular acidosis or Bartter syndrome. Hypertension may suggest obstruction or other systemic disorders or renal scarring. Bone abnormalities/rickets may also suggest renal tubular abnormalities.

Imaging

Ultrasound is the first choice for imaging in pediatrics, given its availability and lack of radiation [38]. Ultrasound also gives information on stone size, renal size, anatomic abnormalities, or obstruction. Nephrocalcinosis is also best assessed by ultrasound. Ureteral stones, however, may not be as well visualized by ultrasound. Non-contrast, low-dose radiation stone protocol CT identifies nearly all stones. Generally in pediatrics, CT is reserved for assessment of stone burden if ultrasound findings are not clear, especially for the surgeon to best determine stone location and size prior to a procedure. This may be particularly useful if body habitus or immobility limit ultrasound results. If there is evidence of obstruction or hydronephrosis persists post stone passage/removal, other studies may be indicated to assess for obstruction such as Technetium-99m mercaptoacetyl triglycine scan (MAG 3 renal scan) [16]. In children with urinary tract infections, a voiding cystogram may be indicated to evaluate for vesicoureteral reflux.

Metabolic Evaluation

Stone analysis when available is extremely helpful in guiding ongoing evaluation and treatment. Thus, families should be encouraged to strain the urine and save any fragments that are passed. Stones can be sent to a laboratory specializing in stone analysis [7].

The examination of a freshly voided urine is critical at the initial visit and at follow-up visits. The specific gravity helps predict the child's fluid intake. The urine dipstick may pinpoint abnormalities such as proteinuria or glycosuria that result in consideration of renal tubular or genetic disorders such as renal tubular acidosis or Dent disease. Microscopic examination may delineate lower tract appearing red cells indicative or an irritative process or crystalluria that may be pathognomonic of the diagnosis such as in cystinuria or APRT deficiency. The presence of white cells or bacteria could indicate infection and a urine culture should be sent.

Serum studies should include assessment of electrolytes, CO2, BUN, creatinine, calcium, magnesium phosphorous, and uric acid, to help pinpoint any abnormalities that would suggest a potential metabolic defect in the handling of these substances. Twenty-five hydroxy vitamin D and 1,25 dihydroxy vitamin D and PTH should also be measured.

In pediatrics, many children with nephrolithiasis may not be toilet trained, either due to young age or due to developmental delays. Hence, in these cases, a 24-hour urine collection may not be possible. Random urine solutes can be assessed, and normal for these solute/creatinine ratios are listed in Table 23.1. Initial urine random solutes should include calcium, magnesium, citrate, oxalate, uric acid, and creatinine. If there is a high index of suspicion for a genetic disorder due to large stones in a young patient, a more complete random urine hyperoxaluria panel, including oxalate metabolites, can be sent. Similarly, random urine amino acids can be sent to assess for cystinuria. Random urine calcium/creatinine ratio may be impacted in an infant or tube-fed child by formula or milk fed resulting in transient absorptive hypercalciuria, and it is often best to try to obtain the urine sample distant from a feed where possible. Sometimes, repeat random urine solute analysis is needed to make a diagnosis.

Twenty-four-hour urines, including supersaturation profiles, are invaluable tools and should be first line when the child is toilet trained or where able to place an indwelling foley. These normal 24-hour values are listed in Table 23.1. Twenty-four-hour urines are also critical for follow-up after any preventative measures are undertaken.

Lastly, genetic testing should be considered if specific values or history points to a potential for a genetic diagnosis.

Table 23.1 Normal ranges of urine tests

Solute	Calculation of random solute to creatinine ratio	Random normal urine value by age	Normal 24-hour urine value
Calcium	Calcium/creatinine (mg/mg)	<1 year: 0.6–0.8 >2 years: 0.21	4 mg/kg/24-hour
Oxalate	Oxalate/creatinine (mg/mg)	1 year: 0.15–0.26 1–5 years: 0.11–0.12 5–12 years: 0.006–0.15 >12 years: 0.002–0.083	<45 mg/24-hour
	Oxalate/creatinine (mmol/mol)	0–6 months: <325–360 7–24 months: <132–174 2–5 years: <98–101 5–14 years: <70–82 >16 years: <40	<0.5 mmol/1.73m^2/24-hour
Citrate	mg citrate/g creatinine	Adult female: 300 Adult male: 180	
Uric acid	(urine) uric acid (mg/dl) × serum creatinine (mg/dl)/ urine creatinine (mg/dl)	0.53–0.57 mg/dl GFR	815 mg1.73m^2/24-hour
Cystine	mg/g creatinine mmol/g creatinine	<75 0–100	

GFR glomerular filtration rate
References: [40, 41, 50–55]

Etiologies and Treatment of Pediatric Nephrolithiasis

Similar to adults, idiopathic hypercalciuria is the most metabolic common cause found during evaluation for nephrolithiasis. Treatment includes high fluid intake and no added salt diet [34, 39]. Thiazides to lower urinary calcium levels are used frequently and tolerated well [39]. As in adults, the RDA for calcium and vitamin D is recommended to maintain normal bone health [34].

Primary hyperoxaluria is a rare autosomal recessive disorder resulting in nephrolithiasis, nephrocalcinosis, and, in some cases, chronic kidney disease/end-stage renal disease [9, 20, 40]. There are three types resulting in mutations in one of three liver enzymes. In PH1, the AGT enzyme is mutated and results in overproduction of oxalate, and urinary values of oxalate and glycolate are elevated. In infants with PH1, infantile oxalosis may be the initial presentation with acute renal failure and extremely echogenic kidneys, especially with intercurrent illness or dehydration. PH1 may progress to ESRD. Primary hyperoxaluria type 2 results in a defect in the GR/HPR enzyme. Renal function is usually maintained and systemic involvement rare. In PH2, urinary levels of oxalate and glycerate are elevated. Primary hyperoxaluria type 3 results in a defect of the DHDPSL gene, and elevations in urine oxalate and 4-hydroxy-2-oxoglutarate are found. PH3 also seems to maintain renal function, although this genetic diagnosis has only been known since 2010 and long-term data is limited. Primary hyperoxaluria should be considered in infants and young children, as early diagnosis may help prevent complications such as CKD.

Treatment of primary hyperoxaluria is limited [10, 40]. In PH1, AGT is a pyridoxal phosphate-dependent enzyme, and although only 30% of patients with PH1 will respond to it, pyridoxine therapy is benign and should be initiated for any child with an elevated urine oxalate, pending genetic confirmation of type. High fluid intake should be prescribed, at 2–3 liters/1.73 m^2/day. Occasionally, feeding tubes may be indicated in infants to achieve such high fluid goals. No added salt diet should be followed. The impact of dietary restriction of oxalate in primary hyperoxaluria is not significant, but high intake of oxalate containing foods should be avoided. Solubility agents such as phosphate, citrate, and magnesium are also useful. These children should be seen frequently with imaging and

24-hour urine followed closely to assess impact of above regimen. Renal function should be monitored. In order to prevent acute stone formation and acute kidney injury, families should be instructed to seek immediate medical attention for any illness where the child cannot keep fluids down in order to prevent dehydration.

In many cases of PH type 1, progression to ESRD may occur. However, if the child has an increased creatinine, serum oxalate levels should be followed. As the GFR falls below 30–40 ml/min/1.73 m^2, oxalate levels exceed>30 mmol/l, and this is an indication to start dialysis to help prevent impact of systemic oxalosis (oxalate deposits in the eye, bone, heart). Dialysis is not a long-term treatment option as neither conventional hemodialysis (up to 6–7 days a week) nor peritoneal dialysis can overcome the excess generation of oxalate. Kidney and liver transplantations are treatment options for patients with PH1. Liver transplant allows for replacement of the defective enzyme AGT. Native liver must be removed to prevent ongoing oxalate production, and native kidneys must be removed at the time of transplant as they are a source of oxalate. Posttransplantation dialysis should continue in order to clear the oxalate burden, until systemic oxalate levels are below 20 mmol/l [10, 40].

Secondary hyperoxaluria may occur in many gastrointestinal disorders as well as cystic fibrosis. Treatment is similar to adults, with decrease in dietary oxalate intake, decrease in fat intake, and, where needed, intake of calcium to bind oxalate in the gut [19, 20].

Cystinuria is a rare autosomal recessive disorder of one of two proximal tubular amino acid transporters (SLC3A1 or SLC7A9), resulting in elevations of four dibasic amino acids in the urine (cystine, ornithine, arginine, and lysine—COAL) [10, 41]. Cystine is extremely insoluble in the urine and results in large, recurrent stones. Interestingly, most children do not present with stones until the second decade of life. Cystinuria requires very large fluid intake in order to increase solubility in the urine to below 250 mg/l. Children are often asked to awaken at night to drink and void. Cystine is more soluble in an alkaline urine, and hence potassium citrate is prescribed to achieve a urine pH above 7. If further stone formation occurs despite these measures, chelators such as tiopronin or d-penicillamine which form a bond with cystine and increase solubility can be added to the regimen and are generally tolerated well despite a reported significant side effect profile. These children should be seen frequently and imaging and 24-hour urine followed closely to assess the impact of above regimen. Renal function should be monitored. In order to prevent acute stone formation and acute kidney injury, families should be instructed to seek immediate medical attention for any illness where the child cannot keep fluids down in order to prevent dehydration.

Dent disease is an X-linked recessive disorder caused in most cases by a mutation in CLCN5 (Dent 1) but less commonly OCRL1(Dent 2), resulting in tubular (low molecular weight) proteinuria (specifically elevations in urinary retinol binding protein and alpha 1 microglobulin), variable hypercalciuria, elevations in 1,25 dihydroxy vitamin D, nephrolithiasis/nephrocalcinosis, and progression to ESRD in adulthood [10, 42, 43]. This disorder should be strongly considered if family history of ESRD exists in males or if the child also has proteinuria on initial evaluation. Low-molecular-weight proteins are elevated in the urine five to ten times above normal. Some patients have focal glomerulosclerosis on renal biopsy and hence develop glomerular proteinuria as well. There is no specific treatment for Dent disease. High fluid intake is prescribed for ongoing stone prevention. Hypercalciuria can be treated with thiazides, but may not be as well-tolerated in children with Dent disease compared to those with idiopathic hypercalciuria, as children with Dent disease tend to develop severe hypokalemia and volume depletion. Although angiotensin-converting enzyme inhibitors or angiotensin receptor blockers help with reduction of proteinuria in other renal diseases, these medications do not reduce tubular proteinuria and may only be indicated for those with glomerular changes.

Lowe syndrome (caused by different mutations in OCRL1 than seen with Dent disease), also called oculocerebrorenal syndrome, is an X-linked recessive system disorder, with congenital cataracts, hypotonia, intellectual disability, proximal renal tubular acidosis, hypophosphatemic rickets, aminoaciduria, and low-molecular-weight proteinuria, and stones or nephrocalcinosis may occur [43].

Uric acid stones are rare in pediatrics. With uric acid stones, other causes should be assessed including urinary tract anomalies or abnormalities in uric acid production, reabsorption, or secretion. Rare disorders of purine and pyrimidine metabolism such as phosphoribosyl pyrophosphate synthetase superactivity should be considered if other systemic findings such as gouty arthritis, hyperuricemia, and neurologic symptoms such as deafness, hypotonia, motor delay, or autism are present [9, 44]. This can be treated with allopurinol, low purine diet, high fluid intake, and alkalinization. Lesch-Nyhan syndrome is a very rare X-linked recessive disorder associated with hypoxanthine-guanine phosphoribosyl transferase deficiency and results in uric acid overproduction [44, 45]. Lesch-Nyhan disorder primarily presents with developmental delays and severe self-destructive behaviors. Many families report orange crystals in the diaper beyond early infancy, and these children may form uric acid stones. Allopurinol, high fluid intake, and alkalinization can be used for ongoing stone prevention [45].

Acute issues related to uric acid may be seen in relation to tumor lysis syndrome in lymphoproliferative disorders [46, 47]. Treatment with high fluids and alkalinization prior to chemotherapy and radiation helps prevent uric acid nephropathy. Allopurinol or rasburicase may also be helpful in reducing serum uric acid levels.

Adenine phosphoribosyltransferase deficiency (APRT) is a rare autosomal recessive disorder presenting with early stones and may result in chronic kidney disease [10, 48, 49]. Infants may present with a reddish-brown diaper stain. This disorder results in 2,8 dihydroxyadenine crystals which are round and brown and also have a central Maltese cross pattern under polarized light. Stone analysis may also be diagnostic. APRT activity (absent in APRT deficiency) can be assessed in red blood cell lysates and genetic testing is available. Allopurinol and purine restriction and high fluid intake are used for ongoing stone prevention. APRT deficiency can be associated with progression to ESRD, so early diagnosis and treatment are also critical.

Children with seizure disorders on zonisamide or topiramate as well as the ketogenic diet are at risk for nephrolithiasis [25, 26]. The ketogenic diet has been shown to result in hypocitraturia, and less often, hypercalciuria, and calcium stones. With institution of this diet, citrate therapy is prescribed for stone prevention. Hyperuricemia and uric acid stones are less common. With zonisamide and topiramate, systemic acidosis, hypocitraturia, and/or hypercalciuria may be risk factors for stones. These children should have a high fluid intake, and citrate or thiazide therapy may be indicated.

Glycogen storage disease type 1 is associated with nephrocalcinosis/nephrolithiasis, resulting from hypocitraturia, hypercalciuria, and/or hyperuricemia [23, 34]. Hence, these children should have monitoring for development of nephrolithiasis and nephrocalcinosis with annual renal ultrasound. Serum studies to assess for acidosis or hyperuricemia should be assessed. Urine should be followed for development of hypercalciuria or hypocitraturia. Oral citrate supplementation, thiazides, and allopurinol can be used where indicated.

General Pediatric Guidelines

All children with pediatric stones should follow general pediatric guidelines for maintenance of immunizations, including annual influenza vaccine. For the rare genetic causes of kidney stone, where dehydration is a risk for rapid acute stone formation and/or acute renal failure, these families should be educated on the importance of seeking early medical attention to prevent dehydration if they develop a concurrent illness and cannot keep fluids down. Furthermore, nephrotoxic drugs such as nonsteroidal anti-inflammatory agents should be avoided. This should be emphasized to patients, as often IV formulations of these NSAIDS are first line for pain control in the emergency room setting.

Follow-Up

Since the reported recurrence rate of nephrolithiasis in pediatrics is high, close monitoring after the initial visit is critical for future stone prevention [5]. The pediatric stone patient should have regular scheduled follow-up with the pediatric nephrologist and urologist to assess for further stone formation and to reenforce fluid, diet, and medical therapy. For patients with rare genetic disorders such as primary hyperoxaluria or cystinuria, more frequent follow-up after diagnosis is helpful to insure good medical control. These complex patients are often seen every 3 months initially, with more careful monitoring of their metabolic control, monitoring of their imaging for stone formation, and periodic assessment of renal function. More routine stone formers may be seen every 6 months with ultrasound, urinary studies, and office visit. Often, once the less complex patients are compliant with their regimen and stone-free for more than 2 years, visits may be extended annually.

Conclusion

Pediatric nephrolithiasis is increasing in incidence, and all children should undergo a metabolic evaluation of stone risk factors after their initial presentation. In the majority of children, metabolic risk factors can be found, resulting in tailored medical and dietary therapy and prevention of further stone formation. In pediatrics, careful consideration of genetic causes for stone disease is extremely important, as early diagnosis and metabolic control not only helps prevent further stone formation but may prevent or delay development of chronic kidney disease.

Pediatric Case Study (Fig. 23.2)

A 7-month old baby girl presented to the emergency room with fever and vomiting. As part of evaluation, catheterized urine was obtained, and she was subsequently diagnosed with an *E. Coli* urinary tract infection. On further evaluation, a renal ultrasound demonstrated two normal sized kidneys,

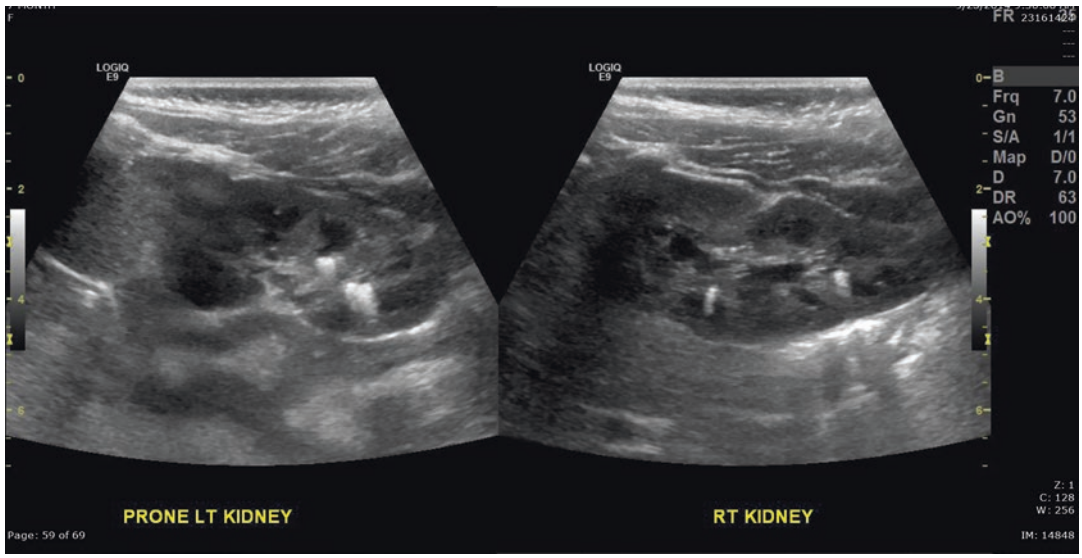

Fig. 23.2 Pediatric patient's ultrasound

with a 5 mm left lower pole stone, and two right lower pole stones, measuring 3 mm each. A VCUG demonstrated right-sided grade 3 vesicoureteral reflux. She was a full-term healthy baby, was product of an uncomplicated pregnancy and delivery, and was on no medications. One week after the urinary tract infection was diagnosed and treated, the family noted blood in a single diaper. She was referred to the kidney stone clinic at age 11 months. Urinalysis had a negative dipstick and microscopy demonstrated many calcium oxalate dihydrate crystals. Serum studies were all normal, including electrolytes, C02, BUN, Cr, Ca, Mg, Phos, uric acid, 25 Vitamin D, 1,25 dihydroxy vitamin D, and PTH. Random urine solutes were assessed. Calcium/creatinine ratio was 0.6, which is normal for an infant her age. Citrate was normal at 1033 mg/g creatinine. A hyperoxaluria panel was sent, and oxalate, glycolate, glycerate were all normal.

She was seen 4 months later due to her young age and presence of stones, and urinalysis demonstrated again many calcium oxalate dihydrate crystals. Follow-up ultrasound showed two echogenic foci on each side, and hence she had made a new stone. Urine solutes were repeated. Calcium/creatinine ratio was again normal for age at 0.6. Hyperoxaluria panel was repeated, and oxalate was elevated at 300 mg/g creatinine (normal at this age<129), and 4-hydroxyglutamate was elevated. Hence, clinically, she was suspected to have primary hyperoxaluria type 3. Genetics confirmed mutations in HOGA1. She was treated with high fluid intake and magnesium gluconate as a solubility agent. By age 2, she was drinking 48 ounces per day. At next few visits, only one stone on each side was seen, and hence no new stone formation in over 1 year of follow-up.

Moral of the story—if ongoing stone formation at young age, despite negative initial work-up, re-evaluate, and pursue genetics.

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Chapter 24
Nephrolithiasis Nutrition Therapy in the Pediatric Population

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Keywords Nutrition · Pediatrics · Nephrolithiasis · Kidney · Children · Stone · Urolithiasis · Renal

Abbreviations

AI	Adequate Intake
BSA	Body surface area
DRI	Dietary Reference Intake
RD	Registered Dietitian
RDA	Recommended Daily Allowance
UL	Tolerable Upper Intake Level
ND	Not Determined

Key Points
- Increasing rates of kidney stone occurrence in children and adolescents are associated with genetic, anatomical, metabolic, and modifiable risk factors.
- Modifiable and nutritional risk factors for kidney stone development include excessive sodium intake, excessive animal protein intake, inadequate fluid intake, inadequate citrate and potassium, excessive oxalate intake, inadequate calcium intake, and inadequate phytate intake.
- Early individualized intervention with medical nutrition therapy provided by a registered dietitian is both inexpensive and effective.

Introduction

The incidence of nephrolithiasis in children and adolescents has increased rapidly over recent decades worldwide and in the United States as evidenced by increased outpatient visits and hospitalizations [1, 2]. The majority of children with kidney stones have at least one metabolic risk factor [3]. While genetic, anatomical, and metabolic risk factors are the main culprits in kidney stone disease for the pediatric population, recent research suggests that modifiable risk factors, such as diet and obesity,

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play a larger role in the recent rising rates of kidney stone prevalence [1]. Though pediatric-focused studies are scarce, findings extrapolated from adult research suggest that these increasing rates of kidney stone occurrence in children and adolescents are attributed to nutritional risk factors, likely related to the increased consumption of processed and fast food as well as changing dietary norms seen both in the United States and other countries.

Medical nutrition therapy provided by a registered dietitian (RD) aims to decrease the risk factors that promote kidney stone formation as well as reduce risk of recurrence in the pediatric populations. Some of these nutritional risk factors include excessive sodium intake, excessive animal protein intake, inadequate fluid intake, inadequate citrate and potassium intake due to lack of fruits and vegetables, excessive oxalate intake, inadequate calcium intake, as well as inadequate phytate intake due to lack of fiber-rich foods [4]. Metabolic abnormalities, such as hypercalciuria, accompanied by one or more of the above nutritional risk factors can pave the way for kidney stone formation and often require a combination of both dietary and pharmacological interventions to prevent recurrence and potential chronic damage to the kidney. Medical nutrition therapy is not only an inexpensive and relatively safe intervention for patients, caregivers, and providers to take advantage of but also integral to ensuring continued growth and development for children and adolescents [5].

Fluids

Increased fluid intake is critical in nephrolithiasis prophylaxis regardless of kidney stone type. Adequate fluid intake reduces the concentration of stone-forming components and subsequently prevents urine supersaturation that can lead to crystallization and stone formation [6]. Some studies show more than half of pediatric patients having inadequate urine output and fluid intake compared to recommendations for their weight and/or age. For adolescents with stone disease, urine output of 2 or more liters/day is recommended, which can typically be achieved by consuming 2400 to 3000 mL per day or 1.5 times "maintenance" fluid needs [3, 6]. In children with kidney stones, it has been suggested that 1 mL/kg/hour of urine output is adequate to avoid supersaturation of stone-forming substances in the urine. This equates to a recommendation of a minimum of 1 oz (30 mL)/kg of body weight per day [7]. Of note, this is a minimum amount and may not reflect the fluid goal recommended to patients. An alternative calculation used in determining daily fluid requirements for children is the Holliday-Segar method, which recommends 100 mL/kg/d for the first 10 kg of body weight, 50 mL/kg/d for the second 10 kg, and an additional 20 mL/kg/d for every kg thereafter [8, 9]. This method provides higher fluid intake goals based upon bodyweight versus the 1 oz/kg body weight recommendation. Another way to calculate the amount of fluid required is using the body surface area (BSA) and using a minimum of 2 L/m^2. Additional urine output goals based on age suggest >750 mL per day for infants, >1000 mL per day for children 1–4 years of age, and>1500 mL per day for children 5–10 years of age [3, 10, 11]. Children and adolescents should increase fluid intake during increased levels of physical activity, hot climates, and for any other situations of increased fluid losses (diarrhea, etc.).

Water should typically make up most of the patient's fluid intake, except in infants, who should consume primarily breast milk and/or formula. Studies have shown that orange, lemon, and lime juices are beneficial as they increase urinary citrate and mixing these with water or into foods may be appropriate [5, 10]. Sugar-sweetened beverages, including sports drinks and soda, may increase risk of stone development and should be avoided and/or limited for reducing not only risk for kidney stone development but also risk for developing diabetes and obesity [3, 5] (Table 24.1).

Table 24.1 Holliday-Segar method for calculating daily fluid needs in children

	Daily fluid needs (mL/kg)
First 10 kg	100
Second 10 kg	50
Every kg thereafter	20

Data from Holliday and Segar [9]

Table 24.2 Dietary Reference Intakes (DRIs): Recommended Dietary Allowance (RDA), Adequate Intake (AI), and Tolerable Upper Intake Level (UL), sodium

Age	DRI/AI (mg/d)	UL (mg/d)
0–6 months	120	ND
7–12 months	370	ND
1–3 years	1000	1500
4–8 years	1200	1900
9–13 years	1500	2200
14–18 years	1500	2300

Data obtained from the Institute of Medicine (USA) [17]

Sodium

Excessive sodium intake in the diet can cause hypercalciuria [3–5, 12]. Higher levels of calcium in the urine increases risk for developing calcium-based kidney stones. Because calcium is a component of approximately 80% of kidney stones, reducing urinary calcium is an important goal for stone prevention [3, 13]. It may be beneficial to reduce sodium intake with other types of stones as well. For example, sodium may increase the risk of cysteine stones [1, 3, 14]. Reducing sodium intake in patients with struvite and uric acid stones may also be beneficial given the long-term risk of stroke and hypertension with kidney stone disease [3, 15].

Recommended sodium intake for infants and children is 2–3 mEq/kg/d (52–69 mg/kg/d) and 2400 mg/day for adolescents [12, 16]. Alternative recommendations by the Institute of Medicine recommend not exceeding the Tolerable Upper Intake Level (UL) for age: <1500 mg/d for children ages 1–3 years, <1900 mg/d for ages 4–8 years, <2200 mg/d for ages 9–13 years, and <2300 mg/d for ages 14–18 years [17]. Food sources that may be high in sodium include cereals, bread products, packaged foods, deli and processed meats, sports drinks, as well as food items from fast food establishments (Table 24.2).

Calcium

Adequate calcium intake is crucial in preventing kidney stone formation. Historically, it was presumed that too much calcium in the diet caused kidney stones; however, it has been well established that greater calcium intake, irrespective of the source, is associated with decreased risk of nephrolithiasis [5]. This is likely attributed to the binding effects of calcium with oxalate in the gut, thus reducing urinary oxalate excretion and preventing hyperoxaluria [5, 18]. The misconception of calcium intake with kidney stones and importance of adequate calcium intake for not only kidney stone prevention but bone health should be explained in depth to patients and

Table 24.3 Dietary Reference Intakes (DRIs): Recommended Dietary Allowance (RDA), Adequate Intake (AI), and Tolerable Upper Intake Level (UL), calcium

Age	DRI/AI (mg/d)	UL (mg/d)
0–6 months	200	400
7–12 months	260	520
1–3 years	700	1400
4–8 years	1000	2000
9–18 years	1300	2500

Data obtained from the Institute of Medicine (USA) [17]

their caregivers [19]. Good sources of calcium include dairy products such as milk and yogurt as well as calcium-fortified grains. Calcium-rich foods and beverages should accompany meals to maximize oxalate and phosphate binding as well as maximize calcium absorption for bone health. Recommendations for calcium intake for children and adolescents with kidney stones are based on the Dietary Reference Intake (DRI) for calcium based upon age: 200 mg/d for infants ages 0–6 months, 260 mg/d for infants ages 7–12 months, 700 mg/d for toddlers ages 1–3 years, 1000 mg/d for children ages 4–8 years, and 1300 mg/d for children and adolescents ages 9–18 years [3, 17, 20, 21] (Table 24.3).

Potassium and Citrate

Potassium and citrate also play an integral role in nephrolithiasis prophylaxis [2–5]. Citrate is found in potassium-rich foods, mainly fruits and vegetables, with the best sources of dietary citrate coming from citrus fruits, including lemons, limes, oranges, grapefruits, and some tangerines [2, 4, 5]. Other good sources of citrate include some non-citrus fruits, such as pineapple, various melons, as well as tomatoes [5]. Higher citrate intake is associated with decreased reabsorption of citrate and subsequent increased urinary excretion. This in turn reduces urinary calcium excretion and crystallization due to the alkali load from both citrate and potassium [3, 5]. Furthermore, citrate binds calcium in a soluble complex, which results in less calcium being available in the urine to bind with oxalates and/or phosphates to form kidney stones. The alkalizing effect of potassium and citrate also reduces the risk of developing uric acid and cystine-based calculi by increasing urine pH [2, 4, 5]. Recommendations for intake include consuming five servings of fruits and vegetables daily and 2 ounces of lemon or lime juice diluted in water daily [4]. Adequate potassium intake for children and adolescents can be determined using the Dietary Reference Intake (DRI) for age: 400 mg/d for infants ages 0–6 months, 70 mg/d for infants ages 7–12 months, 3000 mg/d for toddlers ages 1–3 years, 3800 mg/d for children ages 4–8 years, 4500 mg/d for preadolescents and adolescents ages 9–13 years, and 4700 mg/d for adolescents ages 14–18 years [17] (Table 24.4).

Protein

Protein intake in children and adolescents is crucial to promote healthy growth and development. Recommendations for protein needs for children and adolescents with kidney stones are based on the Recommended Dietary Allowances (RDA) and Adequate Intake (AI), which vary by age: 1.5 g/kg/d ages 0–6 months, 1.2 g/kg/d for ages 7–12 months, 1.1 g/kg/d for ages 1–3 years, 0.95 g/kg/d for ages

Table 24.4 Dietary Reference Intakes (DRIs): Recommended Dietary Allowance (RDA) and Adequate Intake (AI), potassium

Age	DRI/AI (mg/d)
0–6 months	400
7–12 months	700
1–3 years	3000
4–8 years	3800
9–13 years	4500
14–18 years	4700

Data obtained from the Institute of Medicine (USA) [17]

Table 24.5 Dietary Reference Intakes (DRIs): Recommended Dietary Allowance (RDA) and Adequate Intake (AI), protein

Age	DRI/AI (g/kg/d)
0–6 months	1.5
7–12 months	1.2
1–3 years	1.1
4–13 years	0.95
14–18 years	0.85

Data obtained from the Institute of Medicine (USA) [17]

4–13 years, and 0.85 g/kg/d for ages 14–18 years [17]. While adequate protein intake is important for growth and development in pediatrics, overconsumption of animal protein intake can exacerbate risk factors associated with nephrolithiasis [5, 19]. Excessive animal protein intake leads to mild chronic metabolic acidosis, which can worsen hypercalciuria. Acid load generated in the form of sulfuric acid from animal protein contributes to this decreased calcium excretion as well as decreased urinary citrate and pH excretion [22]. In addition, large amounts of animal protein in the diet subsequently increase purine intake and puts patients at risk for hyperuricosuria. Furthermore, patients with cystinuria may benefit from modifying protein intake to include less animal sources and more plant-based sources. Animal-based proteins are richer in cysteine and its precursor methionine [23, 24]. Decreasing animal protein intake may help decrease cystine excretion in the urine. Overall, increasing plant-based protein intake while decreasing animal-based protein intake may prove beneficial in reducing kidney stone risk and also provide protective nutrients including calcium, magnesium, and potassium [5, 19, 25, 26]. If a child or adolescent is consuming mostly plant-based products or is completely avoiding animal products, he or she should take a vitamin B-12 supplement as plant sources are lacking this vitamin [19] (Table 24.5).

Magnesium

Magnesium binds dietary oxalate in the gastrointestinal (GI) tract and is more soluble than calcium oxalate. Low urine magnesium increases the likelihood of oxalates combining with calcium to form calculi [4]. Recommendations for magnesium intake are based on the DRI for age: 30 mg/d for ages 0–6 months, 75 mg/d for ages 7–12 months, 80 mg/d for ages 1–3 years, 130 mg/d for ages 4–8 years, and 240 mg/d for ages 9–13 years, and 410 mg/d for ages 14–18 [17]. If low urine magnesium is found, magnesium-rich food sources such as nuts, oats, and other whole grains or the initiation of magnesium supplementation is recommended (Table 24.6).

Table 24.6 Dietary Reference Intakes (DRIs): Recommended Dietary Allowance (RDA) and Adequate Intake (AI), magnesium

Age	DRI/AI (mg/d)
0–6 months	30
7–12 months	75
1–3 years	80
4–8 years	130
9–13 years	240
14–18 years	410

Data obtained from the Institute of Medicine (USA) [17]

Vitamin C

Vitamin C (ascorbic acid) is converted to oxalate. When consumed in excess, it may increase the risk for kidney stones by increasing urinary oxalate excretion [5, 19]. No significant risk has been established for ascorbic acid obtained from food sources, and thus it is recommended that children obtain vitamin C from food sources rather than supplements. Good sources of vitamin C also happen to be good sources of citrate, including orange, lemons, limes, etc. Daily recommended vitamin C needs for children and adolescents can be met with adequate intake of fruits and vegetables. The daily requirement of vitamin C for children and adolescents ages 4–18 years is 25–75 mg/day [17, 19]. If clinically indicated and necessary, vitamin C supplementation should not exceed 1 g/day for those at risk for calcium oxalate nephrolithiasis [19].

Vitamin D

Vitamin D, a fat-soluble vitamin, plays a large role in bone health due to its role in regulating calcium absorption in the gut, bone mineralization, and calcium reabsorption in the renal tubule. Vitamin D consumed as ergocalciferol (D2) or cholecalciferol (D3) is hydroxylated in the liver to 25-hydroxyvitamin D3 and then to 1–25 dihydroxyvitamin D3 in the kidney. High levels of active vitamin D (1–25 dihydroxyvitamin D3) may contribute to increased calcium excretion in the urine and kidney stones. However, there is no data that supplementing with vitamin D2 or D3 contributes to kidney stone formation. Thus, if serum 25-hydroxyvitamin D3 level is low, it is recommended to provide short-term supplementation until vitamin D insufficiency/deficiency is reversed [19].

Oxalate

Urinary oxalate may result both from dietary intake of oxalate-rich foods and from endogenous synthesis [5, 27]. Excessive oxalate intake may cause increased oxalate absorption and consequently hyperoxaluria resulting in possible calcium oxalate stone formation. While the contribution of dietary oxalate to urinary oxalate excretion is variable, it may be beneficial to encourage decreased oxalate intake, especially in the setting of inadequate calcium intake as oxalate absorption is highly dependent on calcium intake [27]. High-oxalate foods and beverages include spinach, rhubarb, berries, sweet potatoes, beets, chocolate, nuts, and teas [5].The challenge with limiting oxalate-rich foods is these tend to provide good sources of other nutrients for children and adolescents. Clinical judgment should be used when restricting high-oxalate foods. It may also be helpful to ensure that high-oxalate foods are consumed with appropriate amounts of calcium and/or magnesium.

Table 24.7 Dietary Reference Intakes (DRIs): Adequate Intake (AI), fiber

Age	AI (g/d)
0–6 months	ND
7–12 months	ND
1–3 years	19
4–8 years	25
9–13 years (male)	31
9–13 years (female)	26
14–18 years (male)	38
14–18 years (female)	26

Data obtained from the Institute of Medicine (USA) [17]

Phytate

Phytates, antioxidant compounds found in fiber-rich food sources, may impact the risk for kidney stone development. Higher phytate intake is associated with increased urinary citrate excretion, which decreases the amount of urine calcium available to bind with oxalate or phosphorus [17]. Fiber-rich foods include plant seeds, nuts, legumes, and grains. Fiber recommendations to meet the Adequate Intake (AI) for age are based on the following: 1.1 g/kg for ages 1–3, 0.95 g/kg for ages 4–13, and 0.85 g/kg for ages 14–18 [17]. (Table 24.7)

Summary

The frequency of nephrolithiasis seen in pediatrics continues to grow with modifiable risk factors becoming more influential in increasing the risk of children and adolescents developing kidney stones. Plenty of fluids should be encouraged as well as limiting sodium and excessive animal protein intake. Furthermore, consumption of a calcium-rich food or beverage with each meal and consumption of fruits and vegetables throughout the day are highly recommended to help reduce risk. A registered dietitian can help patients and parents with nutrition education regarding kidney stone nutrition therapy at a relatively low cost as well as provide additional recommendations for supplementation if needed.

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Part VI
Resources

Chapter 25
Dietary Database of Oxalates

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Keywords Dietary database · Dietary oxalate content

Key Points
- Dietary oxalate is commonly found in foods.
- Modification of diet to reduce the intake of dietary oxalate is important in the clinical management of nephrolithiasis.
- Determining dietary oxalate found in foods and identifying foods high, moderate, and low in dietary oxalate content are critical for dietary management.
- Published tables and online databases are available that provide the oxalate content of common and ethnic foods.

Introduction

Clinical management of nephrolithiasis includes the reduction of dietary oxalate intake. Foods with the highest amounts of oxalate are plant based and include spinach, rhubarb, beets, chard, wheat bran, and nuts [1, 2]. Chocolate and tea also have high oxalate content [1, 3]. Because oxalate is commonly found in foods, access to sources with information containing food oxalate values is critical to help patients manage their condition. There are various databases and published tables available with oxalate values that are useful for dietary modification. However, there are differences in published oxalate values in the foods. These differences in values can be attributed to biological factors, processing of food items, and the analytical methodology of measuring food oxalate content [4]. Biological factors include varying plant species, variability of the plants themselves, growing conditions, soil composition, sunlight, nutrients during growth, geographic location, rate of growth, and timing of harvest. Processing of the oxalate containing food and cooking methods can affect the content and bioavailability [4]. In addition, there are various analytical methods used to quantify oxalate which may produce varying levels seen in different databases [2, 4].

There are a multitude of resources that provide the oxalate content of food which are published in print form that is found in books or scientific research articles as well as online databases. While

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different tables and databases may have varying oxalate values for similar food items, they can serve as an approximate range for individuals to identify high, moderate, or low oxalate content. There are also multiple international databases that include both common and ethnic foods, as well as specialty items such as phytochemicals, botanicals, and chocolate. The following sections highlight these resources that contain oxalate content information. Table 25.1 highlights commonly consumed foods containing moderate to high levels of oxalate content, and these values represent published ranges compiled from various databases and research studies.

Table 25.1 Published ranges of oxalate content (mg/100 g food) of selected foods

Food item (100 g)	Range of oxalate values (mg)	Food item (100 g)	Range of oxalate values (mg)	Food item (100 g)	Range of oxalate values (mg)
Flours and grains		*Herbs and spices*		*Vegetables*	
Barley flour	56	Black pepper	419	Amaranth leaves, raw	1090
Buckwheat flour	269	Caraway seeds	890–900	Asparagus, raw	130
Bulgur, cooked	47	Cardamom, green	4000–4014	Bamboo shoots, raw	23
Cornmeal	54	Coriander seeds	995–1005	Beet leaves, raw	121–916
Couscous	10–65	Cumin	1500–1505	Beet root, boiled	76–675
Grits, corn	57	Curry powder	1065–1070	Bitter melon, raw	71
Millet, cooked	36	Ginger	1480–1488	Broccoli, raw	190
Oats	16	Nutmeg	200–201	Brussels sprouts, raw	360
Rice, basmati	17	Turmeric powder	1910–1914	Cabbage, Chinese, raw	6
Rice, brown, cooked	12			Cabbage, green, raw	100
Rice flour, brown	37	*Legumes*		Carrot, raw	500
Rice bran	238	Anasazi beans, boiled	80	Cassava root, raw	1260
Rye flour, dark	51	Azuki beans, boiled	25	Cauliflower, raw	150
Semolina flour	48	Black beans, boiled	72	Celery	190
Wheat flour, white unbleached	40	Cowpeas, boiled	4	Chicory, raw	210
Wheat flour, whole	67	Fava beans, boiled	22	Chives, raw	1480
Wheat bran	457	Garbanzo beans, boiled	9	Collard greens, raw	450
Wheat germ	44–269	Great northern beans, boiled	75	Coriander, raw	10
		Kidney beans, boiled	16	Corn, raw	10
		Lentils, boiled	8–118	Cucumber, raw	20
Fruit		Lima beans, boiled	8	Eggplant, raw	190
Apple	9–11	Mung beans, boiled	5	Endive, raw	110
Apricot	48–50	Navy beans, boiled	57	Garlic, raw	360
Avocado	18	Peas, green, raw	50	Kale, raw	20
Blackberries	19	Peas, split, green, boiled	6	Kale, Chinese, raw	23

Table 25.1 (continued)

Food item (100 g)	Range of oxalate values (mg)	Food item (100 g)	Range of oxalate values (mg)	Food item (100 g)	Range of oxalate values (mg)
Blueberries	15	Peas, split, yellow, boiled	5		
		Pink beans, boiled	75	Leek, raw	89
Cherries, canned	8	Pinto beans, boiled	27	Lettuce, raw	330
Currants	19	Red beans, boiled	35	Okra, raw	50
Date	100	Soybeans, boiled	56	Olives	44
Feijoa	60	White beans, small, boiled	78	Onion, raw	50
Figs, dried	57			Parsley, raw	150–1700
Figs, fresh	18	*Nuts*		Parsnip, raw	40
Goji berries	138	Almonds, roasted	431–490	Pepper, raw	40
Gooseberries, green	88	Cashews, roasted	262–2310	Potato, raw	50
Grapes, Concord	25	Hazelnuts, raw	167–222	Purslane, raw	850–1310
Grapefruit	10	Macadamia nuts, raw	42	Radish, raw	480
Guava	17–18	Peanuts, raw	96–705	Rutabaga, raw	30
Kiwifruit	23	Peanut butter	81–705	Snap beans, raw	360
Lemon peel	83	Pecans, raw	64	Spinach, raw	400–970
Lime peel	110	Pine nuts, raw	198	Squash, raw	20
Mango	10–12	Pine nuts, roasted	140	Sweet potato, raw	240
Orange	21	Pistachio nuts, roasted	49–57	Swiss chard, raw	800–812
Papaya	5	Pumpkin seeds, roasted	14	Tomato, raw	50
Pineapple, canned	26	Sunflower seeds, roasted	9	Tomato, sauce	14
Pineapple, dried	38	Walnuts, raw	74	Turnip, raw	210
Prunes, dried	34			Turnip greens, raw	50
Raspberries, black	55	*Soy-based products*		Watercress, raw	310
Raspberries, red	15	Miso	15	Yams, cooked	59
Rhubarb, raw	260–1235	Soy beverage (240 ml)	5–336	Yard long beans, raw	38
Star fruit	80–730	Soy flour	107–183		
Strawberries	15–25	Soy protein	15–496	*Other foods*	
		Soy sauce	11	Chocolate, milk (240 ml)	7
		Soy yogurt	47	Chocolate, milk, candy	42–123
		Soy nuts, roasted	1400	Chocolate syrup	97
		Soy nut butter	38–63	Cocoa powder	170–623
		Tempeh	28	Tea (100 ml), black, brewed	48–92
		Textured vegetable protein	58–584	Tea (100 ml), green, brewed	6–26
		Tofu	2–280	Tea (100 ml) herbal, brewed	0–8

Note: Published ranges of oxalate values compiled from various resources [4–6, 10, 11, 13–17]

Published Books and Scientific Research Articles

Below is a list of published in-print books and scientific research articles that contain information or easy-to-use tables highlighting oxalate content of foods.

Bowes and Church's Food Values of Portions Commonly Used *(19th Edition)*

Bowes & Church's Food Values of Portions Commonly Used is a comprehensive table of nutritional content of over 6000 common foods [5]. The table comprises validated nutritional data derived from primary sources including the US Department of Agriculture's (USDA) Agricultural Research Services, retail food chains, and food manufacturers. In its 19th edition, the data is continuously updated to maintain and reflect nutritional content of foods in the current food market. Oxalate content is provided in the Supplementary Databases for the Composition of Foods section under the Plant Acids subsection.

Journal of Food Composition and Analysis

The *Journal of Food Composition and Analysis* publishes scientific papers focused on the chemical and nutrient composition of human foods. The journal has published a number of manuscripts on analytical studies of oxalate content in various foods, including legumes, nuts and grain-based flours, pasta products, breads and crackers, fruit and vegetable juices, nectars and drinks, fruits native and imported in New Zealand, Thai vegetables, cereal grains and legume seeds, beverages, and cocoa and chocolate products [3, 6–12].

Journal of Food Research

The Canadian Center of Science and Education publishes the *Journal of Food Research* which features research articles in all areas relating to food science and technology. While most manuscripts on oxalate are primarily focused on analytical methods, there is a current published paper with tables of oxalate content of Egyptian fruit, vegetables, and commonly used herbs [13].

Journal of Agricultural and Food Chemistry

The *Journal of Agricultural and Food Chemistry* publishes research on the chemistry and biochemistry of agriculture and food. The journal has featured numerous published papers on biochemical, methodological, as well as analytical studies of oxalate content in foods. Research on oxalate content of soy and cereal and cereal products have been published with data tables of oxalate content [14, 15].

Online Resources

The following is a list of resources that are accessible online. They are primarily comprehensive databases of nutrient content of foods that include oxalate.

USDA Oxalic Acid Content of Selected Vegetables

The USDA Oxalic Acid Content of Selected Vegetables table is based on the original Agriculture Handbook No. 8–11, Vegetables and Vegetable Products, published in 1984 by the USDA [16]. It includes the oxalic acid content of vegetables (in grams) per 100 g serving. This resource is maintained and updated by the USDA and can be accessed via https://www.ars.usda.gov/northeast-area/beltsville-md/beltsville-human-nutrition-research-center/nutrient-data-laboratory/docs/oxalic-acid-content-of-selected-vegetables/.

Harvard TH Chan School of Public Health Oxalate Database

The Harvard TH Chan School of Public Health Oxalate Database is published and maintained by the Harvard TH Chan School of Public Health Nutrition department [17]. The database is based on foods that were analyzed for oxalate content at their laboratories. Tables for food items were developed to provide the absolute oxalate values (in mg per serving) as well as within a range of oxalate content categories (little or no oxalate with 0–1 mg per serving, low with 2–4 mg per serving, moderate with 5–9 mg per serving, high with 10–12 mg per serving, and very high with >12 mg per serving) in varying presentations. The tables are arranged by both food categories (i.e., vegetables, fruits) and meal groups (i.e., breakfast items, snacks, and desserts). Certain food items may be listed in more than one food category when applicable. This database can be accessed at https://regepi.bwh.harvard.edu/health/Oxalate/files.

Food Composition Table for Bangladesh

The Food Composition Table for Bangladesh is published by the Institute of Nutrition and Food Science, Center for Advanced Research in Sciences of the University of Dhaka [18]. The food composition table comprises nutritional data from various sources including research institutes, universities, and governmental and nongovernmental agencies. Data were compiled into a database management system, FAO/INFOODS Compilation Tool, and quality checks were carried out based on the guidelines set forth by the Food and Agriculture Organization of the United Nations and the International Network of Food Data Systems. The table contains common foods as well as ethnic foods native to Bangladesh and surrounding regions. Oxalate content is presented under the "antinutrients" section of the food composition table. Oxalate content in mg is provided per 100 gm serving. The table is published in print form and can be accessed via http://www.fao.org/fileadmin/templates/food_composition/documents/FCT_10_2_14_final_version.pdf.

NUTTAB 2010 Online Searchable Database

NUTTAB 2010 Online Searchable Database is a nutrient database that is maintained by the Commission for Food Standards in Australia and New Zealand [19]. The database information is generated from nutrient analyses of common foods as well as ethnic foods native to Australia and surrounding regions. NUTTAB 2010 is available as a searchable online database or as electronic database files. The searchable online database allows the user to search in four different options. The user can search by the name of the food item, food group, alphabetical listing of foods, or nutrient of interest. The database presents oxalic acid content in grams per 100 grams serving of the food item. This database can be accessed via http://www.foodstandards.gov.au/science/monitoringnutrients/nutrientables/nuttab/Pages/default.aspx.

Dr. Duke's Phytochemical and Ethnobotanical Databases

Dr. Duke's Phytochemical and Ethnobotanical Database is maintained by the Agricultural Research Service of the USDA and includes oxalic acid content of phytochemicals and botanicals [20]. This database is based primarily on the H*andbook of Phytochemical Constituents of GRAS Herbs and Other Economic Plants* and other published quantitative data. This database is not intended for clinical use but rather for research on medicinal plants, their phytochemical components, and biological activity. The values given are in the range of the lowest and highest measured parts per million. This database can be accessed at the following link https://data.nal.usda.gov/dataset/dr-dukes-phytochemical-and-ethnobotanical-databases.

International Network of Food Data Systems (INFOODS) Table/Database Directory

The International Network of Food Data Systems (INFOODS) is a network of international food composition experts [21]. Under the guidance of the Food and Agriculture Organization of the United Nations, its mission is to provide guidelines, standards, compilation tools, databases, and other resources to promote the acquisition and dissemination of adequate and reliable data on the composition of foods worldwide. As part of their resources, they maintain a directory and repository of food composition tables and databases that are published worldwide. These include food composition tables and databases from their own FAO/INFOODS databases as well as for other geographic regions including Asia, Africa, North America, Europe, Latin America, Middle East, and Oceania. This is also a very useful listing for ethnic and regional foods. While not all of these tables and databases that are in their directory currently include oxalate content of foods, the listing is continually updated. Tables and databases available through INFOODS can be accessed at http://www.fao.org/infoods/infoods/tables-and-databases/en/.

Mobile Applications

As use of technology increases, mobile applications can make it fairly easy for individuals to access nutrition information at the touch of their fingertips. There are currently a few available mobile applications that allow one to look up oxalate content of foods as well as track oxalate intake in their diets. Oxalator, OxaBrow, Oxalater, Oox-Gout and Kidney Stones, and Oxalate Lookup are currently available applications developed for use on iOS and Android operating systems. All of them provide oxalate content of foods in varying search methods, either as a standard search by food item, by oxalate content level categories, by alphabetical food listing, or by food categories. Oxalator and Oxalater allow users to record and track their intakes. OxaBrow has a feature that displays food alternatives that have lower or no oxalate content compared to the food that was searched for by the user. While these may be great tools to help patients adhere to their low oxalate diet, caution is strongly advised when using these applications as the sources of oxalate content listed on the applications are not always known.

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Chapter 26
Kidney Stone Disease: Online and Educational Resources

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Keywords Urinary tract · Kidney stones · Kidney stone disease · Patient education · Online resources Urologic disease · Urological

Key Points

- Kidney stone disease is one of the most common problems associated with the urinary tract.
- It is estimated that 10% of individuals in the United States will be affected by kidney stones every year and this number continues to rise related to the increasing rates of obesity.
- The medical costs for the treatment and prevention continue to rise every year in relation to the number of kidney stone-related office and hospitals visits. This is a major health and medical issue that requires a preventative care and nutrition focus.
- It is imperative for the patient with kidney stone disease to be as knowledgeable as possible about every aspect of the treatment plan as well as preventive care to avoid future episodes.
- Patient education is an integral part of the treatment and prevention of kidney stone disease. Nutrition intervention is also a key component in the overall management of kidney stone disease. Thus an individualized and comprehensive patient education program helps to ensure that the prescribed nutrition intervention is adhered to and managed appropriately by the patient under the guidance of the dietitian and medical staff. This approach emphasizes the importance following the prescribed nutrition plan, medication schedule and empowers the patient to assume responsibility for their well being and health.
- It is important to educate and empower patients to routinely consult with their physician and registered dietitian any time they may have a desire to modify their prescribed treatment plan, medication schedule, or nutrition plan related to the treatment and prevention of kidney stone disease.
- There are numerous organizations that provide information and resources for medical staff and patients on the topic of kidney stones and kidney stone disease. The following section will provide a list of organizations that offer extensive online and educational resources for both medical staff and patients.

Kidney stone disease is one of the most common problems associated with the urinary tract. It is estimated that approximately 10% of Americans will develop a kidney stone or experience an issue

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related to kidney stones every year. Unfortunately, this number continues to rise along with increasing medical costs for the prevention and treatment of kidney stone disease.

The occurrence of kidney stones in adolescents has become more common in recent years. Factors such as race, gender, and ethnicity play a role in the development of kidney stones. It is more likely for white individuals to develop kidney stones compared to their black counterparts or any other races. Males tend to have a higher incidence of kidney stones compared to females, but recent studies show the number of females diagnosed with kidney stones is also on the rise. Factors such as nutrition intake (high sodium and protein intakes) and body weight (high body mass index (BMI)) have also been found to increase the risk of kidney stone formation. Typically, individuals tend to develop kidney stones in the middle or later part of their life. During the midlife timeframe, family and work commitments are at their highest, which translates to added stress, and any time spent away from work due to kidney stone issues becomes very costly.

The diagnosis, treatment, and prevention of kidney stones, as well as the time away from work as a result of a kidney stone attack, is estimated to cost over $2 billion yearly [1, 2, 3]. The typical medical costs for an individual that has had a kidney stone attack is twice as much compared to those that have never had a kidney stone incident. Kidney stones are often very painful and may continue to recur in some individuals. It is estimated that kidney stones lead to over 1.3 million emergency room visits yearly and this number continues to rise [1, 2, 3].

Prevalence of Kidney Stones

More recently kidney stones have been found to affect approximately 1 in 11 individuals in the United States. This represents a marked increase in stone disease compared with the NHANES III cohort, particularly in black, non-Hispanic and Hispanic individuals. Nutrition and lifestyle factors likely play an important role in the changing epidemiology of kidney stones. The lifetime incidence of kidney stones is nearly 11% in men and 7% in women. Once an individual has formed a stone, the likelihood of recurrence is 50% or greater at 5 years and up to 80% at 10 years.

A recent study utilized data from the 2007–2010 NHANES to estimate population prevalence of stone disease. There were 12,110 participants who responded to the questions about their related history of stone disease. The key findings included: Overall prevalence of stone disease was 8.8%; men (10.6%) were more likely to report stone disease when compared to women (7.1%); stone disease prevalence was highest among non-Hispanic White individuals (10.3%); stone disease prevalence was higher among obese (11.2%) and overweight (9.2%) individuals as compared to those with normal weight [4].

Another review study using NHANES data conducted by the Urologic Diseases in America Project, also noted that approximately 1 in 11 Americans are affected by urinary stone disease, which can pose a significant health-care burden. New investigations suggest that the increasing prevalence of stone disease is connected to nutrition and lifestyle factors. It was noted in this study review that urinary stone disease prevalence was last measured with 1988–1994 data from the National Health and Nutrition Examination Survey (NHANES) [5].

These studies suggest several reasons for increased prevalence of kidney stones include the rising incidence rates of obesity and increased body weight (BMI). In addition it is also suggested that the medical costs associated with kidneys stones will continue to rise in the United States and should be addressed as a major health-care concern that requires a preventative care focus.

Common Types of Kidney Stones

Calcium Stones The most common type of kidney stone (~80%) is calcium based and found in two types of compounds formed in the urine. The first forms in the presence of high calcium levels that combine with high oxalate levels in the urine and forms calcium oxalate. The second compound that

may form is calcium phosphate which forms in the presence of high calcium levels and increased pH levels in your urine.

Uric Acid Stones The following factors which include a high protein intake, obesity, and gout may lead to an increased uric acid level in the urine and pose a risk for the development of uric acid stones (5–10%). If uric acid becomes too concentrated, which may occur when the urine pH becomes abnormally low(more acidic), or if uric acid combines with calcium, this may cause the formation of an insoluble uric acid stone.

Struvite Stones Individuals that have had previous or current kidney or urinary tract infections may develop struvite stones (~10). These types of stones can grow rapidly and become very large in size. If left untreated, they can cause chronic infection as well as serious and irreversible damage to your kidneys.

Cystine Stones These are the most rare form of kidney stones, less than 1%, and are the result of a genetic disorder. This disorder causes the amino acid, cystine, to leak into the urine and form crystals that may accumulate into insoluble cystine stones.

Modifying nutrition intake, focused and continuous patient education, and taking medications as prescribed may provide viable treatment options to prevent kidney stone formation or the reoccurrence of stones for those affected individuals [6]. Thus nutrition intervention under the direction of the registered dietitian and medical staff is an integral part of the treatment and prevention of kidney stone disease. Nutritional supplements such as magnesium, mineral citrates, probiotics, etc. may be recommended by the physician and registered dietitian to prevent kidney stone formation. It is important to note that any type of nutritional supplements used for the prevention and treatment of kidney stones should only be taken at the direction of your physician and/or registered dietitian. Medical advances have also allowed for significant improvements in imaging tests to diagnose kidney stones as well as newer minimally invasive procedures to treat stones. These advances have enhanced the diagnostic and treatment options for individuals affected by kidney stone disease.

The following section will provide online resources related to the diagnosis, treatment, and prevention of kidney stones. Numerous organizations have extensive online resources available about kidney stones and will be denoted with the organization acronym.

- National Kidney and Urologic Diseases Information Clearinghouse (NKUDIC). https://www.niddk.nih.gov/health-information/urologic-diseases/kidney-stones. Accessed Jan 2018
- Definitions & Facts: (NKUDIC). https://www.niddk.nih.gov/health-information/urologic-diseases/kidney-stones/definition-facts
- Symptoms & Causes: (NKUDIC). https://www.niddk.nih.gov/health-information/urologic- diseases/kidney-stones/symptoms-causes
- Diagnosis: (NKUDIC). https://www.niddk.nih.gov/health-information/urologic-diseases/kidney-stones/diagnosis
- Treatment: (NKUDIC). https://www.niddk.nih.gov/health-information/urologic-diseases/kidney-stones/treatment
- Nutrition Plan: (NKUDIC). https://www.niddk.nih.gov/health-information/urologic-diseases/kidney-stones/eating-diet-nutrition
- Nutrition: (NKUDIC). https://uaf.edu/chc/community-resources/educational-resources/NKUDIC_KidneyStoneDiet_FS.pdf
- Clinical Trials: (NKUDIC). https://www.niddk.nih.gov/health-information/urologic-diseases/kidney-stones/clinical-trials
- National Kidney Foundation (NKF): Kidney Stones. https://www.kidney.org. Accessed Jan 2018
- 6 Easy Ways to Prevent Kidney Stones (NKF). https://www.kidney.org/atoz/content/kidneystones_prevent
- Calcium Oxalate Stones (NKF). https://www.kidney.org/atoz/content/calcium-oxalate-stone

- Cystine Stones (NKF). https://www.kidney.org/atoz/content/what-are-cystine-stones
- Diet and Kidney Stones (NKF). https://www.kidney.org/atoz/content/diet
- Kidney Stones (NKF). https://www.kidney.org/atoz/content/kidneystones
- Kidney Stone Treatment: Shock Wave Lithotripsy (NKF). https://www.kidney.org/atoz/content/kidneystones_shockwave
- Kidney Stone Treatment: Ureteroscopy (NKF). https://www.kidney.org/atoz/content/kidneystones_ureteroscopy
- Kidney Stone Treatment: Nephrolithotomy/Nephrolithotripsy (NKF). https://www.kidney.org/atoz/content/kidneystones_PNN
- Lithotripsy (NKF). https://www.kidney.org/atoz/content/lithotripsy
- National Institute of Diabetes and Digestive and Kidney Diseases (NIDDKD). https://www.niddk.nih.gov/health-information/urologic-diseases/kidney-stones. Accessed Jan 2018
- Eating, Diet, & Nutrition for Kidney Stones (NIDDKD). https://www.niddk.nih.gov/health-information/urologic-diseases/kidney-stones/eating-diet-nutrition
- Urology Care Foundation-Urological Patient Education (Kidney Stones). http://www.urologyhealth.org/urologic-conditions/kidney-stones. Accessed Jan 2018
- European Association of Urology. http://patients.uroweb.org/i-am-a-urology-patient/kidney-ureteral-stones/. Accessed Jan 2018
- National Library of Medicine. https://medlineplus.gov/kidneystones.html. Accessed Jan 2018
- KidneyStoners.org. http://www.kidneystoners.org. Accessed Jan 2018
- Kidney Stones Heath Center (WebMD). https://www.webmd.com/kidney-stones/tc/kidney-stones-topic-overview#1. Accessed Jan 2018
- Mayo Clinic. https://www.mayoclinic.org/diseases-conditions/kidney-stones/symptoms-causes/syc-20355755. Accessed Jan 2018
- American Urological Association-Clinical Guidelines for Medical Management of Kidney Stones. http://www.auanet.org/guidelines/medical-management-of-kidney-stones-(2014). Accessed Jan 2018
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- Harvard Health Publishing: Harvard Medical School – Kidney Stones. https://www.health.harvard.edu/diseases-and-conditions/kidney-stones-common-painful-preventable. Accessed Feb 2018
- Health Protocols: Kidney Stones-Integrative Interventions with Supplements. http://www.lifeextension.com/Protocols/Kidney-Urinary/Kidney-Stones/Page-10. Accessed Feb 2018
- University of Chicago: Kidney Stone Guidebook. https://kidneystones.uchicago.edu/kidney-stone-book/. https://kidneystones.uchicago.edu/the-kidney-stone-diet/. Accessed Feb 2018

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Chapter 27
Medical Nutrition Therapy and Evidence-Based Practice

Rosa K. Hand

Keywords Evidence-based practice · Evidence-based guidelines · Hierarchy of evidence · Research design · Systematic reviews

Key Points
- Evidence-based practice in medical nutrition therapy for kidney stones involves staying up-to-date on evidence-based practice guidelines.
- However, because there are limited practice guidelines in this area, it may be necessary to search and evaluate the primary literature to make practice decisions.
- Searching the literature starts with writing a question in PICO (population, intervention, comparison, outcome) format.
- Search results are then evaluated based on the study design, with randomized controlled trials considered to provide the best evidence.
- When primary literature is unavailable, practitioners can systematically collect outcomes from their own practice in order to advance knowledge in this area.

Evidence-based dietetics practice "involves the process of asking questions, systematically finding research evidence, and assessing its validity, applicability and importance…applying relevant evidence in the context of the practice situation…" [1]. This chapter will apply the principles of evidence-based practice to medical nutrition therapy for kidney stones, moving from the best-available resource, evidence-based practice guidelines, through the searching and evaluation of primary literature, to systematic outcomes tracking.

Existing Guidelines for MNT in Kidney Stones

Evidence-based clinical practice guidelines are considered the best source for making practice decisions [1]. But, some documents that call themselves guidelines are not of the highest quality. The National Guideline Clearinghouse is a web-based resource that indexes clinical practice guidelines [2]. In order to be indexed, the guideline must include "systematically developed statements including

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recommendations intended to optimize patient care" and be based on a systematic review [2]. These are good criteria against which to compare any document which calls itself a guideline. Checking the National Guideline Clearinghouse to determine whether a guideline is indexed there (and thus meets the criteria) or to see whether new guidelines have been released on a particular topic are both good practices.

There is only one National Guideline Clearinghouse-indexed guideline that includes information about nutrition and kidney stones: the American Urological Association Guideline on the Medical Management of Kidney Stones [3]. Because the content of this guideline has been reviewed in depth earlier in this book, this chapter will focus on the methodology behind the guideline, pointing out principles that can be used to understand and evaluate other guidelines that might be published in the future.

The AUA Guideline is based on a systematic review conducted by the Agency for Healthcare Research and Quality (AHRQ) [4], with additional systematic reviews to supplement those findings [3]. The AUA Guideline provides clinical practice statements that are classified as Standards, Recommendations, or Options [3]. The strength of evidence (quality of individual research studies and consistency between findings) behind each Standard, Recommendation, or Option is graded [3]. There are 6 diet therapies, 2 of which are considered Standards with Grade B evidence, and 4 of which are expert opinions[3] (Table 27.1). As defined by the AUA, "Standards are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A or Grade B evidence" while "expert opinion refers to a statement, achieved by consensus of the Panel of authors, that is

Table 27.1 Medical management of kidney stones: AUA guideline statements related to diet

Statement	Classification of statement type[a]	Evidence strength[b]
1. Clinicians should recommend to all stone formers a fluid intake that will achieve a urine volume of at least 2.5 liters daily	Standard	Grade B
2. Clinicians should counsel patients with calcium stones and relatively high urinary calcium to limit sodium intake and consume 1000–1200 mg per day of dietary calcium	Standard	Grade B
3. Clinicians should counsel patients with calcium oxalate stones and relatively high urinary oxalate to limit intake of oxalate-rich foods and maintain normal calcium consumption	Expert opinion	N/A
4. Clinicians should encourage patients with calcium stones and relatively low urinary citrate to increase their intake of fruits and vegetables and limit nondairy animal protein	Expert opinion	N/A
5. Clinicians should counsel patients with uric acid stones or calcium stones and relatively high urinary uric acid to limit intake of nondairy animal protein	Expert opinion	N/A
6. Clinicians should counsel patients with cystine stones to limit sodium and protein intake	Expert opinion	N/A

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[a]"The AUA nomenclature system explicitly links statement type to body of evidence strength and the Panel's judgement regarding the balance between benefits and risks/burdens." The nomenclature system includes standards, recommendations, and options, which are all supported by evidence, or clinical principles and expert opinion when there is insufficient evidence. For the diet statements, only standards and expert opinions were developed. As defined by the AUA, "Standards are directive statements that an action should (benefits outweigh risks/burdens) or should not (risks/burdens outweigh benefits) be undertaken based on Grade A or Grade B evidence," while "expert opinion refers to a statement, achieved by consensus of the Panel of authors, that is based on members' clinical training, experience, knowledge and judgment for which there is no evidence" [3]

[b]"The AUA categorizes body of evidence strength as Grade A (well-conducted RCTs or exceptionally strong observational studies), Grade B (RCTs with some weaknesses of procedure or generalizability or generally strong observational studies) or Grade C (observational studies that are inconsistent, have small sample sizes or have other problems that potentially confound interpretation of data)"

based on members' clinical training, experience, knowledge and judgment for which there is no evidence" [3]. Therefore, it is more important to follow Standards than Clinical Principles or Expert Opinions, and among Standards, to follow those with Grade A evidence, which indicates that there are well-conducted randomized controlled trials or exceptional observational studies to support the Standard.

Were multiple guidelines to be available and to conflict, more weight should be placed on the one which is based on a systematic review [2], and that is transparent about methodology for assigning grades to the statements. Unfortunately, there is a lack of consistency among guideline developers regarding their descriptions of guiding statements and the system they use for grading the body of evidence [5], so when reading a guideline, it is important to understand the criteria and definitions used by that particular organization.

Evaluating Evidence When There Are No Guidelines

Given that there is only one evidence-based practice guideline that includes MNT for kidney stones, there will frequently be practice situations for which there are no published guidelines. In these cases, evidence-based practice requires evaluating published research within the hierarchy of evidence [1]. Systematic reviews, with or without meta-analysis, are the most authoritative type of research, because they evaluate and combine primary research studies to come to a conclusion while taking the strengths and weaknesses of each article into consideration [1]. Systematic reviews and meta-analyses have pre-specified research questions and search strategies, which are designed to find all of the literature on a topic, not just the literature supporting one side of the question [6]. The Cochrane Database of Systematic Reviews is a good place to start searching for systematic reviews, as are standard medical databases.

Narrative reviews can be a helpful way to identify primary papers to read; however, beware as narrative reviews are subject to the bias of their authors in identifying primary research to include. The National Kidney Foundation/*American Journal of Kidney Disease* publishes the Core Curriculum in Nephrology narrative reviews on clinical nephrology topics, written by experts, with the intention of guiding educational programming [7]. The Update on Nephrolithiasis was published in 2016 [8] and is an example of a helpful narrative review. Comparing the Core Curriculum with the AUA Guideline highlights that clinical practice guidelines include specific recommendation statements, while reviews (narrative or systematic) discuss the literature but do not make the jump to a practice recommendation. Narrative reviews generally have a different purpose than influencing practice.

If you are unable to locate a systematic review or meta-analysis to inform your practice, start searching the primary literature. It can be helpful to outline your question in PICO format: population, intervention, comparison, outcome [6]. The population should include the condition and age of the patient(s) you are working with [9]. The intervention is the diet, supplement, etc. that you are interested in recommending [9]. The comparison is another intervention, even if it is standard care [9]. The outcome is what could change (either improve, or potentially an adverse event) as a result of the intervention. Good PICO questions balance specificity with brevity [9]. Once you have outlined the question in PICO format (Table 27.2), use the P and I components to search a medical database for relevant papers. PubMed has several useful tutorials on search strategies. It is generally not recommended to include the outcome component in your search because that can bias your results towards positive papers. If you are using PubMed, it can be a good idea to use the "human" filter.

Once you have results from your search, skim the titles and abstracts for those that sound relevant to your population and intervention of interest [9]. Among the relevant sounding abstracts, you should prioritize your reading of the full text based on the study design, relevance, and sample size, as

Table 27.2 Example of using the PICO format to outline a clinical question

		Example
P	Population	Adults, age >18 years with calcium oxalate stones
I	Intervention	Normal calcium intake achieved primarily through food sources
C	Comparison	Normal calcium intake achieved primarily through supplements
O	Outcome	Stone recurrence, urinary oxalate

discussed below. Remember that abstracts present only a snapshot of the research and usually focus on the positive results. Even though it can be difficult to obtain the full text of articles if you are not affiliated with a teaching institution, it is important not to make clinical/practice decisions based only on abstracts.

The next section briefly reviews study designs and considerations when reading papers with each design.

If your practice question relates to selecting an intervention, the best study design is a randomized controlled trial [9], in which patients are randomly assigned to receive one intervention and are compared to a group randomly assigned to a second intervention or nothing [10]. Because the assignment to interventions is random, the differences in outcomes between the groups can be attributed to the intervention [10]. Randomized studies can also have a crossover design, in which individual patients are compared over time periods when they receive two different interventions (or an intervention and control), with each patient serving as their own comparison [10].

There are also non-randomized controlled trials, which can be helpful but influenced by confounding [9]. In these studies, patients who have received different interventions are compared, but the assignment to the intervention is based on the patient or medical professional's preference [9]. Therefore, there may be underlying differences in who gets which intervention, and therefore not all outcomes can be attributed to the intervention [9].

If comparisons are made between groups of patients over multiple time points, this is a pre/post study [9]. For example, if a clinic implemented a new procedure and compared patient outcomes in the last 3 months of the old procedure and the first 3 months of the new procedure this would be a pre/post study. The assumption is that the patients seen in the two time periods are similar, but again any change cannot necessarily be attributed to the intervention, because other things might have changed in the same time period.

When reading an intervention study, careful consideration should be given to whether the intervention was randomized, in order to decide whether the results are persuasive enough to influence your own practice.

Questions about risk factors for the development of disease (or, conversely, for protective or preventative factors) are answered using cohort or case-control designs [1]. In a cohort study, groups of people are formed based on whether or not they have a theorized risk factor [10, 11]. In a prospective cohort, the groups are formed near the time of exposure, and then individuals are followed forward [10, 11]. These studies take years and require large groups of people because it is unknown whether the outcome of interest will occur [10, 11]. In a retrospective cohort, time is saved by examining existing information (e.g., medical records) to identify the risk factors and outcomes, but the groups for analysis are still formed based on exposure [10, 11]. In a case-control study, individuals are identified and assigned to groups based on whether they have the outcome/disease of interest (cases) or do not (controls) [10, 11]. These studies are used for rare outcomes and allow investigators to explore many predictive factors [10, 11]. However, how people remember these factors (e.g., their diet) can be influenced by whether they are cases or controls [11]. People who have an illness have more acute memories of things that they believe could have influenced their illness, leading to bias [10]. All of these study designs can help to establish evidence of risk factors for disease, but they cannot necessar-

ily change practice recommendations for prevention, because not every single factor can be collected and so there can be other confounding variables.

Finally, cross-sectional studies are used for questions about the prevalence of a disease [11]. In cross-sectional studies, all data are gathered at one point in time. NHANES is an example of a cross-sectional study. While these studies provide important information, they cannot establish any cause and effect relationship, only associations [10, 11]. A cross-sectional study is unlikely to change your practice, except to potentially make you aware of a condition which is increasing in frequency or a nutrient that many people are over- or underconsuming.

There are a few things to keep in mind with any paper you read:

- *Blinding*—In RCTs, the subject should not know which treatment they are getting (although this is not always possible in nutrition) [9]. However, even if this is not possible, or in studies where there is no intervention, the researchers who take the subject measurements or determine whether the subject is considered a case or control should be a different researcher than the one who examines the exposures [9]. This reduces the risk of confirmation bias, or finding what we already believe.
- *Sample size*—In general, a larger sample size is better. Researchers should calculate power, which tells the number of individuals needed to draw a conclusion for their particular question, and then should meet their recruitment goal. If there is no power calculation mentioned, be cautious when drawing conclusions from studies that have high attrition rates, or attrition rates that are higher in one group than another. Be very cautious about drawing conclusions from papers with small sample sizes—fewer than 30 is a good rule of thumb. Fewer subjects mean more variability in the conclusion.
- *Age of the paper*—Look for newest papers available on a topic. And, if you change your practice based on a study, be sure to keep your eye out for follow up on the topic.
- *Papers that conflict*—When two studies on the same intervention conflict, it is appropriate to be cautious. This is the power of systematic reviews and meta-analyses—they evaluate the quality of each paper and allow us to draw conclusions based on the body of science instead of just one study [5].
- *Relevance to your population*—When reading a paper, go back to your PICO question to evaluate whether the paper is relevant to the population you stated you were interested in [9]. For example, if you work with children and you find a study in adults, you will have to decide whether there is a biological reason to believe that the same conclusion would be relevant in children. It is not generally good practice to apply the results of nonhuman studies (test tubes, animal models) to humans.

When you read a paper and think about applying it to practice, ask yourself the four relevance questions from the Quality Criteria Checklist used by the Evidence Analysis Library [9] (Evidence Analysis Library © Academy of Nutrition and Dietetics (Formerly the American Dietetic Association). Reprinted with permission.):

1. Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group?
2. Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?
3. Is the focus of the intervention or procedure or topic of study a common issue of concern to your practice?
4. Is the intervention or procedure feasible?

Taking a research course can help you be a better reader of the medical literature. Other resources to help you along the way include the Academy's Evidence Analysis Manual [9], JAMA's *Users Guide to the Medical Literature*, and the Academy of Nutrition and Dietetics' DIFM Practice Group's decision-making tool (which is applicable to all practice areas).

What if There Are No Papers?

If there is no original research on a topic, or if you make a change in your own practice based on the results of a study, it is important to systematically track outcomes so that you can continually evaluate and add to the evidence base [1]. This can help you, your clients, and the field overall, if done appropriately.

Tracking outcomes is an integral part of the Nutrition Care Process [12]. When a patient returns for follow-up and you complete the monitoring and evaluation step of the NCP, you are assessing patient outcomes [12]. However, documenting this in a consistent manner that can be analyzed is not always done. Consistency means collecting and documenting information on every patient, whether or not they have done well with the intervention. It also means being mindful of collecting similar and meaningful nutrition care outcomes on similar patients.

Nutrition care outcomes are those that can be attributed to and measured by the RDN; are linked to the nutrition diagnosis, signs and symptoms, and/or intervention; and are plausible stepping stones to other health outcomes [9, 12]. To identify meaningful outcomes, think about measures that are comparable across patients. For example, percent weight change can be compared across patients, while pounds or kilograms of weight loss are not comparable based on patients' different starting weights. Meaningful outcomes also have an impact on patient lives—they either improve the disease, reduce the time or cost of care, or increase quality of life. Intermediate measures such as changes in knowledge, behavior, and laboratory values can be tracked but are less meaningful. A meaningful outcome might also be an intermediate outcome that is known to contribute to a patient-oriented outcome. For example, research supports that a 5–10% weight loss is sufficient to reduce the risk of diabetes in a person with prediabetes [13]. Therefore, the number of patients who achieved a weight loss of that magnitude would be a meaningful measure for an RDN working in that population. A good way to identify meaningful outcomes is through evidence-based guidelines or lists of quality indicators. For example, based on the AUA Guideline, meaningful outcomes in kidney stones may include stone recurrence, quality of life, morbidity, or adverse events (patient-oriented) or changes in stone size and intermediate biochemical changes in urine or blood (intermediate) [3].

The Nutrition Care Process and Terminology was designed with the collection of outcomes in mind [12]. The NCPT provides two benefits: (1) it means that nutrition data can be structured in the electronic medical record, making it searchable and extractable [14], and (2) it provides consistency in terminology across RDNs [12]. Therefore, if you are not already doing so, the first step in collecting outcomes is familiarizing yourself with the NCPT.

You may be able to successfully track patient outcomes through your electronic health record (EHR) [14], depending on whether it incorporates the NCPT, and how much control you have over the data extraction process, or whether you have to "wait in line" for IT support for data extraction. If your EHR does not support structured nutrition data or you cannot get reports from the EHR yourself, you can use the Academy of Nutrition and Dietetics Health Informatics Infrastructure (ANDHII) to track patient outcomes [15]. ANDHII is an online system available to all credentialed practitioners through the Commission on Dietetic Registration and allows the collection and aggregation of nutrition care data in a HIPAA de-identified manner [15]. As a practitioner who enters data into ANDHII, you maintain control over your own data and can create both individual and aggregate patient trend reports [15].

Outcomes collection can be a fuzzy area between quality improvement and research. Research is defined by the US Code of Federal Regulations as a "systematic investigation carried out to contribute to generalizable knowledge" [16]. Systematic means that you are doing the same thing for every patient and are basing their care on a research protocol vs. your clinical judgment of what is best for the patient [17]. Contributing to generalizable knowledge means that you are trying to answer a question that would be applicable in multiple clinics, not just your own, and is often also understood to mean that you are planning to disseminate your work through publications [17]. Based on these

criteria, the outcomes collection described above would begin as quality improvement rather than research, but with a significant quality improvement, the finding could transition into research [18]. Research must be reviewed by an Institutional Review Board, to ensure that it is carried out in an ethical manner that protects human subjects [17, 19]. IRBs are generally located at academic institutions including universities and hospitals, and there are also independent commercial IRBs [19]. IRBs can review projects and determine whether your project is crossing into the realm of research [17]. However, sometimes access is limited to individuals who work at an IRB institution, so it can be wise to collaborate to overcome these challenges.

Maintaining an evidence-based practice is an ongoing process and requires maintaining an awareness of new research in the literature as well as carefully monitoring and evaluating your own patient outcomes to make sure that what you expect from the evidence is occurring. However, this process is rewarding and will show the value of Medical Nutrition Therapy.

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Chapter 28
Stone Disease Research

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Keywords Nephrolithiasis and diet · Kidney stone and nutrition · Renal stones and nutrition therapy Renal calculi and diet

Key Points
- Recent research in kidney stones continues to provide evidence on the integral role of nutritional therapy in the management of disease.
- Key dietary factors that appear to have the greatest influence on the formation and management of kidney stones include intake of fluids and overall diet composition.
- Obesity also appears to be an independent factor for the formation of kidney stones when examined observationally.

Introduction

Nutritional management of kidney stones has been a mainstay of therapy for decades [1]. There is burgeoning interest in studying the effects of diet on the prevention and treatment of kidney stones. Thus, the purpose of this chapter is to summarize the recent research on nutrition and stone disease conducted within the past 5 years. The literature search was conducted using electronic databases (PubMed/Scopus from January 2012 to June 2017) using the terms of *nutrition or diet and calcium stone* or *calcium phosphate stone* or *calcium oxalate stone* or *uric acid stone* or *urate stone* or *cystine stone* or *struvite stone*, *nutrition or diet and nephrolithiasis* or *renal calculi* or *kidney calculi*, and *nutrition or diet and kidney stone* or *renal stone*. Both authors screened abstracts independently and selected papers for inclusion. Excluded articles were those that were completed in children or were not directly relevant to the key topic (Fig. 28.1).

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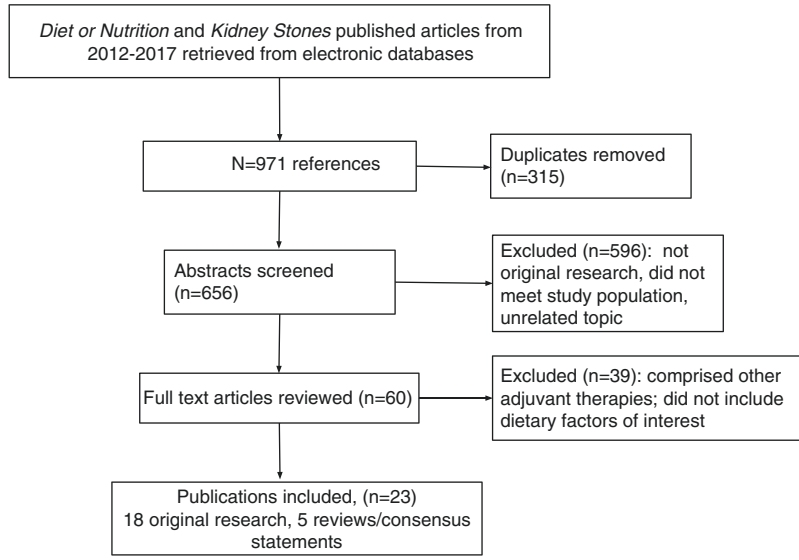

Fig. 28.1 Flow of articles reviewed pertaining to nutrition and kidney stones

Dietary Measures for Kidney Stones

Fluid Intake

Fluid intake is an important component of stone formation because an increase in urine volume decreases saturation of stone-forming salts. Three recent studies published between 2012 and 2014 examined the association between fluid intake and risk of kidney stones. One large prospective study in postmenopausal women who were free of kidney stones found mean daily water intake (as assessed by food frequency questionnaire [FFQ]) was slightly lower in subjects who developed kidney stones during the average 8-year follow-up period compared to those who did not develop stones (1.45 ± 0.65 vs. 1.51 ± 0.62 L/day, $p < 0.001$, respectively). After adjusting for risk factors, the risk of incident kidney stones decreased by 13–31% with higher water intake ($p = 0.002$) [2]. In a case-control study conducted in Southern China with 1019 stone patients and 987 healthy controls, a strong protective effect of fluid intake (as assessed by FFQ) was observed in the prevention of stone formation in men who drank >2000 mL/day (Adjusted OR [AOR] = 0.53, 95% CI [0.31, 0.90]) compared to those who drank <500 mL/day ($p < 0.05$). The association was not significant in women. After adjusting for covariates, no association was found for other fluids such as coffee, tea, fruit juice, and soda [3]. Gordiano et al. [4] found no statistically significant differences in water intake between stone patients ($n = 49$) and healthy controls ($n = 18$) in an observational cross-sectional study. The researchers found that two thirds of the stone patients had inadequate intake of water (i.e., <2 L/day) [4]. Several reviews, consensus statements, and guidelines have recommended that in patients with calcium nephrolithiasis, fluid intake should be sufficient to achieve a urine volume of 2–2.5 L/day [5–8].

Calcium Intake

Dietary Calcium Intake

In 2015 and 2016, consensus statements and guidelines were published addressing the dietary management of calcium stone formers [5–7]. These documents concluded that dietary calcium intake

should not be lower than 1000 mg/day with restrictions in sodium and protein intake. Prezioso et al. [5] further concluded that diets with the above limitations could be protective against the risk of stone formation in hypercalciuric stone-forming adults.

Sorenson, Kahn et al. [2] conducted a secondary analysis of more than 78,000 women with no history of nephrolithiasis from the prospective Women's Health Initiative (WHI) Observational Study. (Food frequency questionnaires were used to assess dietary intake in the WHI.) Results found the risk of incident kidney stones was decreased by 5–28% with higher dietary calcium intake ($p = 0.01$). In addition, the average dietary calcium intake was 39 mg/day lower in women with incident kidney stones (mean 769 ± 456 vs. 808 ± 453 mg/day, $p < 0.001$) [2]. Intake in both groups was below the recommended level of 1000 mg/day.

Three large prospective cohort studies evaluated dietary calcium intake from dairy and nondairy sources and the risk of incident symptomatic kidney stones: The Health Professionals Follow-Up Study (NHPS) and the Nurses' Health Study (NHS) (I and II) [9]. Results showed that in multivariate analysis, higher dietary calcium intake from nondairy or dairy sources, as assessed by FFQ, was independently associated with a lower risk of incident kidney stones in all 3 cohorts [9].

In an observational cross-sectional study, inadequate levels of calcium intake, as determined by 24-hour recall and FFQ, were found in the majority of patients in the stone group (93.5%) compared to the healthy controls (0%). Mean calcium intake (mg/day) was 520.7 ± 436.8 for stone formers vs. 427.5 ± 235.6 for healthy controls, which is below the recommended intake of 1000 mg/day [4].

Supplemental Calcium Intake

One case-control study examined the association between the use of calcium supplements and the risk of kidney stones in men and women in Southern China and found no significant association [3]. In a secondary analysis of data from the WHI, calcium supplementation was found to be less common in women who developed stones vs. those who did not (67% vs. 73%, $p = 0.02$). Moreover, in subjects who did take the supplement, the amount of supplemental calcium was also lower (mean 613 ± 433 vs. 646 ± 435 mg/day, $p < 0.01$, respectively) [2].

Vitamin D

Vitamin D Supplementation

A recently published systematic review aimed to determine whether long-term vitamin D supplementation (≥24 weeks) vs. a placebo increased risk of side effects related to kidney stones. An analysis of nine studies found no increase in risk of kidney stones from vitamin D supplementation (RR = 0.66, 95% CI = 0.41–1.09) [10].

In large prospective cohorts of the HPFS and the NHS I and II, total and supplemental vitamin D intake and the risk of incident kidney stones were investigated using dietary data from a FFQs [11]. During a median follow-up of 11.3–11.7 years for all three studies, 6245 incident kidney stone events occurred. After multivariate adjustment for covariates, the association between total vitamin D intake and risk of kidney stones was not significant in all 3 cohorts. Highest vs. lowest intake of supplemental vitamin D (≥1000 vs. <100 IU/day) was significant for risk of kidney stones only in the NHS II (HR 1.38, 95% CI 1.03–1.95)[11].

Serum Vitamin D Levels

Tang et al. [12] used data from NHANES III (1988–1994) to determine the independent association between serum 25[OH]D concentration and prevalent kidney stone disease in 16,286 individuals.

Among the participants, 4.6% reported a history of previous kidney stones. Mean serum 25[OH] D concentration was similar in stone formers compared to non-stone formers (29.28 ± 0.58 vs. 29.55 ± 0.15, $p = 0.6$). In multivariate analysis, higher serum 25[OH]D concentration was not associated with increased odds ratio for previous kidney stones (OR = 0.99; 95% CI 0.99–1.01) after adjusting for covariates [12].

In a 19-month prospective study of 2012 subjects, Nguyen et al. [13] investigated the association between serum 25 hydroxyvitamin D (25[OH]D) concentration(20–100 ng/mL) and the incidence of kidney stones. Thirteen individuals self-reported a kidney stone during the study period. Results showed that lower serum 25[OH]D levels were associated with higher odds of developing kidney stones, although not significant ($p = 0.42$).

Calcium and Vitamin D Supplements

In a recent consensus statement, Gambaro et al. [7] concluded that combined vitamin D and calcium supplementation may increase the risk of calcium nephrolithiasis. Only one recent study examined the risk of kidney stones in subjects who took both calcium and vitamin D supplements. In a clinical trial, Haghighi et al. [14] compared the metabolic changes in 53 postmenopausal women with no history of kidney stones after supplementation with 500 mg calcium and 200 units of vitamin D for a mean follow-up of 13.5 months. Results found no significant difference in blood and urine markers associated with stone formation before and after the study. The researchers concluded that oral intake of calcium and vitamin D had no effect on urinary calcium excretion rate and the formation of kidney calculi in postmenopausal women.

Sodium Intake

The CLU Working Group recommends a moderate dietary salt restriction to limit urinary calcium excretion, which may be helpful for primary and secondary of nephrolithiasis [5]. The Working Group did not provide an amount (in g/day)for "moderate dietary salt restriction." However, this recommendation was based on one RCT. The American Urological Association (AUA) provides a standard for dietary intake of sodium of <2300 mg/day for calcium stone formers [6]. The European Association of Urology (EAU) recommends limiting sodium intake; however, they do not provide an amount [6]. In the consensus statement, Gambaro et al. [7] recommends a sodium intake not higher than 2.4 g/day (or 6 g of salt per day) for calcium oxalate stone formers with hypercalciuria.

In a secondary analysis of data from the WHI, mean daily sodium intake was significantly higher in women who developed kidney stones vs. those who did not (2577 ± 1152 vs. 2517 ± 1045, $p = 0.01$). The researchers found that higher dietary sodium intake increased the risk of nephrolithiasis by 11–61% ($p < 0.001$), especially in women with the highest sodium intake (i.e., >3000 mg/day) [2].

In a cross-sectional study, Gordiano et al. [4] compared dietary sodium intake between patients with nephrolithiasis ($n = 31$) and healthy controls ($n = 18$). They found no statistically significant differences between the controls and stone patients in dietary sodium intake levels. However, only half of the patients in the stone group had sodium intakes at ideal levels [4].

Oxalate Intake

In the case-control study in Southern China involving 1019 newly diagnosed kidney stone patients and 987healthy control subjects, consumption of leafy vegetables (as determined by FFQ) more than

3 times per day was a risk factor for kidney stones in both men and women (AOR = 2.02, 95% CI [1.04, 3.91] and 3.86 [1.48, 10.04], respectively). The authors surmise that the kidney stone risk may have been caused by the high consumption of leafy vegetables, which are mainly Chinese flowering cabbage and spinach, that also had high level of oxalates [3].

de Oliveira et al. [15] assessed the nutritional state and energy and nutrient adequacy of 31 patients with nephrolithiasis and 25 controls in an observational, cross-sectional study. Nutrient intakes were similar in both groups. However, oxalate intake was significantly higher among the patients with kidney stones compared to the controls (159 ± 119.27 vs. 112 ± 47.9 mg/day, $p = 0.042$). Both groups had oxalate intakes greater than the recommended intake of 55 mg/day.

Zinc Intake

The relationship between dietary zinc intake and prevalent kidney stones was examined in 15,444 adults in NHANES III [16]. Among the participants, 710 self-reported a history of kidney stones. There was no difference in the use of zinc-containing supplements between stone formers and non-stone formers (17% vs. 16%, $p = 0.40$). In addition, mean dietary zinc intake was not statistically different between stone formers and non-stone formers (13.4 ± 0.9 vs. 12.0 ± 0.1, $p = 0.10$). The multivariate-adjusted OR for stone formation was 1.70 (95% CI 1.13–2.57) in subjects who consumed >15 mg zinc/day vs. <7 mg/day) [16]).

Caffeine Intake

Dai et al. [3] found no significant association between coffee intake and the risk of kidney stones in men and women. However, this study did not examine caffeine intake, only coffee intake. The association between caffeine intake and the risk of incident kidney stones was evaluated prospectively using FFQs in 3 large cohort studies: the HPFS and the NHS I and II. Of the 217,883 participants in the analysis, 4982 incident cases of kidney stones occurred. Results found an independent association between caffeine intake and a lower risk of incident kidney stones in all three studies. In more than 6000 patients with 24-hour urine data, intake of caffeine was associated with higher urine volume, calcium, and potassium and with lower urine oxalate and supersaturation for calcium and uric acid [17].

Dietary Protein Intake

A diet high in animal protein may increase the risk of kidney stones [18]. In a review of the CLU Working Group, they concluded that a low to normal protein intake decreases calciuria and could be useful in stone prevention and preservation of bone mass. However, once again, they do not provide an amount for "low to normal protein intake." The more recent consensus statement by Gambaro et al. [7] recommends a moderate intake of nondairy animal protein (i.e., 0.8 g/kg body/day or less) for calcium-oxalate stone formers with hypercalciuria.

The observational cross-sectional study by Gordiano et al. [4] found no significant differences in dietary protein intake (assessed by a semiquantitative FFQ) between 31 stone patients and 18 healthy controls. One third of stone patients were on low protein diets, 12.5% had normal protein intakes, and 54% were on high protein diets compared to the control subjects (55.6%, 11.1%, and 33.3%, respectively). Amounts of dietary protein in g/day or g/kg/day for low, normal, and high intakes were not provided.

In the prospective WHI involving over 78,000 women with no history of nephrolithiasis, animal protein intake was not associated with risk of incident kidney stones in multivariate analysis. However, daily mean animal protein intake was slightly higher in women who developed stones compared to those who did not (47 ± 25 vs. 45 ± 22 g/day, $p = 0.005$), while mean total protein intake was similar between groups ($p = 0.14$) [2].

Turney et al. [19] investigated the association between diet and kidney stone risk in a large cohort in the Oxford arm of the European Prospective Investigation into Cancer (EPIC) and Nutrition Study. In the cohort, 303 participants had a new kidney stone episode. A positive association was observed between the quantity of meat consumed and the risk of developing kidney stones. Compared to high meat eaters (>100 g/day), the hazard ratio for low meat eaters (<50 g/day) and vegetarians was 0.52 (95% CI 0.35–0.80) and 0.69 (95% CI 0.48–0.98), respectively. The authors also examined the association between total meat and meat product intake and the risk of kidney stones. They found that those in the top third of intake had a 64% higher risk compared to those in the bottom third (HR 1.64, 95% CI 1.08–2.48, p trend = 0.04). In addition, red meat was significantly associated with risk (HR for the highest vs. lowest third intake: 1.53, 95% CI 1.04–2.26 (p trend = 0.02) [19].

Fiber, Fruit, and Vegetable Intake

Sorensen et al. [20] evaluated the relationship between dietary fiber, fruit, and vegetable intake and the risk of incident kidney stones in nearly 84,000 postmenopausal women from the WHI Observational Study. After adjusting for nephrolithiasis risk factors such as age, race/ethnicity, calcium supplementation, hormone therapy use, BMI, and dietary intake, the researchers found women with no history of stones with the highest dietary fiber intake (21.9–99.4 g/day) were 22% less likely (AHR 0.78, 95% CI 0.67–0.92) to develop stones compared to women with the lowest intake (0–10.6 g/day). Similar results were observed for fruit and vegetable intake; women with the highest intake of fruit and vegetable intake (3.0–11 portions/day and 3.3–13.3 portions/day, respectively) compared to those with the lowest (0–1 portion/day and 0–1.2 portions/day, respectively) were less likely to report an incident stone event (AHR 0.85 [0.74–0.98] and AHR 0.78 [0.68–0.91], respectively). However, in women with a history of nephrolithiasis, there were no significant protective effects of fiber, fruit, or vegetable intake on the risk of recurrent kidney stones [20].

Additional analysis in the EPIC-Oxford study also found that fresh fruit intake (g/day) was inversely associated with risk of kidney stones (HR for the highest vs. lowest third of intake = 0.70, 95% CI 0.53–0.93, p trend = 0.03). However, fresh vegetable intake (g/day) was not associated with risk [19].

Dietary Energy Intake

In a longitudinal, prospective cohort of postmenopausal women enrolled in the WHI Observational Study ($n = 84{,}225$), the researchers found that as dietary energy intake increased to ≥2500 kcal/day, the risk of incident stones increased by 42% (AHR 1.42; 95% CI = 1.02–1.98). However, energy intake <1800 kcal/day was not protective against stone formation [21].

Vitamin C Supplementation

In the consensus statement by Gambaro et al. [7], they concluded that vitamin C supplementation increases the risk of calcium nephrolithiasis. One recent study conducted by [22] used data 3 large prospective cohorts (NHS I and II and the HPFS) to examine the independent associations of total,

supplemental, and dietary vitamin C and the risk of kidney stones. After multivariate adjustment for covariates, no association was found between the independent variables and the risk for incident kidney stones in women; however, there was a positive association in men—total and dietary intake in the HPFS (HR for ≥1000 vs. <90 mg/day = 1.43, 95% CI 1.15–1.79) and supplemental intake (HR for ≥1000 vs. no use = 1.19; 95% CI 1.01–1.40) [22].

Acid Load

Vezzoli et al. [23] compared dietary acid load in 157 calcium stone formers and 141 controls using 3-day food records. The records were analyzed for oxalate, electrolyte, and mineral content and estimated potential renal acid load (PRAL). Results found that stone formers had a significantly higher mean PRAL than the controls (12.7 ± 17.36 vs. 6.1 ± 14.65 mEq/day, $p = 0.0001$).

Ferraro, Mandel et al. [24] examined whether protein type or net acid load was associated with risk of kidney stones in the HPFS and the NHS I and II. Intake of protein (dairy, nondairy animal, and vegetable), potassium, and animal protein-to-potassium ratio (an estimate of net acid load) were evaluated. Within the 3 cohorts, 6308 incident cases of kidney stones occurred. In a pooled analysis of the three studies, the dietary acid load was associated with a higher risk of incident kidney stones after adjusting for covariates (AHR 1.41, 95% CI = 1.18–1.68).

Obesity

Evidence suggests that the risk of kidney stones is associated with obesity [25]. Gordiano et al. [4] failed to find a significant association between BMI and kidney stone formation in healthy controls vs. stone patients. In the WHI, obese and overweight women had an increased risk of incident stones compared to women of normal weight after adjusting for covariates (morbidly obese OR = 2.01, 95% CI [1.6, 2.53]; severely obese (1.84 [1.52, 2.22]); obese (1.59 [1.37, 1.82]); and overweight (1.19 [1.06, 1.35]) [2]. In a multivariate model that included body mass index (BMI), dietary energy intake, and weekly physical activity, BMI remained an independent predictor of incident kidney stones in a large cohort of postmenopausal women (BMI categories: overweight (AHR 1.21; 95% CI = 1.07–1.37); moderately obese (AHR 1.36 [1.13–1.63]); and severely obese (AHR 1.31 [1.02–1.68]). However, underweight was not protective against incident stones (AHR 0.79 [0.47–1.34]) [21].

Trinchieri et al. [26] compared data from renal stone formers collected retrospectively between 1990 and 2014 to data for the Italian general population in 2004. Results showed that in nearly 1700 stone formers who consumed a Mediterranean diet, rates of overweight and obesity were higher than rates reported in the general Italian population for men in the age group 25–44 years only (43.1 vs. 36.2%, $p = 0.029$). In females, rates of overweight and obesity in renal stone formers were lower than in the general population for age groups 25–44 and > 60 years only (12.2 vs.17.6, $p = 0.033$ and 36.7 vs. 52.6, $p = 0.007$, respectively) [26].

Summary/Conclusions

Recent research in kidney stones continues to provide evidence on the integral role of nutritional therapy in the management of disease. Table 28.1 provides a summary of the research published from 2012 to 2015 on nutrition and kidney stones. This review found key dietary factors that appear to have the greatest influence on the formation and management of kidney stones include the overall intake

Table 28.1 Summative table of original research published from 2012 to 2015 on nutrition and kidney stones

Author, year	Study purpose	Study population	Methods	Outcomes	Conclusion
Sorenson, Kahn, Reiner et al. *J Urol*, 2012 [2]	To examine the relationship between key dietary factors and the formation of kidney stones	78,293 women from the prospective Women's Health Initiative Observational Study (WHI-OS) with no medical history of kidney stones and who completed the food frequency questionnaire (FFQ)	Secondary analysis using multivariate logistic regression to identify demographic characteristics, dietary factors inclusive supplement use, and formation of kidney stones	Risk of kidney stones was decreased in women with higher calcium and fluid intakes Individuals with higher BMI and increased dietary sodium intake had the greatest risk for renal calculi Animal protein was not associated with kidney stones in this analysis	Evidence to support the role of dietary factors in reducing risk for nephrolithiasis
Tang, McFann, and Chonchol, *Nephrol Dial Transplant*, 2012 [12]	To evaluate the role of serum 25-hydroxyvitamin D [25(OH) D] in kidney stone disease	16,286 men and women who were 18 years and older who participated in the National Health and Nutrition Examination Survey (NHANES III)	Prevalent kidney stone disease was operationalized as a self-reported previous episode of kidney stones ($n = 759$ subjects) Logistic regression was used to determine whether serum 25(OH)D was associated with the history of kidney stone disease	Concentrations of serum 25(OH)D were not different between stone formers and non-formers In adjusted models did not reveal that higher serum 25(OH)D were associated with a higher odds ratio for kidney stones	High serum 25(OH)D levels were not associated with the prevalent kidney stone disease
Tang, McFann, and Chonchol, *Am J Nephrol*, 2012 [16]	To examine the potential relationship between dietary zinc intake and prevalent kidney stone disease	15,444 men and women who were 18 years and older that participated in the National Health and Nutrition Examination Survey (NHANES III)	Prevalent kidney stone disease was operationalized as a self-reported previous episode of kidney stones ($n = 710$ subjects) Logistic regression was used to determine whether dietary zinc intake was associated with the history of kidney stone disease	Individuals who experienced kidney stones had a higher dietary zinc intake when compared to those who did not have a history of stones In the adjusted models, the higher dietary zinc intake did place them at increased risk for stone development When split into tertiles, the highest dietary zinc intake (>15 mg/day) were associated with the greatest risk	There appears to be a relationship between dietary zinc intake and kidney stones, but it must be studied prospectively

Dai, Zhao, Liu et al. *J Ren Nutr*, 2013 [3]	To identify dietary risk factors for kidney stones	2006 men and women from Southern China; 1019 newly diagnosed incident kidney stone patients and 987 healthy controls	Participants were asked about regular eating habits using a brief FFQ derived from the China National Nutrition and Health Survey 2002 Information about dietary supplements and anthropometrics was also obtained Logistic regression was used to determine the association between dietary risk factors and incident kidney stones	In women, consuming more grains and bean products was associated with higher kidney stone risk In men, fluid intake was shown to provide a protective effect against stone formation In both men and women, a diet higher in leafy vegetables (>3 times per day) was associated with increased risk of kidney stone disease	Among a population with higher kidney stone prevalence, there are elements within the eating patterns of individuals residing in southern China that may potentially explain this risk
Haghighi, Samimagham, and Gahardehi, *Iran J Kidney Dis*, 2013 [14]	To evaluate the metabolic changes and risk of stone formation after supplementation with calcium and vitamin D	53 postmenopausal women without history of kidney stones, bone disease, and metabolic or rheumatic disorders	At baseline and 1 year post-supplementation of calcium (500 mg/day) and vitamin D (200 IU), renal ultrasound for stone diagnosis, serum 24-hour urinary calcium levels were obtained Differences in incidence of kidney stone, serum, and urinary calcium levels were determined by t-test or Wilcoxon rank sum	After 1 year of supplementation, 1 of the 53 patients was diagnosed with nephrolithiasis. No significant differences were identified in 24-hour urinary or serum calcium levels	Within the context of a small prospective study, there appears to be no impact of exogenous supplementation of vitamin D or calcium at these levels on kidney stone formation
Taylor and Curhan, *J Urol*, 2013 [9]	To explore the relationship between dietary calcium from nondairy and dairy sources and renal calculi	Data analyzed from the prospective studies of Health Professionals Follow-Up Study ($N = 30{,}762$) and the Nurses' Health Study I and II ($N = 195{,}865$). Men ≥60 years of age were excluded	FFQs were used to obtain calcium intake every 4 years. Cox proportional hazards regression was used to adjust for age, BMI, supplemental calcium, diet, and other factors	There were 5270 incident kidney stones during the combined 56 years of follow-up Individuals with the highest intake of calcium from dairy and nondairy sources were associated with lower risk for kidney stones	Consuming higher amounts of calcium from either dairy or nondairy sources appears to lower risk for nephrolithiasis

(continued)

Table 28.1 (continued)

Author, year	Study purpose	Study population	Methods	Outcomes	Conclusion
de Oliveira, Hauschild, Barros et al. *J Ren Nutr*, 2014 [15]	To determine the nutritional status of patients diagnosed with renal calculi in comparison with individuals without disease	31 patients diagnosed with kidney stones and 23 healthy controls	All participants were measured using a nutritional assessment, which included dietary history and serum (e.g., creatinine, calcium, phosphorus, etc.) and urinary markers (calcium, uric acid, citrate, etc.)	Participants diagnosed with kidney stones experienced higher BMIs, abdominal circumferences, and body fat percentages Oxalate intake was significantly higher in the stone formers than in the non-formers 30% of those with kidney stones had hypercalciuria in comparison with 12% in the healthy controls	This small study suggests that there may be modifiable behaviors that could reduce kidney stone risk but needs to be further investigated in a larger trial
Ferraro, Taylor, Gambaro, and Curhan, *Am J Clin Nutr*, 2014 [17]	To explore the relationship between caffeine intake and incidence of nephrolithiasis	Using data from three ongoing cohort studies, Health Professionals Follow-Up Study and Nurses' Health Study I and II: (N = 217,883 participants)	Information on caffeine intake and incidence of kidney stones were obtained via validated questionnaires Associations were analyzed using linear regression models, adjusting for age, BMI, presence of diabetes, high blood pressure, gout, history of kidney stones, use of thiazides, urine volume, and other urinary components	In the adjusted models, the individuals with the highest quintile of caffeine intake had the lowest risk for kidney stones Caffeine intake was associated with higher urine volume, calcium and potassium, and lower urine oxalate	Caffeine appears to be independently associated with the risk for nephrolithiasis
Gordiano, Tondin, de Miranda et al. *J Bras Nefrol*, 2014 [4]	To compare the dietary and metabolic characteristics of individuals diagnosed with kidney stones and healthy adults	31 patients with kidney stones and 18 healthy individuals in Brazil	A nutritional assessment was completed to collect anthropometric data. Dietary intake was also obtained via semiquantitative FFQ Urinary excretion of citrate and oxalate were also monitored Comparisons between groups were evaluated statistically using parametric and nonparametric tests	There were no significant differences identified in food intake, BMI, or oxalate excretion between groups	More prospective studies are needed to have a greater understanding of the dietary and metabolic factors that may further characterize kidney stone disease risk

Nguyen, Baggerly, French et al. *Am J Public Health*, 2014 [13]	To explore the relationship between 25(OH)D serum levels and incident kidney stones	Grassroots Health data repository of 2012 participants followed prospectively for a median of 19 months	25(OH)D levels were measured via assay Participants self-reported whether they experienced kidney stones (n = 13) Multivariate logistic regression was used to study the relationship between vitamin D and kidney stone formation	There were no significant associations between serum 25(OH) D and incident kidney stones BMI was significantly higher in patients reporting kidney stones	A serum 25(OH)D level of 20–100 nanograms per milliliter is not associated with increased incident kidney stones
Sorenson, Chi, Shara et al. *J Am Soc Nephrol*, 2014 [21]	To study the relationship of obesity, dietary energy intake, physical activity, and incident kidney stones	84,225 women who participated in Women's Health Initiative Observational Study and had no history of kidney stones	Data obtained from validated questionnaires and prospective monitoring of participants	In the adjusted models, women with greater levels of physical activity had decreased risk of kidney stones, independent of BMI and caloric intake Women with higher BMIs and greater dietary energy intake were at higher risk for nephrolithiasis	Physical activity, the amount not intensity, is protective against kidney stone risk in women
Sorenson, Hsi, Chi et al., *J Urol*, 2014 [20]	To explore the association between dietary fiber, fruit and vegetable intake, and incident kidney stones	83,992 women who participated in Women's Health Initiative Observational Study Women with a history of kidney stones (n = 3471) were analyzed separately	Data obtained from validated questionnaires and prospective monitoring of participants Cox proportional hazards regression analyses were used to test relationships while adjusting for nephrolithiasis risk	Practically 4% of the women experienced a kidney stone during the median follow-up of 8 years Women with no history of kidney stones that had higher dietary fiber, fruit, and vegetable intake were at lower risk for kidney stones In women with a history of kidney stones, there was no protective effect of fiber, fruit, or vegetable intake on future kidney stones risk	Greater intakes of fiber, fruit, and vegetable intake lowers kidney disease risk in postmenopausal women These same effects are not experienced in women with a history of kidney stone disease
Turney, Appleby, Reynard et al., *Eur J Epidemiol*, 2014 [19]	To identify the relationship between diet and risk for nephrolithiasis	51,336 participants in the Oxford arm of the European Prospective Investigation into Cancer and Nutrition	In the cohort, 303 participants were diagnosed with kidney stones Cox proportional hazards regression was used to determine risk for kidney stones	Individuals who consumed a vegetarian diet vs. a high intake of meat had reduced risk for kidney stones Additionally, those who had a higher intake of fruits, vegetables, whole grain cereals, and magnesium were at lower risk Individuals who consumed a high intake of zinc were at greater risk	Individuals who consume a more plant-based diet may be at lower risk for the development of kidney stone disease

(continued)

Table 28.1 (continued)

Author, year	Study purpose	Study population	Methods	Outcomes	Conclusion
Vezzoli, Dogliotti, Terranegra et al. *Nutr Metab Cardiovasc Dis*, 2015 [23]	To compare dietary acid load in individuals diagnosed with kidney stones and healthy controls	Participants included 147 individuals with history of kidney stones and 144 healthy controls from Italy	Using a three-day food diary, diets were analyzed by computer software to determine potential renal acid load (PRAL).Twenty-four hour urine excretion of ions and citrate were collected in stone formers Regression analyses, inclusive of multiple linear and logistical methods, were used to determine the association of PRAL to kidney stone risk	Individuals that consumed a higher fiber and lower PRAL were at the lowest risk for kidney stones Citrate excretion was related to high PRAL and animal protein consumption in stone formers Calcium excretion not associated with PRAL	Stone formers may have a higher PRAL as evident by the lower fiber and vegetable intakes and is mediated by decreasing citrate excretion Calcium excretion more related to sodium intake than PRAL
Ferraro, Curhan, Gambaro, and Taylor, *Am J Kidney Dis*, 2016 [22]	To determine the relationship of total, supplemental, and dietary vitamin C intake and incident kidney stones	156,732 women in the Nurses' Health Study I and II and 40,536 men in the Health Professionals Follow-Up Study	Information on vitamin C intake and incidence of kidney stones was obtained via validated questionnaires Cox proportional hazards regression analyses were used to test relationships while adjusting for nephrolithiasis risk	In the adjusted models, total and supplemental vitamin C intake was not associated with incident kidney stones in women, but it was in men Dietary vitamin C was not associated with increased risk for kidney stones in either sex	Vitamin C intake seems to be more predictive of kidney stone disease risk in men than in women
Ferraro, Mandel, Curhan et al. *Clin J Am Soc Nephrol*, 2016 [24]	To examine whether protein type or net acid load is related to nephrolithiasis	150,757 women in the Nurses' Health Study I and II and 42,919 men in the Health Professionals Follow-Up Study	Dietary intakes of protein (dairy, animal, and vegetable), potassium, and animal protein-to-potassium ratio (estimate of net acid load) and risk of kidney stones were examined Multivariable models were adjusted for age, BMI, diet, and other factors	Dairy protein was associated with lower risk in the Nurses' Health Study II Potassium intake was indicative of reduced kidney stone risk among all three cohorts Greater net acid load was related to increased risk for nephrolithiasis	Risk for kidney stones may vary by type of protein Diets high in potassium may have a protective effect

Ferraro, Taylor, Gambaro, and Curhan *J Urol*, 2017 [11]	To determine the relationship between vitamin D intake and incident kidney stones	193,551 participants in the Nurses' Health Study I and II and the Health Professionals Follow-Up Study	Participants were stratified by total and supplemental vitamin D intake Cox proportional hazards regression models adjusted for age, BMI, comorbidities, use of medications, and intakes of other nutrients	There was no significant relationship between vitamin D intake (>100 IU/day) and kidney stones for Nurses' Health Study I and Health Professionals Follow-Up Study; a slight risk found in Nurses' Health Study II Supplemental vitamin D found similar results	Typical intakes of vitamin D does not appear to pose a greater risk for kidney stones, but higher or supplemental intakes of vitamin D require further inquiry
Trinchieri, Croppi, and Montanari *Urolithiasis*, 2017 [26]	To examine the role of overweight/obesity on risk of kidney stone formation among a population consuming a Mediterranean diet	Retrospective chart review of 1698 stone formers who attended clinics in Milan and Florence	Records were reviewed for demographics and metabolic characteristics One-way analysis of variance with post hoc Bonferroni analyses was used to study differences	In males, the rate of obesity and overweight was higher in those that exhibited kidney stones; this was not repeated in women Rates of obesity/overweight was variable by type of kidney stones: e.g., higher rates in those with uric acid stones	Weight status may explain some of the risk for kidney stone formation and should be more carefully evaluated in future investigations

of fluids and dietary composition (e.g., plant-based vs. animal protein or content of micronutrients). Obesity also appears to be an independent factor for the formation of kidney stones when examined observationally.

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Appendices

Medical Nutrition Therapy (MNT) Order

MNT Referral ICD10 Codes TMC

Please note that your patient cannot be seen until this form is completed and faxed to 617-636-8325
Frances Stern Nutrition Center at Tufts Medical Center

MEDICAL NUTRITION THERAPY (MNT) REFERRAL FORM
*Indicates required information for Medicare order

PATIENT INFORMATION

Patient Name (Last, First, Middle): Gender: ☐ male ☐ female

Pt MR#: Pt DOB:

Pt Insurance:

Height: Weight:

***MEDICAL NUTRITION THERAPY (MNT)**

Requested service: Check one box only

**Check the type of MNT and/or number of additional hours requested:*

☐ Initial MNT (3 hours if Medicare)
☐ Annual follow-up MNT (2 hours if Medicare)
☐ Additional MNT hours in the same calendar year per RD recommendations. # of hours requested:_____

Please specify change in diagnosis, condition, or treatment regimen:

***REQUIRED/RELEVANT LAB DATA**

Please attach current results or complete following:

Test	Result (Date)	Test	Result (Date)
Fasting BG		Cholesterol	
Casual BG		Triglycerides	
HgbA1c		HDL / LDL	
Urine-Alb/CR		Urine Protein	
GFR/Creatinine		Serum Albumin	
Uric Acid		PTH / Ca /Phos	

CURRENT MEDICATIONS

Please attach medication list or complete following:

☐ Glucophage (Metformin)
☐ Glucotrol (Glipizide)
☐ DiaBeta (Glyburide)
☐ Actos (Pioglitazone)
☐ Avandia (Rosiglitazone)
☐ Precose / Glyset
☐ Prandin / Starlix
☐ Insulin _____
☐ Byetta / Symlin
☐ Other: _____
☐ Cozaar / Lisinopril /Enalapril
☐ Procardia / Cardizem
☐ Norvasc / Verapamil
☐ Atenolol / Metoprolol
☐ Labetalol
☐ Hydrochlorothiazide
☐ Lasix / Aldactone
☐ Lipitor / Zocor / Pravachol
☐ Niaspan / Zetia

***PHYSICIAN'S SIGNATURE**

MNT is a necessary part of the patient's medical treatment for the medical diagnosis(es) indicated.

*Signature _____
*Print name _____
*NPI# _____
*Clinic _____
*Date _____

***MEDICAL DIAGNOSES (check all that apply)**

	ICD-10	ENDOCRINE & METABOLIC
	R73.09	pre-diabetes NOS
	E05.90	hyperthyroidism
	E03.9	hypothyroidism
	E11.9	Type 2 Diabetes (DM)
	E10.9	Type 1 Diabetes (DM)
	E11.65	Type 2 DM, uncontrolled
	E10.65	Type 1 DM, uncontrolled
	E13.10	Diabetes with ketoacidosis
	E11.29	Type 2 DM w/ **renal** manifestations
	E10.29	Type 1 DM w/ renal manifestations
	E11.29	Type 2 DM, uncontrolled w/ renal manifestations
	E10.29	Type 1 DM, uncontrolled w/ renal manifestations
	E11.39	Type 2 DM w/ ophthalmic manifestations
	E10.39	Type 1 DM w/ **ophthalmic** manifestations
	E11.39	Type 2 DM, uncontrolled w/ ophthalmic manifestations
	E10.39	Type 1 DM, uncontrolled w/ ophthalmic manifestations
	E11.49	Type 2 DM w/ **neurological** manifestations
	E10.49	Type 1 DM w/ neurological manifestations
	E11.49	Type 2 DM, uncontrolled w/ neurological manifestations
	E10.49	Type 1 DM, uncontrolled w/ neurological manifestations
	E11.51	Type 2 DM w/ **peripheral circulatory** disorders
	E10.59	Type 1 DM w/ peripheral circulatory disorders
	E11.59	Type 2 DM, uncontrolled w/ peripheral circulatory disorders
	E10.51	Type 1 DM, uncontrolled w/ peripheral circulatory disorders
	E11.69	Type 2 DM w/ **specified** manifestations (i.e. hypoglycemia)
	E10.69	Type 1 DM w/ **specified** manifestations (i.e. hypoglycemia)
	E11.69	Type 2 DM, uncontrolled w/ specified manifestations
	E10.69	Type 1 DM, uncontrolled w/ specified manifestations
	E13.8	DM with unspecified complication
	E16.1	Hypoglycemia, unspecified (reactive)
	E28.2	**P**oly**C**ystic **O**varian **S**yndrome
	E88.81	Dysmetabolic syndrome X
	O24.419	Gestational Diabetes Mellitus

		RENAL			
	N18.1	CKD, Stage 1		N18.9	CKD, unspecified
	N18.2	CKD, Stage 2		N25.0	Renal osteodystrophy
	N18.3	CKD, Stage 3		Z94.0	Kidney transplant
	N18.4	CKD, Stage 4		N20.0	Kidney stones
	N18.5	CKD, Stage 5			*Specify:*

		CARDIOVASCULAR
	E78.0	Pure hypercholesterolemia
	E78.1	Pure hypertriglyceridemia
	E78.2	Mixed hyperlipidemia
	E78.5	Hyperlipidemia, unspecified
	E78.6	Low HDL
	I10	HTN, benign/unspecified
	I25.0	Coronary atherosclerosis

OTHER – indicate other medical dx's below:

The information requested above is Protected Health Information (PHI), and is the minimum necessary to execute delivery of patient services. Please understand as a link in the "Chain of Trust", all PHI will remain confidential as mandated by the Treatment, Payments, and Healthcare Operation Laws mandated by HIPAA.

H. Han et al. (eds.), *Nutritional and Medical Management of Kidney Stones*, Nutrition and Health,
https://doi.org/10.1007/978-3-030-15534-6

Urine Test Order Forms

Calcium Content of Foods

Food	Portion size	Amount (mg)	Food	Potion size	Amount (mg)
Dairy products			**Animal protein**		
Milk (whole, 2%, 1%, and skim)	8 floz (1 cup)	280–305 mg	Beef (all types: cooked)	3 oz	19
Evaporated milk	2 floz (1/4 cup)	164	Salmon (cooked)	3 oz	13
Lactaid milk	8 floz (1cup)	300	Chicken (cooked)	3.5 oz	12
Cheese[a] (American)	1 oz	296	Shrimp (cooked)	3 oz	60
Cheddar[a] cheese	1 oz	201	Scallop (cooked)	3.5 oz	42
Swiss cheese	1 oz	252	Mussel (cooked)	3 oz	28
Bleu cheese[a]	1 oz	150	Sardine[a] (canned with bones)	1 oz	108
Cottage cheese[a]	½ cup	69	Pork (cooked)	3 oz	5
Goat cheese (soft)	1 oz	40	Cod (cooked)	3 oz	12
Low-fat plain yogurt	1 cup (8 oz)	448	**Bread/Grains**		
Low fat (fruit)	1 cup (8 oz)	372	Various breads (white, whole wheat, multigrain)	1 slice (based on weight of each slice)	20–45
Greek yogurt (low fat)	1 item (5.3 oz)	150			
Frozen yogurt	½ cup	103	Oatmeal cooked with water	1 cup	21
Ice cream	½ cup	125	Cheerio	1 cup	100
Nondairy calcium-fortified drinks			Raisin bran	1 cup	5
Soy milk	8 floz (1 cup)	451	Brown rice (cooked)	1 cup	3
Almond milk (fortified)	8 floz (1 cup)	451–516	White rice enriched (cooked)	1 cup	16
Rice milk	8 floz (1 cup)	283	**Vegetables**		
Coconut milk	8 floz (1 cup)	473	Broccoli (raw)	1 cup	42
Beans and products			Kale (raw)	1 cup	53
Tofu (prepared with Ca sulfate)	½ cup	434	Tomato (fresh)	1 cup	18
Hummus	½ cup	58	Broccoli (cooked)	½ cup	31
Lentil (boiled)	1 cup	38	Kale (cooked)	1 cup	177
Soy beans	½ cup	81	Cabbage (raw)	1 cup	36
Red beans (cooked)	½ cup	40	Tomato sauce (canned)[a]	½ cup	17
Pinto beans	½ cup	50	Carrots (raw)	½ cup	21
Kidney beans (cooked)	1 cup	50	**Nuts and seeds**		
Fruits			Peanuts[b] (roasted)	¼ cup	20
Orange	1 medium	60	Almond[b] (roasted)	¼ cup	80
Banana	1 medium	6	Walnut[b] (chopped)	¼ cup	29
Apple	1 medium	11	Sunflower seeds[b]	¼ cup	20
Orange juice (Ca fortified)[c]	8 floz (1 cup)	349	Flaxseeds[b]	1 Tbsp	26

Database: USDA Nutrient Database (2018)
[a]High in sodium
[b]High in oxalate
[c]Use with caution (recommend to discuss with a nutrition specialist)

Diet Recommendation for Kidney Stones

General recommendations

Drink plenty of fluid: at least 3L/day or more

- Any type of fluids such as water, coffee and lemonade except grapefruit juice and soda have shown beneficial effect.
- Produce less concentrated urine with good volume (at least 2,5L/day)

Avoid foods with high oxalate

- Spinach, lot of berries, chocolate, wheat bran, nuts, beets, tea and rhubarb should be eliminated from the diet.

Consume adequate amount of dietary calcium

- 3 servings of dairy consumption per day will help lower the risk of calcium stones. Consume with meals.

Avoid extra calcium supplements

- Calcium supplement should be individualized by physician.

Avoid high protein diet

- With high protein intake, kidney will excrete more calcium therefore it will form more stones in the kidney.
- Cut down animal protein to lower acid load.

Avoid high salt diet

- Hi sodium diet can increase calcium in the urine so increase the stone risk.
- Blood pressure control is also important for stone formation and high salt diet can lead to high blood pressure.

Avoid high dose of vitamin C supplement

- Recommend to take 60mg/day (US Dietary Reference Intake).
- Excess amount (1000mg/day) may produce more oxalate in the body.

Harvard Vanguard Medical Associate Department of Nephrology

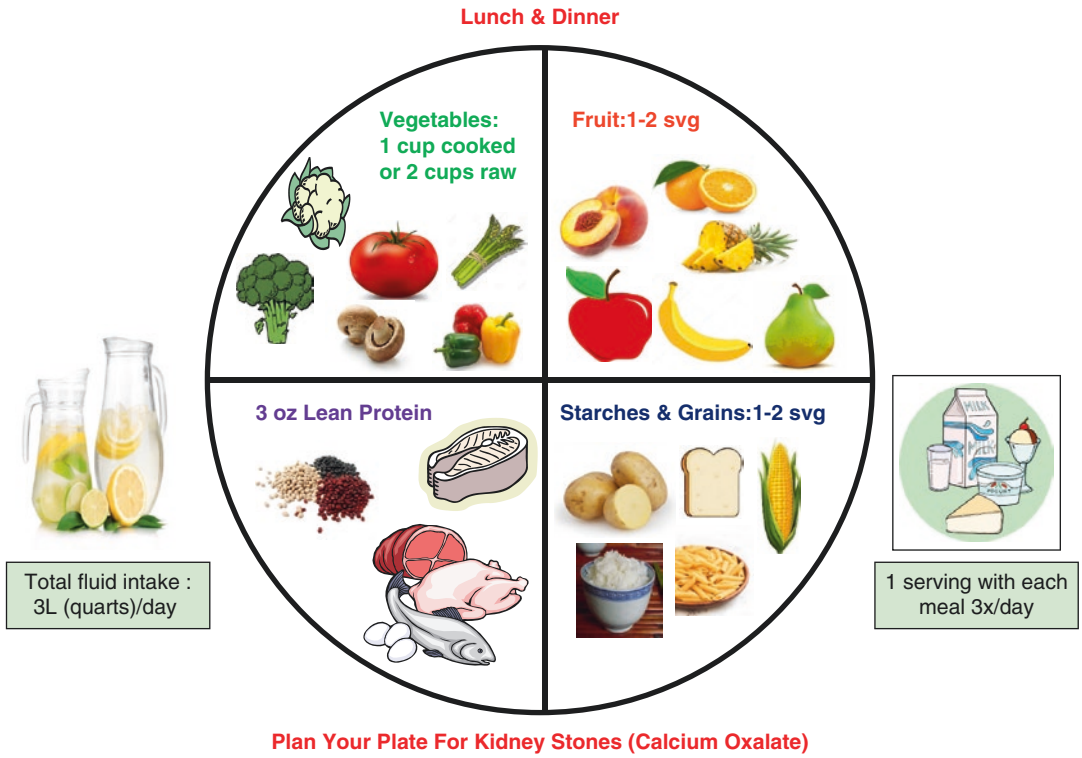
Oxalate Content of Foods

You should avoid very high oxalate foods and choose foods from low and moderate lists.

Foods	Highest Oxalate (>10mg/serving)	Moderate Oxalate (2 – 10mg/serving)	Low Oxalate (< 2mg/serving)
Beverage	Draft beer Ovaltine and other beverage mixed with tea Tea Cocoa**	Coffee	Beer (bottle) Carbonated soda Distilled alcohol Lemonade Wine: red, rose, white
Milk			Buttermilk Whole, low-fat or skim milk Yogurt with allowed fruits
Meat and substitutes	Baked beans canned with tomato sauce Peanut butter** Tofu**	Sardines	Eggs Cheese Beef, lamb or pork Poultry Fish and shellfish
Vegetables	Beans; green, wax, dried Beets**: tops, roots, greens Celery Chives Collards Dandelion greens Eggplant Kale Leeks Mustard greens Okra Parsley** Green peppers Pokeweed Sweet potato** Rutabagas Spinach** Summer squash Swiss chard** Watercress**	Asparagus Broccoli Carrots Corn: sweet, white Cucumber, peeled Green peas, canned Lettuce Lima beans Parsnips Tomato, 1 small or juice Turnips	Avocado Brussels sprouts Cauliflower Cabbage Mushrooms Onions Peas, green, fresh or frozen White potato Radish
Fruits/juices	Blackberries Blueberries Currants, red Dewberries Fruits cocktail Grapes, purple Gooseberries Lemon peel** Lime peel** Orange peel** Raspberries Rhubarb** Strawberries Tangerine Juices made from the above fruits	Apple Apricots Black currants Cherries, red, sour Cranberry juice Grape juice Orange, fruit and juice Peaches Pears Pineapple, plum, purple Prunes	Apple juice Banana Cherries, bing Grapefruit, fruit and juice Mangos Melons, cantaloupe, cassava honeydew, watermelon Nectarines Peaches Pineapple juice Plums, green or yellow
Bread/ starches	Fruit cake Grits, white corn Soybean crackers** Wheat germ**	Cornbread Sponge cake Spaghetti, canned in tomato sauce	Breakfast cereals Macaroni Noodles Rice Spaghetti Bread
Fats and oils	Nuts** Peanuts, almonds, pecans, cashews, walnuts		Bacon Mayonnaise Salad dressing Vegetable oils Butter, margarine
Miscellaneous	Chocolate**, Cocoa,** Vegetable soup, Tomato soup Marmalade	Chicken noodle soup, dehydrated	Coconut Jelly or preserves (made with allowed fruits) Lemon, lime juice Salt, pepper Soups with allowed ingredients, Sugar

** typed in red: Very high oxalate foods: Avoid as much you can

CaOx My Plate



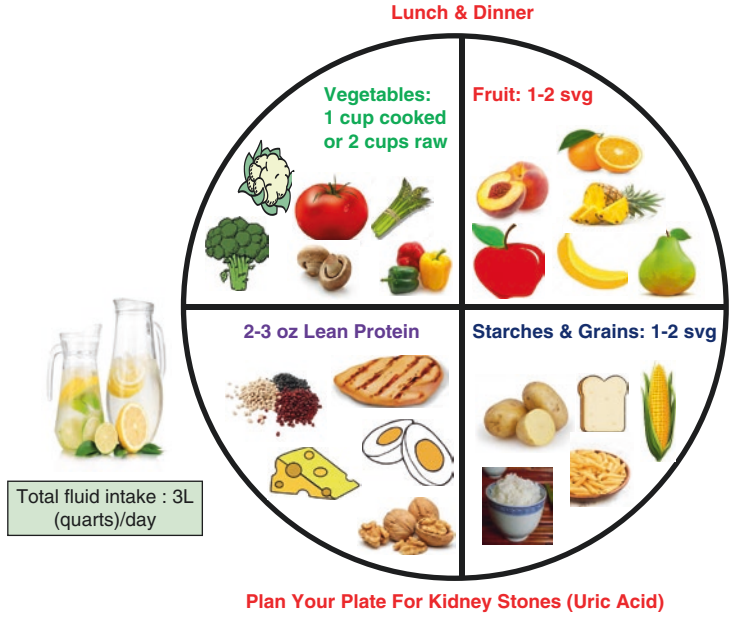
High- and low-oxalate foods

Foods	Avoid	Recommend	Foods	Avoid	Recommend
Beverages	Draft beer Ovaltine Cocoa	Coffee Beer (bottle) Carbonated soda Distilled alcohol Lemonade Wine: red, rose, white Buttermilk; whole, low-fat, or skim milk; yogurt with allowed fruits; soy, almond, and rice milk	**Miscellaneous**	Nuts[a] Peanuts, almonds, pecans, cashews Chocolate[a], cocoa[a], vegetable soup, marmalade	Bacon Mayonnaise Salad dressing Vegetable oils Butter, margarine Coconut Jelly or preserves (made with allowed fruits) Lemon, lime juice Salt, pepper Soups with allowed ingredients, sugar

Foods	Avoid	Recommend	Foods	Avoid	Recommend
Vegetables	Beets[a]: tops, roots, greens Collards Kale Leeks Mustard greens Okra Parsley[a] Sweet potato[a] Rutabagas Spinach[a] Swiss chard[a] Watercress[a]	Asparagus Broccoli Carrots Corn: sweet, white Cucumber, peeled Green peas, canned Lettuce Lima beans Parsnips Tomato, 1 small, juice Turnips Avocado Brussels sprouts Cauliflower Cabbage Mushrooms Onions Peas, green White potato Radish	**Fruits**	Currants, red Dewberries Grapes, purple Gooseberries Lemon peel[a] Lime peel[a] Orange peel[a] Rhubarb[a]	Apple Apricots Cherries, red, sour Cranberry juice Grape juice Orange, fruit, and juice Peaches Pears Pineapple, plum, purple Prunes Apple juice Banana Cherries, bing Mangos Melons, cantaloupe, cassava honeydew, watermelon Nectarines Peaches Pineapple juice Plums, green, or yellow
Meat and meat substitutes	Peanut butter Tofu (if it is processed with Ca, it is allowed in small amount)	Eggs Cheese Beef, lamb, or pork Poultry; Fish and shellfish Sardines	**Starch**	Fruit cake Soybean crackers[a] Wheat germ[a]	Corn bread Sponge cake Spaghetti, canned in tomato sauce Rice Quinoa All bread

[a]Very high-oxalate content

Uric Acid My Plate



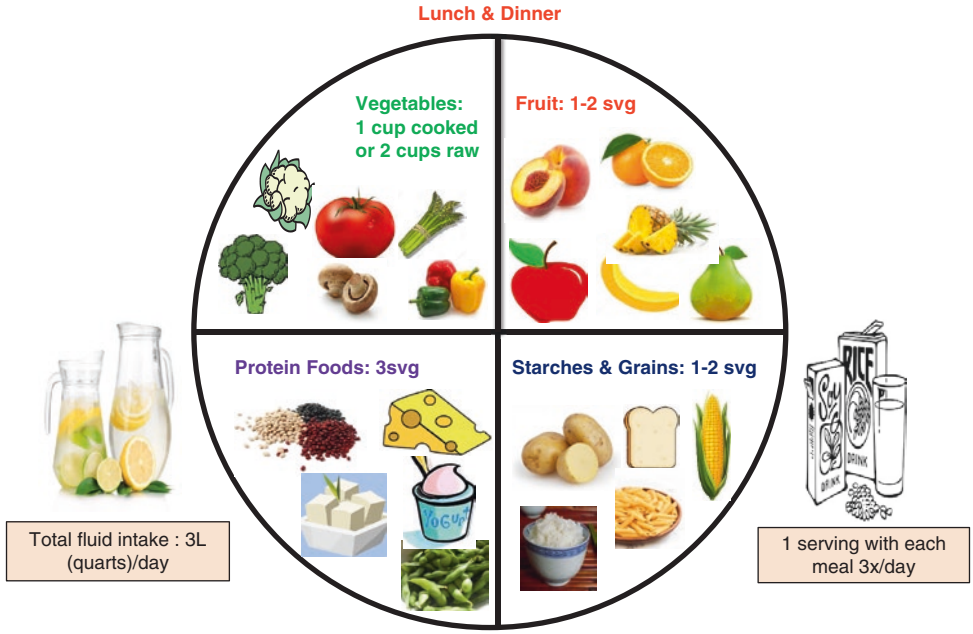
High and low purine foods

Foods	Avoid	Recommend	Foods	Avoid	Recommend
Beverages	Beer and wine (alcoholic beverages)	Water Juices Tea, coffee	**Miscellaneous**	Meat-based gravies	All other sauces (low sodium is recommended)
Vegetables	None	All fresh and frozen	**Fruits**	None	All fresh and frozen
Meat and meat substitutes	Anchovies, sardines, herring, tuna, codfish, shellfish (scallops, mussel, lobster, shrimp, oyster) trout and haddock, bacon, organ meats, tripe, sweetbreads, wild game, goose	Eggs, cheese, peanut butter Lean beef, lamb or pork, poultry	**Starch**		Breads, pastas, rice, cakes, corn breads, popcorn Oatmeal, wheat bran

Acid ash and alkaline ash foods

	Acid ash foods	Alkaline ash foods
Meat/protein	Bacon, beef, pork, labs, shellfish, organ meats Turkey, chicken, eggs	Tofu, beans
Dairy products	Milk, cottage cheese	Goat milk, rice milk, soy milk
Beverages	Alcohol, cranberry juice, coffee, black tea, soda	Almond milk, herbal tea
Starch/grains	White bread, pasta, white rice	Quinoa, brown rice, potatoes, lentils, beans,
Vegetables	None	All types of vegetables, broccoli, kale, tomato, cabbage
Fruits	Cranberries, plums, prunes, dried fruits	Lemon, lime, most fruits
Miscellaneous	Most nuts, mayonnaise, honey, syrup, corn syrup sucrose, artificial sweetener	Coconut oil, sunflower oil,

Vegetarian CaOx My Plate



High- and low-oxalate foods

Foods	Avoid	Recommend	Foods	Avoid	Recommend
Beverages	Draft beer Ovaltine Cocoa	Coffee Beer (bottle) Carbonated soda Distilled alcohol Lemonade Wine: red, rose, white Buttermilk; whole, low-fat, or skim milk Yogurt with allowed fruits Soy, almond, and rice milk	**Miscellaneous**	Nuts[a] Peanuts, almonds, pecans, cashews Chocolate[a], Cocoa,[a] vegetable soup, marmalade	Bacon Mayonnaise Salad dressing Vegetable oils Butter, margarine Coconut Jelly or preserves (made with allowed fruits) Lemon, lime juice Salt, pepper Soups with allowed ingredients, sugar

Foods	Avoid	Recommend	Foods	Avoid	Recommend
Vegetables	Beets[a]: tops, roots, greens Collards Kale Leeks Mustard greens Okra Parsley[a] Sweet potato[a] Rutabagas Spinach[a] Swiss chard[a] Watercress[a]	Asparagus Broccoli Carrots Corn: sweet, white Cucumber, peeled Green peas, canned Lettuce Lima beans Parsnips Tomato, 1 small, juice Turnips Avocado Brussels sprouts Cauliflower Cabbage Mushrooms Onions Peas, green White potato Radish	**Fruits**	Currants, red Dewberries Grapes, purple Gooseberries Lemon peel[a] Lime peel[a] Orange peel[a] Rhubarb[a]	Apple Apricots Cherries, red, sour Cranberry juice Grape juice Orange, fruit, and juice Peaches Pears Pineapple, plum, purple Prunes Apple juice Banana Cherries Mangos Melons, cantaloupe, cassava honeydew, watermelon Nectarines Peaches Pineapple juice Plums, green, or yellow
Meat substitutes	Peanut butter Tofu (if it is processed with Ca, it is allowed in small amount)	Eggs Cheese Beans Lentils Kefir	**Starch**	Fruit cake Soybean crackers[a] Wheat germ[a]	Corn bread Sponge cake Spaghetti, canned in tomato sauce Rice Quinoa All bread

[a]Very high-oxalate content

Diet Education

Low Sodium Diet

What is Sodium?

Sodium is a mineral found naturally in foods and it is the major part of table salt.

Why do I need to limit my sodium intake?

Some salt or sodium is needed for body water balance. However when you have high blood pressure, congestive heart failure or a kidney problem, you lose the ability to control sodium and water balance therefore you may experience the following:

- Thirst
- Fluid gain
- High blood pressure

By using less sodium in your diet, you can control these problems.

Hints to cut down sodium intake

- Cook with herbs and spices instead of salt
- Read food labels and choose foods low in sodium
- Avoid salt substitutes and especially low sodium foods made with salt substitutes because they are high in potassium. You should discuss with the dietitian if you have questions on salt substitutes.
- When eating out, ask for meat or fish without salt. Ask for gravy or sauce on the side: these may contain large amounts of salt and should be used in small amounts.
- Limit use of canned, processed and frozen foods.

Information about reading labels

• Sodium free	Only a trivial amount of sodium per serving
• Very low sodium	35 mg or less per serving
• Low sodium	140 mg or less per serving
• Reduced sodium	Foods in which the level of sodium is reduced by 25%
• Light or lite in sodium	Food in which the sodium is reduced by at least 50%

Rule of thumb: If salt is listed in the first five ingredients, the item is probably too high in sodium to use.

- All food labels have milligrams (mg) of sodium listed. Follow these steps when reading the sodium information on the label:

Know how much sodium you are allowed each day.

- Remember that there are 1000 mg in 1 gram. If your diet prescription is 2gm of sodium your limit is 2000 mg per day. Consider the sodium value of other food to be eaten during the day. New guideline of sodium allowance is 2.3gm (2300mg) per day.

Look at the package label.

- Check the serving size. Nutrition values are expressed per serving. If the sodium level is 500mg or more per serving, the item is not a good choice.

Compare labels of similar products.

- Select the lowest sodium level for the same serving size.

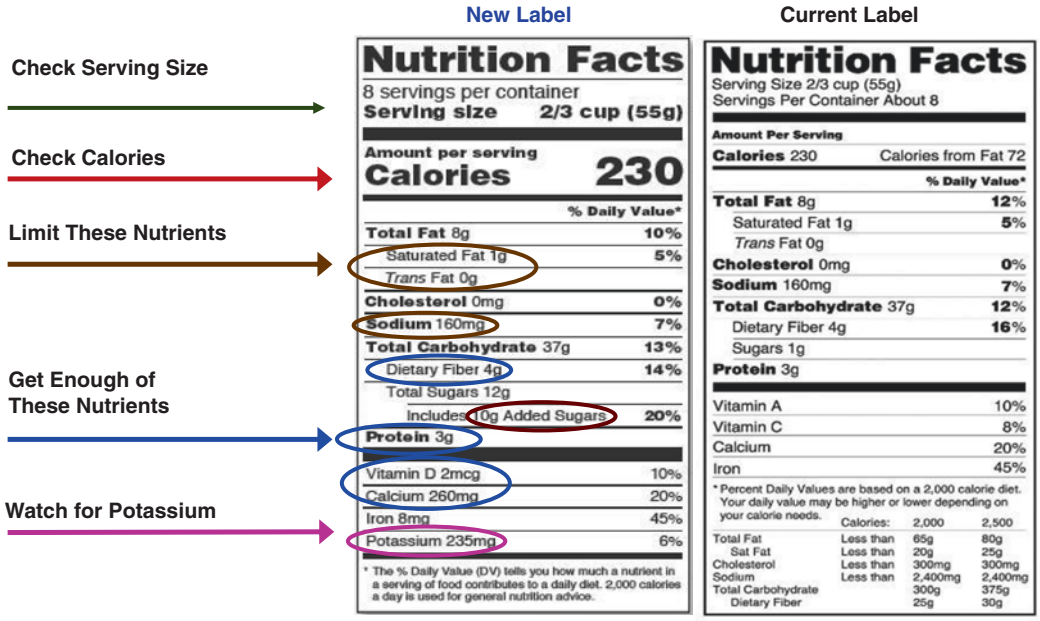
What kind of spices and herbs should I use instead of salt to add flavor?

All spices, basil, bay leaf, caraway, cardamom, curry, dill, ginger, marjoram, rosemary, thyme, sage, tarragon and Mrs. Dash

Foods	Avoid	Choose
Dairy	Buttermilk, Cottage cheese, regular cheese	2%, 1% or skim milk, low fat yogurt, low sodium cheese
Meats	**Processed and luncheon meats** Ham, bacon, salt pork, sausage Hotdogs, corned beef, Spam, Pastrami **Breaded or fried meats** Chicken, fish pork or beef **Canned meats in oil** Sardines, salmon, tuna	Fresh beef, veal, pork, poultry, fish, eggs Low -salt deli meat
Starches	Salted crackers or bread, Pretzels Potato chips, corn chips, tortilla chips popcorn Instant mashed potatoes Mixed muffins, pancakes, potatoes, noodles, some dry cereals	Fresh bread, most commercial breads Unsalted chips, crackers, pretzels Read labels for dry cereals Unsalted popcorn
Vegetables	Canned vegetables Pickles, sauerkraut, olives, relish, vegetable juice, vegetable soup tomato products Frozen vegetables with cheese or cream sauces	All plain fresh and frozen vegetables Low sodium canned vegetables Low sodium tomato sauces Homemade or low sodium soups
Fruits	None	All
Condiments	Table salt, garlic salt, celery salt Lite salt, Bouillon cubes, seasoning salt, onion salt, lemon pepper, meat tenderizer, flavored enhancers, salt substitutes, catsup/ketchup, mustard, salad dressing, soy sauce, steak sauce, barbecue sauce, teriyaki sauce, oyster sauce, hot sauce, Worcestershire sauce	Fresh garlic, fresh onion, garlic powder, onion powder, black pepper, lemon juice, low-sodium or salt-free seasoning blends, vinegar, homemade or low sodium sauces and salad dressings, dry mustard
Other	**Convenience foods** TV dinners, Chili, spaghetti, frozen prepared foods, fast foods, canned raviolis, macaroni & cheese **Most Chinese, Mexican and Pizza restaurants**	Low sodium frozen dinner, homemade casseroles without added salt, soups made with fresh or raw vegetables, fresh meat, rice, pasta or unsalted canned vegetables Request no salt on foods when eating out. Ask for sauces on the side when dinning out.

Harvard Vanguard Medical Associate Department of Nephrology

Understanding Nutrition Label



1. **Portion Check: Make sure to look at the serving size and how many servings are in the container.**
   - **Example: one serving of this food = 2/3 cup. If I eat this whole package, I will eat about 5 cups.**

2. **Calorie Control: Calories tell us how much energy we get per serving.**
   - **Example: one serving of this food will give me 230 calories. If I eat the whole package, I will eat 1840 calories.**
   - **In General: Low = 50 Calories per serving; High = 400 Calories per serving**

3. **Limit These Nutrients: Saturated Fat, Trans Fat, Sodium, and Added Sugars.**
   - **Low Fat = 3 g or less of total fat per serving**
   - **Low Sodium = 140 mg or less per serving; it is ok to choose less than 200 mg per serving**

4. **Get Enough of These Nutrients: Look for foods higher in Fiber, Protein, and Vitamins and Minerals. These nutrients are important for health!**
   - **Dietary fiber lowers cholesterol and keeps you feel full longer.**
     Good Sources = 3 g or more per serving
     High Fiber = 5 g or more per serving
   - **Protein is important for keeping you energized, building and maintaining muscle mass, as well as wound healing.**
   - **Vitamin D, Calcium and Iron**
     Consult with your dietitians about your individual requirements.

5. **Watch for Potassium:**
   - **Based on your individual requirement, you may need to aim for low potassium (less than 200 mg per serving).**
   - **Make sure to consult with your dietitian about your potassium requirement.**

Harvard Vanguard Medical Associate Department of Nephrology

Potassium and Diet

What Is Potassium and Why Is It Important to You?

Potassium is a mineral found in many of the foods you eat. It plays a role in keeping your heartbeat regular and your muscles working properly. It is the job of healthy kidneys to keep the right amount of potassium in your body. However, when your kidneys are not healthy, you often need to limit certain foods that can increase the potassium in your blood to a dangerous level.

Also, if you have high blood pressure and take medications called "ACE Inhibitors" or "ARB" such as enalapril, lisinopril, losartan, or irbesartan or valsartan, these medications may increase your potassium level in the blood. You may feel some weakness, numbness, and tingling if your potassium is at a high level. If your potassium becomes too high, it can cause an irregular heartbeat or a heart attack.

How Can You Keep Your Potassium Level from Getting Too High?

You should limit foods that are high in potassium. Your renal dietitian will help you plan your diet so you are getting the right amount of potassium.

Eat a variety of foods but in moderation.

If you want to include potatoes (a high-potassium food) in your meal, you should peel, cut into small pieces, soak in water, boil, and then drain them to remove some of their potassium.

Do not drink or use the liquid from canned fruits and/or vegetables or juices from meats.

Remember that almost all foods have some potassium. The size of the serving is very important. Eating a large amount of low-potassium foods can turn it into a high-potassium meal.

What Is a Safe Level of Potassium in Your Blood?

Ask your doctor or dietitian about your recent blood potassium level and enter it here: _____

If it is 3. 5–5.0:	You are in the SAFE zone
If it is 5.1–6. 0:	You are in the CAUTION zone
If it is ≥6.0:	You are in the DANGER zone

What Foods Are High in Potassium? (200 mg or Higher Per Portion)

The following table lists foods that are high in potassium. The portion size is ½ cup unless otherwise noted. Avoid high-potassium foods. You should not consume the following foods more than twice per week.

Usually meats, meat products, egg, fish, poultry, and cheese are high in potassium; however, you should have these good protein sources in your diet because they are necessary to maintain good nutritional status.

High-Potassium Foods

Fruits	Vegetables	Other foods
Avocado – ¼	Artichoke	Bran/bran products
Banana – ½[a]	Broccoli	Chocolate – 1.5—2 oz
Cantaloupe	Brussels sprouts	Granola
Dates	Carrots – raw	Milk (all type) – 1cup
Dried fruits	Dried beans/peas	Yogurt
Figs	Escarole	Organ meat – 3 oz
Honeydew	Greens, except kale	Molasses – 1 Tbsp
Kiwi – 1	Kohlrabi	Nuts and seeds – 1 oz
Mango – 1	Lentils/legumes	Peanut butter – 2 Tbsp
Nectarine – 1	Lima beans	*Salt substitute or lite salt*[a]
Orange – 1	Mushrooms – canned	
Papaya – ½	Parsnips	
Prunes	*Potatoes – white or sweet*[a]	
Raisins	Pumpkin	
Orange juice[a]	Rutabagas, spinach	
Prune juice[a]	*Tomatoes/tomato products*[a]	
Coconut/coconut milk[a]	*Vegetable juices*[a]	
	Winter squash (acorn, hubbard)	

[a]Avoid as much as you can

What Foods Are Low in Potassium? (200 mg or Higher Per Portion)

The following table lists foods that are low in potassium. A portion is ½ cup unless otherwise noted. Choose foods from the following list. You can eat the following foods daily.

Low-Potassium Foods

Fruits	Vegetables	Other foods
Apples – 1	Alfalfa sprouts	Rice
Applesauce	Asparagus – 6 spears	Noodles
Apricots (fresh) – 1 medium	Beans: green or wax	Pasta
(canned) – ½ cup	Bean sprouts	Bread and bread products – not whole grain
Blackberries	Beets, cooked	Cereals – not bran or whole grain
Blueberries	Cabbage	Cake – not carrot or chocolate
Cherries	Carrots, cooked	Coffee – limit 1 cup
Cranberries	Cauliflower	Cookies – without nut or chocolate
Fruit cocktail	Celery – 1 stalk	Pies – without chocolate or high-potassium fruits
Grapefruit – ½	Corn	Tea – limit 2 cups
Grapes	Cucumber	
Mandarin oranges	Eggplant	
Peaches (fresh) – 1 small	Kale	
(canned) – ½ cup	Lettuce	
Pears (fresh) – 1 small	Mixed vegetables	
(canned) – ½ cup	Mushroom – fresh	
Pineapple	Okra	
Plum – 1	Onions	
Raspberries	Parsley	
Strawberries	Peas, green	
Tangerines – 1	Radish	

Fruits	Vegetables	Other foods
Watermelon – 1 cup	Rhubarb	
Apple, cranberry, grape, grapefruit, and pineapple juice	Squash (summer, zucchini)	

Potassium Content of Foods

Food	Amount	Potassium (mg)
Fruits, Dried Fruits and Fruit juices		
Avocado	¼	149
Banana	7"	422
Cantaloupe	¾ cup (1/8)	320
Dates	¼ c	292
Honeydew	¾ cup (1/8)	303
Kiwi	1	237
Mango	1	323
Nectarine	1	277
Orange	1	237
Prunes	1 cup	796
Raisins	¼ cup	272
Orange Juice	8 floz	496
Prune Juice	8 floz	706
Coconut milk	8 floz	631
Vegetables		
Artichoke	1	343
Broccoli	½ cup	229
Brussels Sprouts	½ cup	248
Carrots–raw	1 cup	390
Beans (kidney, pinto, red, white and Lima)	½ cup	380–500
Mushrooms–canned	½ cup	331
Parsnips	½ cup	287
White Potatoes	1 (small) baked	925
Sweet (Yam)	¾ cup	918
Pumpkin	½ cup	252
Spinach	1 cup	167
Tomato	1 (small fresh)	291
Tomato sauce	½ cup	807
Vegetable juices (V8)	8 floz	520
Winter squash	½ cup	448
Other Foods		
Chocolate	1 bar (1.5 oz)	150
Granola	½ cup	330
Milk (all type)	8 fl oz	348
Yogurt	8 oz	380
Organ meat	3 oz	340
Molasses	1 Tbsp	292
Nuts and seeds	1 oz	206
Peanut butter	2 Tbsp	207
Lite salt	¼ tsp	354

Harvard Vanguard Medical Associate, Department of Nephrology

Cases

Case1: CaOx Stone

A 45-year-old male with a history of recurrent stones had three renal colics in the past 4 years and he has passed all stones. He strained the last stone and he sent it for analysis. He turned out to have calcium oxalate stone. The patient is 298 lbs. He was referred to a nephrologist stone prevention. He has a history of hypertension and prediabetes.

1. What are the first initial evaluation steps strategy for the evaluation of the patient?
   (a) Urinalysis, basic metabolic panel, parathyroid hormone (PTH), uric acid level, magnesium level
   (b) Twenty-four-hour urine collection with values for the various elements and supersaturations
   (c) Review of imaging studies if done; otherwise, consider a CT scan of the abdomen and pelvis to check stone burden
2. In analysis of the 24-hour urine collections, what are the modifiable risk factors for calcium oxalate stone formation in this case?
   (a) Urine volume
   (b) Sodium
   (c) Oxalate diet
3. What are the initial medical and dietary recommendations?
   (a) Increase fluid intake to more than 2.5 liters a day.
   (b) Decrease salt intake to less than 2300 mg/day; follow DASH diet. Low-sodium diet will lower the risk of hypercalciuria.
   (c) Decrease animal protein and increase plant protein: total goal of protein intake is 1.0–1.2 g/kg/day.
4. What are the follow-up plans?
   (a) After the dietary changes, repeat one collection 24-hour collection in 6 months to check for improvement.
   (b) Ultrasound of the kidneys in 1–2 years to check the stone burden.
5. His urine calcium and calcium oxalate supersaturation remain elevated on follow-up as shown before; what are your treatment strategies?
   (a) If his urine sodium remains very high and it is increasing the risk of hypercalciuria; discuss diet with him again.
   (b) If his urine sodium improves to goal, consider to start low dose of HCTZ to lower hypercalciuria.

Stone Panel (24-Hour Urinalysis)

Stone risk factors

	Urine vol	SSCaOx	Ca 24	Ox 24	Citrate 24	SSCaP	pH	SSUA	UA 24
2/2/17	1.72	8.51	363	48	820	1.02	5.483	3.85	1.458
2/1/17	1.02	10.79	221	24	497	0.64	5.327	4.07	0.74
Reference	>2.5 L	6–10	Male < 250 Female < 200	20–40	Male > 450 Female > 550	0.8–2	5.8–6.2	0–1	Male < 0.8 Female < 0.75

Dietary risk factors

	Na 24	K 24	Mg 24	P 24	NH4 24	CL 24	Sul 24	UUN 24	PCR
2/2/17	285	76	260	1.965	63	277	54	19.4	1.1
2/1/17	189	73	94	0.98	37	170	91	20.2	1.2
Reference	50–100 mEq	20–100	30–120	0.6–1.2	15–60	10–250	20–60	6–14	0.8–1.4

Normal values

	Weight	Cr 24	Cr24/kg	Ca 24/kg	Ca 24/Cr 24
	127 kg	3243	25.5	2.9	112
	127 kg	2768	21.8	1.7	89
Reference			Male 18–24 Female 15–20	< 4	<140

Case #2: Renal Tubular Acidosis

A 34-year-old female presented to the emergency room with fevers, flank pain, and hand paresthesias. Blood pressure was stable. She was not on any medications. She did not have any other complaints.

She did not have any other medical history.

Basic work-up showed Na: 138, K:2.1, HCO3 8, Cl 107, BUN 27, Cr 1.1.

Urinalysis showed a pH of 9.0.

KUB was done and showed: extensive bilateral calculi and nephrocalcinosis.

CT scan revealed nephrocalcinosis suggestive of medullary sponge disease or metabolic disease.

1. What is the underlying mechanism for the nephrocalcinosis in her case and how do you further investigate the case?

   Most likely the patient has a distal renal tubular acidosis. The differential for renal tubular acidosis is Sjogren's syndrome, SLE, medullary sponge disease, and chronic urinary tract infections. Nephrocalcinosis can also be seen in hyperparathyroidism and in sarcoidosis, but they do not necessarily cause low potassium and bicarbonate.
2. What further tests would you to order?

   (a) To complete the work-up, anti-SSA and anti-SSB, ANA, and PTH. You may order a vitamin D1,25, but it is an expensive medication
   (b) 2 × 24-hour urine collection
3. What is the management in this case?

   (a) 3 liters a day
   (b) Potassium citrate 1080 mg PO tid
   (c) Follow-up with a 4-hour collection in 3 months

Stone Panel (24-Hour Urinalysis)

Stone risk factors

	Urine vol	SSCaOx	Ca 24	Ox 24	Citrate 24	SSCaP	pH	SSUA	UA 24
	2.74 L	3.68	124	44	< 41	1.22	7.524	0.02	0.664
	2.22 L	4.34	93	43	< 33	0.74	7.032	0.06	0.581
Reference	>2.5 L	6–10	Male < 250 Female < 200	20–40	Male > 450 Female > 550	0.8–2	5.8–6.2	0–1	Male < 0.8 Female < 0.75

Dietary risk factors

	Na 24	K 24	Mg 24	P 24	NH4 24	CL 24	Sul 24	UUN 24	PCR
	136	58	49	0.811	48	133	28	7.36	1.0
	132	59	41	0.493	19	145	26	8.49	1.1
Reference	50–100 meq	20–100	30–120	0.6–1.2	15–60	10–250	20–60	6–14	0.8–1.4

Normal values

	Weight	Cr 24	Cr24/kg	Ca 24/kg	Ca 24/Cr 24
	58.5	1148	19.6	2.1	108
	59	1024	17.4	1.6	90
Reference			Male 18–24 Female 15–20	< 4	< 140

Case # 3: Uric Acid Stone

A 56-year-old male presented to nephrology to evaluate hematuria. CT urogram was done showing a 4 mm non-obstructing left renal stone. Previous KUB 2009 did not reveal any calcifications. CT scan 2007 right lower pole renal calculi. Pt had a 24-hour urine collection showing the following:

No stone analysis was done for the first time, and he had an 80% UA stone and 20% CaOx stones in 2012 when he passed stones.

PMH: hypertension, prediabetes

Meds: MVI, Goji berries, ibuprofen, drank alcohol 1–2×/week

Weight 270lbs, BMI 38

1. What are the first steps of renal calculi management? Would you start medication for management of kidney stone?

   (a) According to the urine test, the patient has high uric acid supersaturation with high protein intake. UUN, sulfa, and phosphorus are high which indicate a high-protein diet especially animal protein.
   (b) Urine Cr was in normal range, and urine volume was acceptable.
   (c) Recommendations will be lower animal protein and weight loss.

(d) We don't recommend hypouricosuric agent such as allopurinol until the patient follows dietary management first. Since his citrate is high and pH was normal, there was no reason to add citrate med.
(e) If there is no reduction of urine uric acid, consider allopurinol.

2. Would you start any medication? Follow-up urine test showed low citrate and pH.

(a) The patient lost weight and cut down animal protein; however, the patient has high Ox, low citrate, and low pH.
(b) Started K citrate and education on low Ox diet.

3. When would you follow-up?

(a) Since patient has weight management, 6 months would be appropriate.

Stone Panel (24-Hour Urinalysis)

Stone risk factors

	Urine vol	SSCaOx	Ca 24	Ox 24	Citrate 24	SSCaP	pH	SSUA	UA 24
Follow-up	3.61	2.81	156	52	330	0.05	5.149	1.54	0.804
Initial	3.34	2.67	198	41	788	0.33	5.810	1.26	1.473
	2.78	4.75	243	48	552	0.46	5.858	1.23	1.307
Reference	>2.5 L	6–10	Male < 250 Female < 200	20–40	Male > 450 Female > 550	0.8–2	5.8–6.2	0–1	Male < 0.8 Female < 0.75

Dietary risk factors

	Na 24	K 24	Mg 24	P 24	NH4 24	CL 24	Sul 24	UUN 24	PCR
Follow up	139	73	224	1.202	53	164	59	16.43	1.1
Initial	231	85	193	1.480	68	234	74	21.07	1.3
	171	106	1.83	1.535	70	172	73	22.37	1.4
Reference	50–100 meq	20–100	30–120	0.6–1.2	15–60	10–250	20–60	6–14	0.8–1.4

Normal values

	Weight	Cr 24	Cr24/kg	Ca 24/kg	Ca 24/Cr 24
Follow-up	112	2408	21.5	1.4	65
Initial	119.8	2493	20.8	1.7	81
	119.8	2211	18.5	2.1	113
Reference			Male 18–24 Female 15–20	< 4	< 140

Case 4: Wrong Collection

A 68-year-old male patient with a history of calcium oxalate stone, hypertension, prediabetes, and obesity collected one 24-hour urine collection for follow-up. Currently, he presented with hematuria at the clinic.

- Weight: 220.1 lbs., height: 5′8″ BMI: 33.6
- Medications: K-citrate 20 meq twice a day, HCTZ 25 mg daily, multivitamin

The patient has been following a low-sodium diet and more fluid intake after the first consult with a nephrologist and nephrology nutritionist (second urinalysis). However, the patient has difficult time to follow low oxalate because he feels hungry and consumes nuts as snacks, especially patient was instructed by a general dietitian for blood sugar control and weight management.

No current blood work.

1. What diet modification patient should follow? Can he consume high-oxalate foods?
   (a) Total fluid intake >3 L/day to produce urine volume > 2.5 L
   (b) Low oxalate
   (c) Low sodium: goal 2300 mg per day
   (d) Moderate protein: 1.0–1.2 g/kg/day
2. Does the patient need potassium citrate?
   (a) The patient has high urine pH and he doesn't have renal tubular acidosis. He doesn't show any sign of low serum bicarbonate. However, his citrate level is low, so he can cut down potassium citrate and add lemon juice in water.
3. What is wrong with the most recent 24-hour urine test?
   (a) The patient seems to have over collection indicated by Cr24/kg, which is the indication of Cr excretion. Other collections had more consistent of Cr24/kg with his weight.
   (b) His Na, protein, sulfa, Mg, K, Ox, and Ca levels were all higher than usual.
4. What is your recommendation?
   (a) Repeat a 24-hour urine test.
   (b) Continue encouragement of fluid intake >3 L with lemon juice.
   (c) Continue to recommend low Ox, low Na, and moderate protein diet.
   (d) Make sure the patient consumes adequate amount of dairy products with meal time (1000–1200 mg/day).

Stone Panel (24-Hour Urinalysis)

Stone risk factors

	Urine vol	SSCaOx	Ca 24	Ox 24	Citrate 24	SSCaP	pH	SSUA	UA 24
Second follow-up	2.98	8.22	323	97	655	1.29	6.240	0.54	1.304
Follow-up	2.94	3.06	125	47	385	0.81	6.612	0.18	0.812
Initial	1.28	8.62	228	43	238	1.21	6.246	0.96	1.000
Reference	>2.5 L	6–10	Male < 250 Female < 200	20–40	Male > 450 Female > 550	0.8–2	5.8–6.2	0–1	Male < 0.8 Female < 0.75

Dietary risk factors

	Na 24	K 24	Mg 24	P 24	NH4 24	CL 24	Sul 24	UUN 24	PCR
Second follow-up	444	191	206	1.763	67	474	77	21.83	1.8
Follow-up	142	86	124	1.149	40	151	43	13.63	1.0
Initial	191	49	65	1.032	46	185	41	12.48	1.0
Reference	50–100 meq	20–100	30–120	0.6–1.2	15–60	10–250	20–60	6–14	0.8–1.4

Normal values

	Weight	Cr 24	Cr24/kg	Ca 24/kg	Ca 24/Cr 24
Second follow-up	100.2	3016	30.1	3.2	107
Follow-up	101.8	1989	19.6	1.2	63
Initial	98.9	2025	20.5	1.0	48
Reference			Male 18–24 Female 15–20	<4	<140

Case #5: Cystinuria

AD is a 46-year-old female who has history of cystinuria known since age 16, but she has never passed a stone. She has had a past history of recurrent urinary tract infections and at least two episodes of pyelonephritis with fever. She had ESWL when she was 16 and without positive result. She developed a staghorn calculus of the right kidney and many stones on her left including an obstructed stone that led to an episode of pyelonephritis in July of 2001. As a result she underwent percutaneous stone removal for the right and the left kidneys few months apart. Of note, her cystinuria was noted incidentally as crystalluria, and she has essentially been untreated; she had a very brief course of penicillamine more than 15 years ago which she discontinued because of sore muscles. During adolescence, she briefly had a trial of baking soda, which she did not like, and she drinks only 9–10 glasses of fluid per day.

CT Scan of the Abdomen and Pelvis Kidneys: Numerous bilateral non-obstructing renal calculi. The largest two calculi on the left are within the lower pole measuring 9 and 7 mm. There is a 5 mm left lower pole calculus and three 2 mm calculi within the upper and lower poles. On the right, the largest two calculi are within the mid to lower pole measuring 9 mm and 5 mm. An additional 3 mm calculus is within the right upper pole. No ureteral calculi.

On follow-up AD is currently asymptomatic.

Her Litholink urinary volume was 1.54 liters, which is low. Her supersaturation of calcium oxalate was normal at 3.79. Urine calcium is normal at 97; oxalate normal is at 30; citrate slightly decreased at 336. Supersaturation of calcium phosphate slightly elevated at 1.18, and the pH of the urine was alkaline at 6.55. Supersaturation of uric acid was normal at 0.24. Uric acid excretion normal at 557. Creatinine was 1205, sodium 131, consistent with low-salt diet. Her weight was 65.9 kilograms. Ammonium 25, sulfate 18, and urea nitrogen 8.2, all consistent with a modest protein intake. The supersaturation of cystine was 1.02, where we would like to keep it less than 1. Total cystine excretion was 534 mg, for a cystine concentration at ambient pH of 1.37 and only a 0.07 increase after incubation at pH 9.5. The cystine concentration after 48 hours was 1.41, which is not significantly different.

1. What is the next step in management?

   (a) Increase fluid intake to 3.0–3.5 liters a day to ensure a urine output of 2.5 liters per day.
   (b) Decrease salt intake as it has been shown to slightly decrease cystine excretion. The goal of sodium intake is 100 mEq (2300 mg)/day.
   (c) Moderately decrease protein intake: goal 0.8–1.2 g/kg of total protein intake but less 50% of animal protein intake is recommended. Methionine is an essential amino acid and precursor of cystine; therefore complete elimination is not desirable.
   (d) Unfortunately, the patient did not tolerated sodium bicarbonate previously which can alkalize the urine and prevent crystallization.
   (e) Yearly imaging with ultrasound is preferred, but if symptoms develop, CT scan of the abdomen and pelvis is recommended.

2. Is captopril a choice?

   (a) Captopril has been shown to decrease cystine excretion but only at high doses of 150 mg/day. Those doses are avoided due to the side effects of hypotension.

3. The patient returns for follow-up with a 24-hour urine collection. She has also been passing gravel. She had one episode of UTI. What is the next step in treatment to prevent more kidney stone formation?

   (a) Tiopronin starting at 400 mg/day is another treatment. Although Tiopronin has the same side effects as D-penicillamine, they are much milder. Tiopronin dose can go up to 1200 mg/day divided over three times a day.
   (b) Repeat a 24-hour urine collection to check if the excretion of cystine has decreased

Oxalate Content and Internet Info

Oxalate Content of Common Foods

Published ranges of oxalate content (mg/100 g food) of selected foods

Food item (100 g)	Range of oxalate values (mg)	Food item (100 g)	Range of oxalate values (mg)	Food item (100 g)	Range of oxalate values (mg)
Flours and grains		Herbs and spices		Vegetables	
Barley flour	56	Black pepper	419	Amaranth leaves, raw	1090
Buckwheat flour	269	Caraway seeds	890–900	Asparagus, raw	130
Bulgur, cooked	47	Cardamom, green	4000–4014	Bamboo shoots, raw	23
Cornmeal	54	Coriander seeds	995–1005	Beet leaves, raw	121–916
Couscous	10–65	Cumin	1500–1505	Beet root, boiled	76–675
Grits, corn	57	Curry powder	1065–1070	Bitter melon, raw	71
Millet, cooked	36	Ginger	1480–1488	Broccoli, raw	190
Oats	16	Nutmeg	200–201	Brussel sprouts, raw	360
Rice, basmati	17	Turmeric powder	1910–1914	Cabbage, Chinese, raw	6
Rice, brown, cooked	12			Cabbage, green, raw	100

Food item (100 g)	Range of oxalate values (mg)	Food item (100 g)	Range of oxalate values (mg)	Food item (100 g)	Range of oxalate values (mg)
Flours and grains		Herbs and spices		Vegetables	
Rice flour, brown	37	*Legumes*		Carrot, raw	500
Rice bran	238	Anasazi beans, boiled	80	Cassava root, raw	1260
Rye flour, dark	51	Adzuki beans, boiled	25	Cauliflower, raw	150
Semolina flour	48	Black beans, boiled	72	Celery	190
Wheat flour, white unbleached	40	Cowpeas, boiled	4	Chicory, raw	210
Wheat flour, whole	67	Fava beans, boiled	22	Chives, raw	1480
Wheat bran	457	Garbanzo beans, boiled	9	Collard greens, raw	450
Wheat germ	44–269	Great northern beans, boiled	75	Coriander, raw	10
		Kidney beans, boiled	16	Corn, raw	10
		Lentils, boiled	8–118	Cucumber, raw	20
Fruit		Lima beans, boiled	8	Eggplant, raw	190
Apple	9–11	Mung beans, boiled	5	Endive, raw	110
Apricot	48–50	Navy beans, boiled	57	Garlic, raw	360
Avocado	18	Peas, green, raw	50	Kale, raw	20
Blackberries	19	Peas, split, green, boiled	6	Kale, Chinese, raw	23
Blueberries	15	Peas, split, yellow, boiled	5		
		Pink beans, boiled	75	Leek, raw	89
Cherries, canned	8	Pinto beans, boiled	27	Lettuce, raw	330
Currants	19	Red beans, boiled	35	Okra, raw	50
Date	100	Soybeans, boiled	56	Olives	44
Feijoa	60	White beans, small, boiled	78	Onion, raw	50
Figs, dried	57			Parsley, raw	150–1700
Figs, fresh	18	*Nuts*		Parsnip, raw	40
Goji berries	138	Almonds, roasted	431–490	Pepper, raw	40
Gooseberries, green	88	Cashews, roasted	262–2310	Potato, raw	50
Grapes, Concord	25	Hazelnuts, raw	167–222	Purslane, raw	850–1310
Grapefruit	10	Macadamia nuts, raw	42	Radish, raw	480
Guava	17–18	Peanuts, raw	96–705	Rutabaga, raw	30
Kiwifruit	23	Peanut butter	81–705	Snap beans, raw	360
Lemon peel	83	Pecans, raw	64	Spinach, raw	400–970
Lime peel	110	Pine nuts, raw	198	Squash, raw	20

Food item (100 g)	Range of oxalate values (mg)	Food item (100 g)	Range of oxalate values (mg)	Food item (100 g)	Range of oxalate values (mg)
Flours and grains		Herbs and spices		Vegetables	
Mango	10–12	Pine nuts, roasted	140	Sweet potato, raw	240
Orange	21	Pistachio nuts, roasted	49–57	Swiss chard, raw	800–812
Papaya	5	Pumpkin seeds, roasted	14	Tomato, raw	50
Pineapple, canned	26	Sunflower seeds, roasted	9	Tomato, sauce	14
Pineapple, dried	38	Walnuts, raw	74	Turnip, raw	210
Prunes, dried	34			Turnip greens, raw	50
Raspberries, black	55	*Soy-based products*		Watercress, raw	310
Raspberries, red	15	Miso	15	Yams, cooked	59
Rhubarb, raw	260–1235	Soy beverage (240 ml)	5–336	Yard long beans, raw	38
Star fruit	80–730	Soy flour	107–183		
Strawberries	15–25	Soy protein	15–496	*Other foods*	
		Soy sauce	11	Chocolate, milk (240 ml)	7
		Soy yogurt	47	Chocolate, milk, candy	42–123
		Soy nuts, roasted	1400	Chocolate syrup	97
		Soy nut butter	38–63	Cocoa powder	170–623
		Tempeh	28	Tea (100 ml), black, brewed	48–92
		Textured vegetable protein	58–584	Tea (100 ml), green, brewed	6–26
		Tofu	2–280	Tea (100 ml) herbal, brewed	0–8

Note: Published ranges of oxalate values compiled from following resources

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Frequently Ask Questions (FAQ)

1. What is kidney stone?

   Definition of kidney stones is hard pieces of material that form in one or both of kidneys. These are composed of minerals in the urine – the stone-forming minerals – calcium, oxalate, urate, cystine, and phosphate. Usually these minerals are eliminated via urine, but if someone doesn't consume enough fluid, the stones can be formed and travel down the urinary tract into the ureter. Small stones usually do not cause much pain or blockage, but if the stone is large, it can cause backup of urine in the kidney, ureter, and bladder which cause pain and blood in the urine. Kidney stones rarely cause permanent damage if treated by a health-care professional.
2. What are the symptoms with kidney stone?

   Some stones are small like sand but others are large as pebble. Most common symptoms include severe pain of the lower back, blood in the urine, nausea or vomiting, fever and chills, and cloudy or bad small urine.
3. What kind of tests to be done?

   Blood tests reveal too much calcium or uric acid. Blood test results help monitor the other health problems of your kidneys.

   Imaging tests may show kidney stones in the urinary track, and tests include simple abdominal X-rays, which can miss small kidney stones, and computerized tomography (CT), which may reveal even tiny stones.

   Other imaging options include an ultrasound, a noninvasive test, and intravenous urography, which involves injecting dye into an arm vein and taking X-rays (intravenous pyelogram) or obtaining CT images (CT urogram) as the dye travels through your kidneys and bladder.

   The 24-hour urine test may show that the urine contains too many stone-forming minerals or too few stone-preventing substances.
4. Why is a 24-hour urine test important?

   A 24-hour urine collection gives information about most importantly the urine volume which is the reflection of how much patients drinks. Also, it provides information about the concentration of the metabolites that crystallize to form stones as well as the supersaturations of the crystallizing components. It also provides information on the acidity of the urine which is a risk factor for multiple stones. Dietary information like salt intake and protein intake can be elucidated from the collection. Twenty-four-hour urine collections are usually done in pair for the first evaluation of recurrent stones, and then one is repeated every 3–6 months depending on the clinical scenario and the management plans.
5. Are there different types of stones?

   People don't understand there are different kinds of stones.

   The most common stone type are calcium oxalate stones followed by uric acid stones. These two types of stones are about 90% of all stone formers.

   The third type of stone is called "struvite" which is due to infection and three times more in women than men.

   Also there is another type of stone which is cystine and it is genetic.

   Calcium and uric acid stones are prevented well with dietary changes along with medication. All stone formers are recommended to drink large quantity of fluid which will dilute urine to prevent stone formation.
6. What are treatments of kidney stone?

   The most common stone removal procedure is extracorporeal shock wave lithotripsy (ESWL) which can breakdown stone to pieces and then eliminate them.

   Medical treatment is the use of drugs which can help the spontaneous passage of stone.

   Diet management is very important for the prevention of recurrence of stones.
7. What is the best type of fluid to drink?

   The best fluid for stone prevention is water. Usually more than 3 L (3 quart) of fluid intake daily is recommended. Regular soda, sweetened punch, and grapefruit juice are not recommended for

stone patients. These fluids were found to increase stone formation as shown in a large epidemiological study. Coffee, tea, beer, and alcohol showed preventive effects in this study; however, the recommendation should be individualized based on stone types and patients. Lemon juice is commonly recommended for prevention of kidney stones. Lemon, lime, or orange juice have high citrus content which can increase urine citrate level. High urine citrate increases urine pH which lowers calcium oxalate stones as well as uric acid stone risks which favors acidic urine. For example, addition of lemon juice will be good for patients who have calcium oxalate stone with acidic urine but not always good for patients with calcium phosphate stone with very alkaline urine.

8. What is the recommendation for calcium intake in patients with calcium-based stones? What is the best source of calcium?

   When patients have calcium stones, especially calcium-oxalate stones, they often eliminate calcium-rich foods from the diet. However, this can increase the risk of calcium-oxalate stones. Free oxalate is easily absorbed in the intestine, but with consumption of dairy products (or calcium rich foods), oxalate is bound to calcium and excreted through stools. Therefore, less oxalate is absorbed in the body which can lower the calcium oxalate stone formation. Calcium is available from food sources or supplements. Usually dairy products, fortified cereals, soymilk, or almond milk are good sources of calcium.

   Calcium supplements are usually taken between meals to maximize absorption of calcium, especially if given with vitamin C. However, high doses of calcium supplement or calcium-fortified orange juice can increase calcium excretion in the urine which can cause elevation of stone risks.

   Calcium supplement with meals can be used as oxalate binders when people have too high free oxalate available in the intestine such as in Crohn's disease, malabsorption problems, or after a bariatric surgery (gastric bypass surgery). Calcium supplements should be used carefully after discussion with the care provider.

   Most people can consume three servings of dairy products per day with meals to meet dietary calcium recommendation and prevent stones.

9. What is oxalate and where is it found?

   Oxalate is one of the common solutes to form a stone with calcium in the urine. It is found in many foods such as vegetables, fruits, nuts and chocolates. Oxalate is easily absorbed in the gastrointestinal (GI) tract as a free form. Oxalate forms an insoluble complex with calcium in the GI and is then eliminated through stools. Therefore, calcium consumption with oxalate foods is important to prevent stones. In the intestine, the bacteria *Oxalobacter formigenes* degrade the oxalate we consume, but long-term antibiotic use kills this bacteria; therefore oxalate can be absorbed easily. If someone has GI problems, usually free oxalate is more available; therefore, people with malabsorption problem develop more stones.

10. Is plant protein better than animal protein to prevent kidney stones?

    There are two sources of proteins, animal protein (high biological value) and plant protein (low biological value). Animal protein contains "purine" the precursor of uric acid and is metabolized in the body and produces acid ash. This can make the urine more acidic which favors uric acid stone formation. Uric acid is not soluble in acidic pH; therefore, individuals with a history of uric acid stones should consume moderate amount of animal protein. Plant protein does not decrease the pH; however, it can be high in oxalate which is also part of oxalate stones. For example, people have increased consumption of nuts and almonds due to the health benefits. Despite the increase in plant protein, this probably increases the oxalate in the diet.

11. Do we evaluate for kidney stones during pregnancy?

    In general, collecting **24**-hour urines should be avoided for stone evaluation in pregnant women. Most women develop hypercalciuria during pregnancy, so there is little benefit in doing the collection when pregnant to determine what their risk factors will be for the rest of their life, most of which will be spent in the nonpregnant state. Because nursing also affects mineral metabolism, patients wait until after pregnancy and nursing are completed and their menstrual cycles have restarted.

Index

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