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THE EFFECTS OF CURCUMIN SUPPLEMENTATION ON GLYCAEMIC PROFILE IN WOMEN WITH POLYCYSTIC OVARIAN SYNDROME: AN EVIDENCE BASED CASE REPORT

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Abstract

Background: Polycystic ovarian syndrome (PCOS) is the most common cause of infertility in the world. It is associated with impaired glucose tolerance and higher tendency to develop type 2 diabetes. Curcumin, which is known for its anti-inflammatory, antioxidant, and antidiabetic properties, may show promising effect in regulating blood glucose.
Objective: This study aims to evaluate the effect of curcumin supplementation on improving glycaemic profile in women with PCOS.
Methods: Literature searching was conducted by advanced searching in Pubmed, Cochrane Library, Scopus, and ProQuest database using MeSH Terms combined with Title/Abstract. After removing duplicates, the literatures were screened based on the eligibility criteria. Critical appraisal and level of evidence of the selected literatures were determined based on Oxford Centre for Evidence-Based Medicine.
Results: Two selected literatures were relevant to answer our clinical question. The first literature is a systematic review/meta-analysis study by Chien et al (2021) and the latter is a randomized controlled trial by Asan et al (2020). Both literatures show that curcumin supplementation is beneficial in improving glycaemic profile in PCOS patients. These effects were marked by lower fasting blood glucose, insulin level, and HOMA-IR in curcumin group compared to the control group. Curcumin supplementation for at least 6 weeks significantly improve glycaemic profile in women with PCOS.
Conclusion: Curcumin supplementation ranging from 93,42 mg to 500 mg until 1500 mg per day orally for at least 6 weeks significantly improve glycaemic profile in women with PCOS. It is also considered safe and well tolerable. However, more studies are needed to investigate further regarding the long-term effects of curcumin supplementation.

Clinical Scenario

A 26-year-old, unmarried woman was referred by her obstetrician and gynecologist (OBGYN) to the clinical nutrition physician. She was diagnosed with polycystic ovarian syndrome (PCOS). She had been struggling with her irregular menstrual cycle for years, along with acne breakouts and weight gain. All vital signs and general examination were within normal limits. Her current body mass index was 27.8 kg/m^2. Based on the laboratory examination, her fasting blood the glucose was 108 mg/dL and the HbA1C was 5.6%.

She refused to consume any medication from her OBGYN as she read on the internet that healthy lifestyle, especially eating unprocessed food, was the most essential in PCOS treatment. Then she asked about the beneficial effect of curcumin for PCOS patients like her, because she also got an information from her relatives that consuming curcumin would help to regulate her menstrual cycle and blood glucose.

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Introduction

Polycystic ovarian syndrome (PCOS) is one of the most prevalent disorders that affects 4% to 21% women of reproductive age and contributes to 70–80% of infertility cases globally.[1,2] PCOS is characterized by chronic anovulation and excessive androgen secretion by ovarian and/or adrenal glands. This was due to many factors, one of them is insulin resistant-hyperinsulinemia.[3] Besides the reproductive disorders, PCOS is associated with other metabolic features, including impaired glucose tolerance, type 2 diabetes, cardiovascular disease, and cardiovascular risk factors like dyslipidemia. Approximately 50% of the PCOS patients develop these conditions and metabolic syndrome as well. Another hypothesis also found that oxidative stress and inflammation have roles in PCOS pathogenesis.[4] Even though some medications, like metformin, are used to treat PCOS, healthy lifestyle is the mainstay of PCOS management. Recent developments in PCOS management are concentrating on some nutraceuticals, especially curcumin.

Curcumin is an active phytochemical that derived naturally from turmeric or *Curcuma longa,* an herbal plant that widely used in Asia, including Indonesia, as spices and natural yellow colouring in food and herbal medicine, known as *jamu.* Curcumin exhibits antioxidant and anti-inflammatory properties. As an antioxidant, curcumin can increase the gene expression of superoxide dismutase (SOD) and glutathione peroxidase (GPx). Curcumin can also reduce the pro-inflammatory cytokines, such as tumour necrosis factor alpha (TNF-α) and interleukin-1 (IL-1), IL2, IL-6, IL-8, and IL-12.[5] Curcumin also has antidiabetic effect by increasing glucose uptake, glycolysis, and glycogen synthesis in the skeletal muscle. Moreover, curcumin can also affect the liver to increase glycolysis and glycogen synthesis while decreasing gluconeogenesis.[2] Due to these promising effects, curcumin is expected to help improving PCOS complications and regulating blood glucose.

From previous studies, curcumin has been shown to improve fasting blood glucose in patients with metabolic syndrome. However, the effects of curcumin on glycaemic control and insulin resistance in PCOS patients remain inconclusive. This evidence-based case report aims to evaluate the effect of curcumin supplementation on PCOS patients' glycaemic profile.

Clinical Question

The clinical question is "in women with polycystic ovarian syndrome, could curcumin improve the patients' glycaemic profile?" From this question, we can state that the population is women with polycystic ovarian syndrome, the intervention is

curcumin supplementation, the comparison is placebo, and the outcome is glycaemic profile.

Methods

Searching Strategy

Literature searching was conducted by advanced searching using combination of both MeSH Terms and Title/Abstract in four databases: Pubmed, Cochrane Library, Scopus, and Proquest. Keywords that were used include *"Polycystic Ovarian Syndrome", "PCOS", "Stein Leventhal Syndrome", "Curcumin*", "Curcuma longa", "Turmeric", "Turmeric Yellow", "Placebo", "Glycaemic Profile", "Glycaemic Control"*. Authors used the guideline from Oxford Centre for Evidence-Based Medicine to critically appraise the literature and determine the level of evidence.

Eligibility Criteria

Some inclusion and exclusion criteria are set to select the suitable articles. The inclusion criteria are: 1) women diagnosed with PCOS; 2) patients received curcumin supplementation; 3) the study output was PCOS patients' glycaemic profile, including fasting blood glucose, glycated hemoglobin (HbA1C), HOMA-IR, or insulin resistance level; 4) the study design is randomized controlled trial or systematic review/meta-analysis of randomized controlled trials; 5) articles were published in English. The exclusion criteria are: 1) studies that were not conducted on humans; 2) the published article was not available in full text.

Results

The authors found 2 articles from Pubmed database, 3 articles from Cochrane Library, 4 articles from Scopus, and 1 article from ProQuest using searching strategy that shown in Table 1. Duplicated articles were removed first, then remaining articles were assessed for eligibility based on Population, Intervention, Comparison, and Outcomes (PICO) and eligibility criteria (Figure 1). We eventually selected 2 articles from Chien et al and Asan et al, whose details are shown in Table 2.[4,5] The level of evidence for each article is 1A and 2, respectively. Both articles were valid and relevant to answer our clinical question (Table 3, Table 4).

Discussion

One of the common complications related to PCOS is glucose tolerance impairment that eventually can lead to type 2 diabetes. Forslund et al found that women with PCOS develop type 2 diabetes more frequently than women without PCOS (19%, compared with 1% in control group).[6] Curcumin, which is known to have anti-inflammatory, antioxidant, and antidiabetic properties, has been proposed to be beneficial in regulating blood glucose in PCOS patients.

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Table 1. Literature Searching Strategy

Database	Search Strategy		Hits
Pubmed	("polycystic ovarian syndrome"[Title/Abstract] OR "polycystic ovary syndrome"[MeSH Terms] OR "PCOS"[Title/Abstract] OR "stein leventhal syndrome"[Title/Abstract]) AND ("curcumin"[MeSH Terms] OR "curcum*"[Title/Abstract] OR "curcuma longa"[Title/Abstract] OR "turmeric"[Title/Abstract]) AND ("placebo*"[Title/Abstract] OR "placebo*"[MeSH Terms]) AND ("glycaemic profile"[Title/Abstract] OR "glycaemic control"[MeSH Terms])		2
Cochrane	#1	("polycystic ovary syndrome"):ti,ab,kw (Word variations have been searched)	3
	#2	(PCOS):ti,ab,kw (Word variations have been searched)	
	#3	MeSH descriptor: [Polycystic Ovary Syndrome] explode all trees	
	#4	("Stein Leventhal syndrome"):ti,ab,kw (Word variations have been searched)	
	#5	#1 OR #2 OR #3 OR #4	
	#6	(curcumin):ti,ab,kw (Word variations have been searched)	
	#7	MeSH descriptor: [Curcumin] explode all trees	
	#8	(curcuma longa):ti,ab,kw (Word variations have been searched)	
	#9	MeSH descriptor: [Curcuma] explode all trees	
	#10	(turmeric):ti,ab,kw (Word variations have been searched)	
	#11	#6 OR #7 OR #8 OR #9 OR #10	
	#12	MeSH descriptor: [Placebos] explode all trees	
	#13	(placebo):ti,ab,kw (Word variations have been searched)	
	#14	#12 OR #13	
	#15	(glycaemic profile):ti,ab,kw (Word variations have been searched)	
	#16	MeSH descriptor: [Glycaemic Control] explode all trees	
	#17	#15 OR #16	
	#18	#5 AND #11 AND #14 AND #17	
Scopus	(TITLE-ABS-KEY(pcos) OR TITLE-ABS-KEY(polycystic AND ovarian AND syndrome) OR TITLE-ABS-KEY(stein AND leventhal AND syndrome)) AND (TITLE-ABS-KEY(curcum*) OR TITLE-ABS-KEY(curcuma AND longa) OR TITLE-ABS-KEY(turmeric)) AND TITLE-ABS-KEY(placebo) AND (TITLE-ABS-KEY(glycaemic AND control) OR TITLE-ABS-KEY(glycaemic AND profile))		4
ProQuest	(ti(Polycystic Ovary Syndrome) OR ti(PCOS) OR ti(stein leventhal syndrome)) AND (ti(Curcumin) OR ti(curcuma longa) OR ti(Turmeric)) AND (ti(placebo)) AND (ti(glycaemic control) OR ti(glycaemic profile))		1

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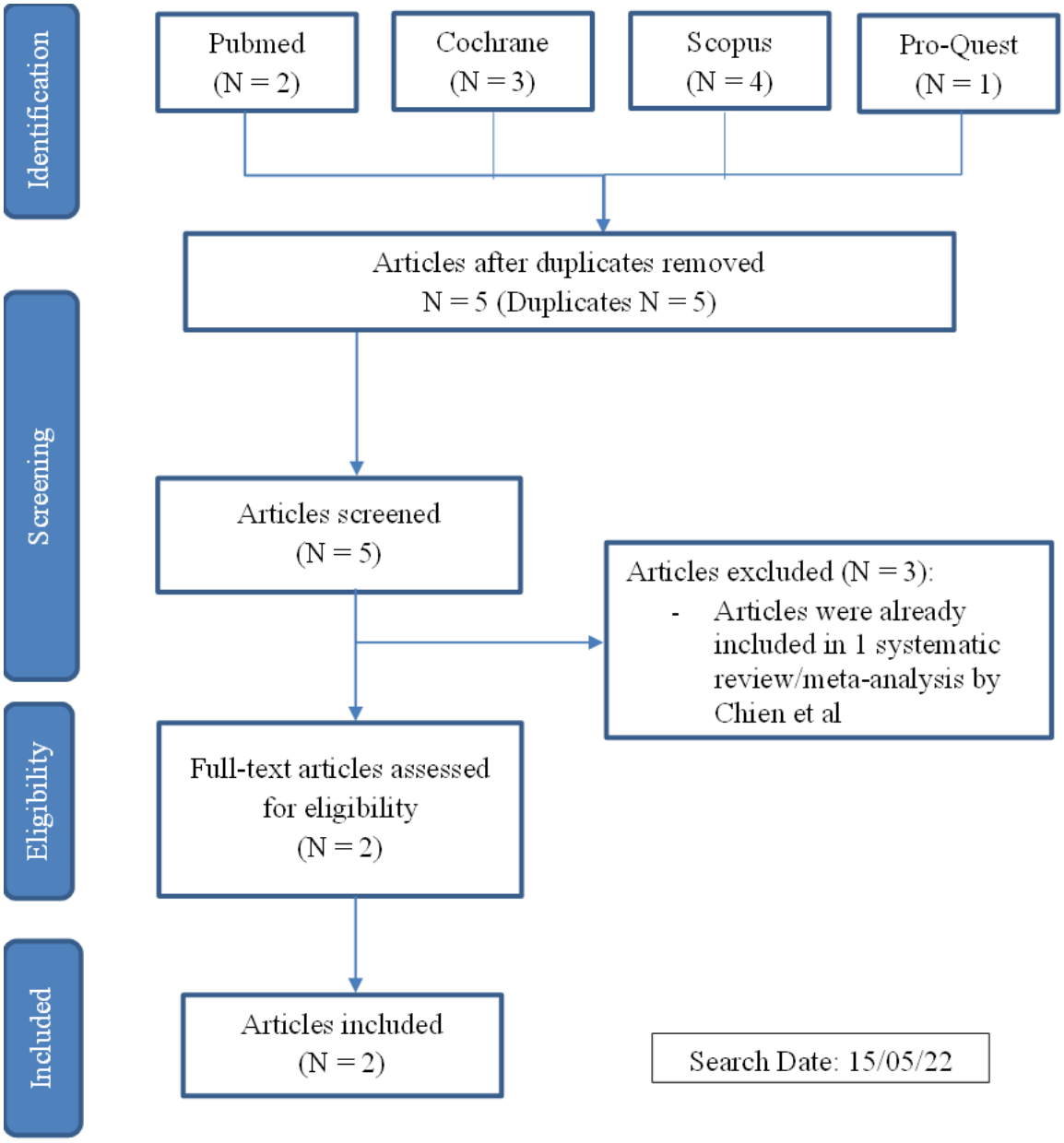

Figure 1. Prisma's Flow Chart

Table 2. Study Characteristic

Articles	Study Design	Population/Intervention	Outcome
Chien et al (2021)[5]	Systematic review/Meta-Analysis of Randomized Controlled Trials	Three studies involving 168 patients with PCOS, based on Rotterdam Criteria, were included. Intervention group received curcumin supplementation doses range from 1x500 mg/day – 3x500 mg/day for 6–12 weeks. Control group received placebo.	Glycaemic control, including fasting glucose, fasting insulin, HOMA-IR, QUICKI. Lipid profile, including HDL, LDL, and total cholesterol.
Asan et al (2020)[4]	Randomized Single-Blinded Controlled Trial	Thirty PCOS patients were randomly assigned to curcumin group (n=15) or placebo group (n=15). Curcumin group received 93.34 mg (2 capsules) of curcumin per day for 8 weeks. Despite that, each group received same diet intervention.	Anthropometric characteristics, such as: weight, body mass index, body fat, waist circumference. Serum biochemical levels, such as: fasting blood glucose, insulin level, HOMA-IR, total cholesterol, triglyceride, LDL, and HDL level.

From the literature research, two studies by Chien et al and Asan et al showed that curcumin supplementation significantly improved glycaemic profiles in PCOS patients, including fasting blood glucose, fasting insulin, and HOMA-IR biomarker.[4,5]

The study by Chien et al found that curcumin supplementation, whose doses ranged from 500 mg to 1500 mg per day for 6–12 weeks, is useful to lower the fasting glucose (MD: –2.77, 95% CI: –4.16 to –1.38; $p < 0.001$; $I^2 = 0\%$), fasting insulin (MD: –1.33, 95% CI: –2.18 to –0.49, $p = 0.002$, $I^2 = 0\%$), HOMA-IR (MD: –0.32, 95% CI: –0.52 to –0.12; $p = 0.002$, $I^2 = 0\%$), and improve QUICKI (MD: –0.32, 95% CI: –0.52 to –0.12; $p = 0.005$, $I^2 = 69\%$), compared to placebo.[5] Asan et al also found that compared to the control group, administration of oral curcumin supplementation as much as 93.34 mg for 8 weeks in PCOS women revealed a significant effect on anthropometric status and glycaemic profile, that was marked by fasting blood glucose level, fasting insulin, and HOMA-IR.[4] Both studies only used curcumin supplementation and compared it with placebo. Chien et al as well as Asan et al did not mention any history of hormonal therapy such as metformin in their participants.

Curcumin affects glycaemic profile by various mechanisms. Curcumin can increase glucose uptake by upregulating the translocation of glucose transporter (GLUT4)

Table 3. Validity Criteria for Chien et al

Article	Study Design	Question	Find	Appraise	Inclusion	Total Up	Heterogenity	Result	Applicability
Chien et al[5]	Systematic Review / Meta-Analysis of Randomized Controlled Trials	+	+	+	+	+	+	A	+

A = There are significant improvement of fasting glucose (MD: –2.77, 95% CI: –4.16 to –1.38; $p < 0.001$; $I^2 = 0\%$), fasting insulin (MD: –1.33, 95% CI: –2.18 to –0.49, $p = 0.002$; $I^2 = 0\%$); HOMA-IR (MD: –0.32, 95% CI: –0.52 to –0.12; $p = 0.002$; $I^2 = 0\%$), and QUICKI (MD: 0.010, 95% CI: 0.003–0.018; $p = 0.005$; $I^2 = 69\%$) in patients taking curcumin than those taking placebo.

Table 4. Validity Criteria for Asan et al

Article	Study Design	Randomisation	Similarity	Equally treated	Intention to treat analysis	Blinding	Result	Applicability
Asan et al[4]	Randomized Controlled Trials	?	+	+	+	Single-blind	B	+

B = Fasting blood glucose level decreased by 6.8 ± 3.8 mg/dL after intervention in curcumin group ($p < 0.05$) and 1.2 ± 3.5 mg/dL in placebo group ($p > 0.05$). Fasting plasma insulin and HOMA-IR decreased only in curcumin group ($p < 0.05$). There were significant differences in fasting blood glucose level, fasting insulin level, and HOMA-IR in curcumin group ($p < 0.05$).

to the membrane of adipocyte and skeletal muscle cells. This effect was mediated by stimulating the phosphatidylinositol 3-kinase (PI3K)/Akt pathway and activating adenosine monophosphate-activated protein kinase (AMPK). This AMPK activation is also resulting in reduced hepatic glucose production and increased proliferator-activated receptor (PPAR) γ, which contributes to control the genes involved in glucose, lipid metabolism, and inflammatory response.[5,7,8] In addition to that, the anti-inflammatory and antioxidant properties of curcumin itself may also help in improving glucose metabolism. Curcumin's anti-inflammatory effect was mediated by inhibiting the induction of cyclooxygenase-2 and lipogeneses, which leads to suppression of prostaglandins. Moreover, curcumin also inhibit activation of TNF-α in the NF-kB pathway. Whereas as an antioxidant, curcumin can increase the activity of antioxidant enzymes, such as superoxide dismutase, catalase, and glutathione peroxidase.[7,9]

Chien et al stated that PCOS patients are associated with higher oxidative stress and proinflammatory cytokines. Both will lead to insulin-resistant hyperinsulinemia, which contributes to an increase of luteinizing hormone by activating the cytochrome P450c17. High level of insulin and luteinizing hormone caused hyperandrogenism symptoms in PCOS patients.[5,9] Curcumin may play a role in improving hyperandrogenism by reducing cytochrome P450c17. This theory was successfully shown in a study by Heshmati et al, that administration of 1500 mg curcumin supplement per day for 12 weeks in patients with PCOS significantly reduced not only fasting blood glucose, but also dehydroepiandrosterone (DHEA), precursor of the androgens.[10] Moreover, curcumin is also considered safe, as Joint United Nations and World Health Organization Expert Committee on Food Additives recommended the daily intake of 0–3 mg/kg body weight of curcumin. Some clinical trials even show good tolerability and safety at doses from 4000 to 8000 mg/day.[9]

Both studies by Chien et al and Asan et al have strength and limitation. Some of the limitation in Chien's study: first, only a few studies are included in the meta-analysis. These studies also have different duration of curcumin intervention, ranging from 6–12 weeks. Second, studies included did not put thorough explanation regarding the preparation of the curcumin supplement formulation.[5] Curcumin is hydrophobic and has poor bioavailability, which is characterized by its poor absorption, rapid metabolism and elimination. In animal studies, oral administration of curcumin showed 40% excretion in rats' faeces. Therefore, various curcumin formulations are developed in order to prevent curcumin hydrolysis inactivation, such as nanocurcumin to increase its water solubility.[9] In contrast to Chien et al, Asan et al mentioned that they used a highly bioavailable formulation of curcumin. This was probably due to microemulsions formulation that increase curcumin solubility in duodenum.[4] Marked limitations in Asan's study are the small sample size and duration of the supplementation. Despite that, studies by Chien et al and Asan et al are valid to answer our clinical question. Chien et al show to us the effect of curcumin supplementation in improving glycaemic profile with a detailed forest plot, narrow confidence interval, and minimal heterogeneity. Furthermore, Asan et al also add new information about curcumin effects in improving anthropometrical status, such as lower the body weight, body fat mass, and waist circumference, compared to the placebo group ($p < 0.05$).[5,9] This effect was first studied by Asan et al during 8 weeks of

intervention. Effects of curcumin on anthropometrical and clinical status of PCOS patients are needed to be investigated further with longer duration. Curcumin is one of the nutraceuticals that could be recommended as an adjuvant therapy for women with PCOS, since PCOS women tend to have hyperglycaemia and higher risk to develop type 2 diabetes in later life.

Conclusions and Recommendation

Based on the critical review for both articles, it was found that curcumin supplementation, for at least 6 weeks of duration, could be considered in improving glycaemic profile in PCOS patients. We recommend taking the curcumin in a supplement form rather than consuming it from food or beverage, to ensure that we can get a proper dose to have the anti-inflammatory, antioxidant, and antidiabetic properties of curcumin. From both literatures, the recommended dosage for curcumin supplementation ranging from 93,42 mg to 500 until 1500 mg per day orally. Even though curcumin supplementation is well tolerable and considered safe in both studies, we still need more studies with longer duration and larger sample size to determine curcumin effects and possible side effects for at least a year. Curcumin effects on improving hyperandrogenism clinical symptoms may also be investigated later in the future.

Competing Interest

The authors declare that there are no competing interests related to the study

List Of Abbreviations

DHEA	: dehydroepiandrosterone
HbA1C	: glycated hemoglobin
HDL	: high-density lipoprotein
HOMA-IR	: Homeostatic Model Assessment Insulin Resistance
GLUT	: glucose transporter
GPx	: glutathione peroxidase
IL	: interleukin
LDL	: low-density lipoprotein
OBGYN	: Obstetrician and gynecologist
PCOS	: Polycystic Ovarian Syndrome
PPAR	: proliferator-activated receptor
QUICKI	: Quantitative Insulin Sensitivity Check Index
SOD	: superoxide dismutase
TNF-α	: tumor necrosis factor alpha

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SUPLEMENTASI ASAM FOLAT PRAKONSEPSI DALAM PENCEGAHAN BIBIR SUMBING : *EVIDENCE - BASED CASE REPORT*

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Abstract

Cleft lip is a congenital abnormality that is often found in newborns, especially in developing countries. Risk factors include exposure to cigarettes and chemicals, alcohol consumption, and inadequate intake of micronutrients during pregnancy. Higher doses of folic acid supplementation in the preconception period were associated with a reduced risk of cleft lip. Objective: To determine the relationship between preconception folic acid supplementation with the risk of cleft lip. Methods: The literature search was carried out by advanced searching on Pubmed, Cochrane Library, Scopus, and ProQuest with the eligibility criteria determined by the author. Results: A systematic review-meta-analysis study by Jayarajan, et al. (2019) explained that there was a strong relationship between high-dose folic acid supplementation and cleft lip. A case-control study that assessed the association of preconception folic acid supplementation with a reduced risk of cleft lip was conducted by 2 investigators. Xu W, et al. (2021) explained that preconception folic acid supplementation reduced the risk of cleft lip (aOR = 0.52, 95% CI 0.30-0.90), while Mendonca VJ, et al. (2019) explained that to get side effects in 1 patient, 71 patients needed folic acid supplementation for 1 year. Conclusion: Based on two studies, it was found that preconception folic acid supplementation can reduce the risk of cleft lip, but further research is needed.

Key words: cleft lip, folic acid supplementation, preconception

Abstrak

Bibir sumbing merupakan kelainan bawaan yang sering dijumpai pada bayi baru lahir, terutama di negara berkembang. Faktor risikonya antara lain paparan terhadap rokok dan bahan kimia, konsumsi alkohol, serta asupan mikronutrien yang tidak memadai selama kehamilan. Dosis suplementasi asam folat yang lebih tinggi pada masa prakonsepsi berhubungan dengan penurunan risiko bibir sumbing. Tujuan: Mengetahui hubungan antara suplementasi asam folat prakonsepsi dengan risiko terjadinya bibir sumbing. Metode: Pencarian literatur dilakukan dengan *advanced searching* pada Pubmed, Cochrane Library, Scopus, dan ProQuest dengan kriteria eligibilitas yang ditentukan oleh penulis. Hasil: Studi *systematic review*-meta analisis oleh Jayarajan, *et al*. (2019) menjelaskan bahwa terdapat hubungan kuat antara suplementasi asam folat dosis tinggi dengan bibir sumbing. Studi kasus-kontrol yang menilai hubungan suplementasi asam folat prakonsepsi dengan penurunan risiko bibir sumbing dilakukan oleh 2 peneliti. Penelitian Xu W, *et al*. (2021) menjelaskan bahwa suplementasi asam folat prakonsepsi menurunkan risiko bibir sumbing (aOR = 0,52, 95% CI 0,30-0,90), sedangkan penelitian Mendonca VJ, *et al*. (2019) menjelaskan bahwa untuk mendapatkan efek samping pada 1 pasien diperlukan 71 pasien dengan suplementasi asam folat selama 1 tahun. Kesimpulan: Berdasarkan dua penelitian didapatkan hasil bahwa suplementasi asam folat prakonsepsi dapat menurunkan risiko bibir sumbing, namun diperlukan penelitian lebih lanjut.

Kata kunci : bibir sumbing, suplementasi asam folat, prakonsepsi

Pendahuluan

Bibir sumbing merupakan kondisi malformasi kraniofasial tersering yang terjadi pada bayi baru lahir. Terdapat tiga tipe bibir sumbing, yaitu hanya celah bibir (*labioschisis*), celah bibir disertai celah langit-langit (*labiopalatoschisis*), dan hanya celah langit-langit (*palatoschisis*).[1,2] Kondisi

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ini merupakan kelainan bawaan yang terjadi sejak embrio berusia empat minggu, yang mengenai bibir sampai dengan langit-langit mulut.[3] Penyebabnya multifaktorial, di antaranya interaksi faktor genetik dan lingkungan, seperti ibu merokok, konsumsi alkohol, paparan bahan kimia selama kehamilan, serta asupan mikronutrien yang tidak memadai.[1,4-6] Beberapa mikronutrien yang berperan penting dalam etiologi bibir sumbing antaranya lain asam folat, vitamin B6, dan vitamin B12.[4] Berdasarkan penelitian Loho JN[3] di Manado pada Januari 2011 – Oktober 2012, didapatkan prevalensi sebesar 57% dengan etiologi berupa faktor genetik sebesar 25%, faktor lingkungan 62%, dan faktor tidak diketahui sebesar 13%. Studi Salari, et al.[7] mengatakan bahwa prevalensi bibir sumbing sekitar 0,3-0,45 per 1000 kelahiran hidup.

Seperti telah disebutkan di atas bahwa insidensi bibir sumbing berhubungan dengan asupan asam folat maternal, risikonya meningkat empat kali lipat pada ibu yang tidak mengonsumsi asam folat selama tiga bulan pertama kehamilan.[8,9] Sebelumnya telah diketahui bahwa kekurangan asam folat selama awal kehamilan dapat menyebabkan defek tabung saraf, seperti spina bifida.[8-10] Terdapat bukti kuat bahwa asupan asam folat prakonsepsi dapat mencegah defek tabung saraf, tetapi belum diketahui efeknya pada bibir sumbing.[9] Pada studi meta-analisis, model hewan, dan studi in vitro menunjukkan terdapat efek protektif asam folat terhadap bibir sumbing, namun masih diperlukan penelitian lanjutan mengenai dosis dan metode pemberian.[11] Hubungan suplementasi asam folat pada masa prakonsepsi dalam pencegahan bibir sumbing belum diketahui secara pasti, oleh sebab itu penulis ingin lebih mendalami topik ini melalui *Evidence-Based Case Report* (EBCR).

Kasus Pasien

Ny. R, 41 tahun, dirawat di RSAB Harapan Kita dengan diagnosis G7P6(AH5)A0 hamil 37 minggu 1 hari dengan janin kelainan anomali multipel dengan hipoperfusi. Pasien lupa kapan hari pertama haid terakhir (HPHT). Pasien mengaku rutin memeriksakan kehamilan di bidan dan rumah sakit terdekat. Selama kehamilan, pasien sering diberikan obat, namun tidak ingat namanya karena tidak rutin diminum. Pada pasien dilakukan operasi sesar, dilahirkan bayi laki-laki, dengan nilai APGAR 6/9 dan cairan ketuban ibu jernih. Bayi diketahui dengan kelainan kongenital multipel (mikrosefali, *labiognatopalatoschisis*, polidaktili, omfalokel, mikropenis, *rocker bottom feet*, *clunched fingers*) serta hidronefrosis bilateral. Berat badan lahir (BBL) 2675 gram, panjang badan (PB) 46 cm, lingkar kepala (LK) 31,5 cm, lingkar dada (LD) 30 cm, lingkar perut tidak dilakukan pemeriksaan,

dan lingkar lengan (LiLA) 11 cm. Dokter sudah menjelaskan kondisi anak kepada orangtua dan diputuskan *do not resuscitate* (DNR). Anak keempat pasien juga menderita bibir sumbing dan sudah meninggal saat berusia 3 hari.

Sejak sebelum hamil, pasien makan besar sebanyak 3 kali sehari dengan selingan sebanyak 1 kali berupa gorengan. Makan besar biasanya berupa nasi ½ gelas dengan lauk tahu goreng 1 biji besar atau tempe goreng 2 potong sedang. Dari analisis asupan didapatkan pasien hanya mengonsumsi sayuran hijau berupa kangkung sebanyak ½ mangkuk setiap hari. Pasien jarang mengonsumsi buah, biasanya pisang sebanyak 1 buah per minggu. Pasien tidak suka kacang-kacangan. Pasien tidak rutin mengonsumsi suplementasi asam folat yang diberikan oleh dokter kandungan.

Material dan Metode

Pencarian literatur dilakukan dengan *advanced searching* pada Pubmed, Cochrane Library, Scopus, dan ProQuest pada tanggal 16 Desember 2021. Digunakan *MesH Term* dan *Title/Abstract* dalam pencarian. Kata kunci yang digunakan adalah "Maternal", "Preconceptional", "Periconceptional", "Folic Acid", "Folic Acid Intake", "Folic Acid Supplementation", "Oral Cleft", dan "Orofacial Cleft". Kriteria inklusi adalah pasien perempuan dewasa yang sedang hamil sebagai subjek penelitian, desain penelitian *systematic review* meta-analisis, kohort, atau kasus-kontrol, publikasi penelitian dalam kurun waktu 5 tahun terakhir, dan penelitian dipublikasi dalam bahasa inggris. Sedangkan kriteria eksklusi adalah artikel publikasi yang tidak dapat diakses secara *fulltext*.

Hasil Penelitian

Studi ini mendapatkan 2060 literatur dari Pubmed, 1 literatur dari Cochrane, 14 literatur dari Scopus, dan 439 literatur dari ProQuest. Studi ini melakukan seleksi literatur berdasarkan kriteria inklusi dan eksklusi, didapatkan 3 literatur dengan teks lengkap dan sesuai kriteria eligibilitas. Tiga literatur tersebut berupa satu literatur *systematic review* meta-analisis dan dua literatur kasus-kontrol. Ketiga literatur tersebut memiliki tujuan serupa dengan pertanyaan klinis studi ini, yaitu "Apakah suplementasi asam folat prakonsepsi dapat mencegah bibir sumbing pada janin yang dikandung?". Artikel terpilih dilakukan telaah kritis, meliputi aspek validitas penelitian, kepentingan klinis (*importancy*) hasil, dan aplikabilitasnya atau relevansinya terhadap masalah klinis yang ada, serta dilakukan penentuan derajat kekuatan bukti atau *level of evidence*.

Diskusi

Insidensi bibir sumbing banyak ditemukan di negara berkembang. Seperti di Indonesia, anak lahir hidup cukup sering

ditemukan dengan bibir sumbing, yaitu sebesar 50,53%. Penyebabnya multifaktorial, namun dikatakan memiliki hubungan erat dengan asam folat, baik dari bahan makanan sumber maupun suplementasi. Obat yang mengganggu metabolisme folat (misal fenitoin) diketahui memiliki efek teratogenik, seperti bibir sumbing, retardasi pertumbuhan, defek ekstremitas, dan deformitas kraniofasial lain.[12]

Folat berperan sebagai ko-enzim, baik akseptor maupun donor, dari 1 unit karbon dalam reaksi biokimia yang melibatkan metabolisme asam amino. Dalam sintesis purin dan pirimidin yang merupakan komponen DNA dan RNA, folat memiliki peran penting. Hal ini berhubungan dengan regulasi ekspresi gen dan diferensiasi sel. Sintesis DNA dalam jumlah banyak dibutuhkan dalam proses proliferasi jaringan yang cepat. Defisiensi folat akan terlihat pertama kali dalam sistem hematopoetik yang mengakibatkan anemia, permukaan sel epitel, dan gonad. Selain itu, juga dapat dilihat dari peningkatan homosistein sebagai akibat dari kegagalan remetilasi oleh enzim yang terikat folat. Peningkatan level homosistein berhubungan dengan peningkatan risiko kelainan kongenital, terutama *neural tube defects* dan bibir sumbing. Keduanya dikaitkan dengan sel *neural crest* yang berperan dalam penutupan *neural tube* dan pada perkembangan struktur oral. *Neural walls fuse* terjadi pada 21-22 hari setelah konsepsi, penutupan *cranial neural pore* terjadi pada hari ke-24, dan *caudal neural pore* terjadi pada hari ke-26. Daerah mesenkim wajah merupakan derivat dari *neural crest*, sehingga suplementasi asam folat prakonsepsi dapat mengurangi risiko terjadinya bibir sumbing.[12] Namun, sampai saat ini masih dilakukan penelitian untuk mencari dosis suplementasi asam folat yang sesuai, terutama yang diberikan pada periode prakonsepsi dan saat awal kehamilan (trimester pertama), untuk mencegah terjadinya bibir sumbing semua tipe.

Jayarajan R, et al.[6] melakukan penelitian *systematic review* dari 4 studi (1 *randomized control trial*, 2 *prospective case-control trials*, dan 1 *single case-control surveillance*). Seluruh studi ini menilai suplementasi asam folat prakonsepsi dikaitkan dengan penurunan insiden bibir sumbing. Keseluruhan studi melibatkan 9513 partisipan dari Brazil, Prague, New Jersey, dan Hungaria. Penelitian tersebut mengumpulkan data penelitian yang telah dilakukan sejak 1958 sampai dengan 2009 melalui 4 *database* besar, yaitu Medline, Cochrane, Embase, dan Lilacs. Dari empat studi yang digunakan pada penelitian ini, didapatkan dosis asam folat prakonsepsi yang bervariasi untuk kelompok kasus. Penelitian Wehby GL, *et al*.[13] pada tahun 2004-2009, kelompok kasus diberikan suplementasi asam

folat sebesar 4 mg, sedangkan kelompok kontrol diberikan asam folat sebesar 0,4 mg. Suplementasi tersebut diberikan sejak saat prakonsepsi sampai dengan trimester pertama. Dari hasil penelitian, didapatkan bahwa rekurensi bibir sumbing pada kelompok kontrol lebih besar daripada kelompok kasus (2,9% vs 0,8%) dengan pengecualian pada kasus *palatoschisis.* Insidensi *labio* dengan/tanpa *palatoschisis* dan *palatoschisis* juga ditemukan bahwa rekurensinya lebih tinggi pada kelompok kontrol (2,9%) dibandingkan dengan kelompok kasus (1,6%). Hasil ini tidak menunjukkan rasio rekurensi yang berbeda bermakna.

Hal ini sesuai dengan penelitian terdahulu yang dilakukan oleh Tolarova M dan Briggs RM. Tolarova M dan Harris J[14] melakukan penelitian pada tahun 1976-1992 mengenai suplementasi asam folat selama 2 bulan prakonsepsi dilanjutkan 3 bulan kemudian. Kelompok kasus diberikan suplementasi asam folat sebesar 10 mg, sedangkan kelompok kontrol diberikan suplementasi asam folat yang tidak diketahui dosisnya. Dari penelitian tersebut disimpulkan bahwa terjadi penurunan risiko rekurensi *labio* dengan/tanpa *palatoschisis* sebesar 65% pada kelompok kasus. Briggs RM[15] melakukan penelitian pada tahun 1958-1976 mengenai suplementasi asam folat prakonsepsi yang diteruskan sampai dengan usia kehamilan 5 bulan. Kelompok kasus mendapat dosis 5 mg, sedangkan kelompok kontrol tidak diketahui dosisnya. Penelitian tersebut memberikan hasil rasio insidensi *labio* dengan/tanpa *palatoschisis* maupun *palatoschisis* lebih rendah daripada kontrol (3,1% vs 4,8%). Dari ketiga penelitian tersebut tidak didapatkan adanya efek samping.

Penelitian *The Hungarian Case-Control Surveillance of Congenital Abnormalities* mengenai asam folat prakonsepsi yang diberikan sebesar 0,8 mg tidak memberikan efek proteksi. Sedangkan suplementasi asam folat sebanyak 6 mg, yang diberikan pada saat periode kritis (trimester pertama dan kedua), memberikan efek proteksi terhadap *labiopalatoschisis.* Insidensinya sebesar 12,4% untuk kelompok kontrol dan 91% pada kelompok kasus. Pada kasus *palatoschisis*, suplementasi asam folat 4 bulan pertama juga memberikan efek proteksi, dengan insidensi sebesar 39% pada kelompok kontrol dan 32,2% pada kelompok kasus.[16] Hal ini sesuai dengan teori mengenai jalur folat yang memberikan kontribusi berupa elemen penting yang diperlukan untuk proses penting dalam sel, seperti sintesis dan proliferasi DNA.[17] Di dalam sel, folat diubah menjadi dihidrofolat, kemudian direduksi menjadi tetrahidrofolat oleh enzim dihidrofolat reduktase. Tetrahidrofolat adalah prekursor untuk sintesis timidin dan purin,

serta S-adenosil-L-metionin (SAM). Timidin dan purin penting untuk sintesis dan perbaikan DNA/RNA, sehingga inhibisi metabolisme folat dapat mempengaruhi pertumbuhan embrio. SAM mentransfer gugus metil ke substrat seperti nukleotida, protein, dan lipid, sehingga reduksinya berdampak besar pada perubahan epigenetik seperti DNA dan metilasi histon yang terjadi selama perkembangan embrio.[18-22]

Pada penelitian Jayarajan R, et al.[6], kami menemukan kekurangan pada bagian hasil dan diskusi. Dari keempat studi yang digunakan, tidak dilakukan pembahasan lebih lanjut mengenai hasil yang didapat, sehingga data yang ditampilkan terasa kurang lengkap. Selain itu tidak ditampilkan heterogenitas dan *forest plot*, serta *funnel plot* untuk dinilai bias publikasi dan *standard error* penelitian.

Xu W, et al.[10] melakukan penelitian terhadap anak tunggal hidup yang dilahirkan sekitar Oktober 2010 sampai September 2015 di Chengdu, China. Penelitian ini meneliti subjek sebanyak 807 anak dengan bibir sumbing dan 8070 anak sehat. Data diambil dari setiap ibu hamil yang memeriksakan kandungan sebanyak 5 kali selama kehamilan dan 3 kali postpartum (hari ke-7, 28, dan 42). Data mengenai pemeriksaan selama kunjungan, faktor risiko (penyakit ibu, riwayat keluarga, dan kondisi medis lain), serta keluaran kehamilan (abortus spontan, lahir mati, lahir hidup, cacat bawaan) dicatat oleh dokter spesialis obgyn dan perawat. Ibu hamil yang rutin mengonsumsi asam folat 400 µg/hari selama periode perikonsepsi setidaknya 1 bulan disebutkan sebagai “pengguna perikonsepsi”. Ibu hamil yang memulai suplementasi asam folat sebelum hari haid terakhir disebut sebagai “pengguna prakonsepsi”, sedangkan yang memulai setelah hari haid terakhir disebut sebagai “pengguna postkonsepsi”. Ibu hamil yang tidak mengonsumsi asam folat atau mengonsumsi asam folat kurang dari 1 bulan disebut sebagai “bukan pengguna”. Perbedaan karakteristik ibu dan anak pada kelompok kasus dan kontrol dianalisis menggunakan tes *Pearson chi-square*.

Pada subjek bukan pengguna, paling banyak ditemukan pada kelompok *labioschisis* (21%), *labio* dengan/tanpa *palatoschisis* (20,6%), dan *labiopalatoschisis* (20,3%). Pada subjek pengguna perikonsepsi, paling banyak ditemukan pada kelompok kontrol (90,8%) disusul dengan *palatoschisis* (87,5%). Pada subjek pengguna prakonsepsi, paling banyak ditemukan pada kelompok *labioschisis* (24,7%), kelompok kontrol (23,7%), dan kelompok *labio* dengan/tanpa *palatoschisis* (21,3%). Pada subjek pengguna postkonsepsi, paling banyak ditemukan pada kelompok *palatoschisis* (70,2%), kelompok kontrol (67,1%), dan *labiopalatoschisis*

(60,7%). Hasil ini ditemukan pada hubungan suplementasi asam folat prakonsepsi pada kelompok kasus dan kontrol. Sedangkan hubungan suplementasi asam folat perikonsepsi dengan bibir sumbing memberikan hasil sebagai berikut. Insidensi *labio* dengan/tanpa *palatoschisis* paling banyak ditemukan pada kelompok pengguna prakonsepsi (aOR 0,43, 95% CI 0,33-0,56), sedangkan pada kelompok pengguna perikonsepsi dan postkonsepsi memberikan hasil serupa. Insidensi *labioschisis* paling banyak ditemukan pada kelompok prakonsepsi (aOR 0,51, 95% CI 0,34-0,75) dan paling sedikit ditemukan pada kelompok postkonsepsi (aOR 0,39, 95% CI 0,28-0,55). Insidensi *labiopalatoschisis* paling sedikit ditemukan pada kelompok pengguna prakonsepsi (aOR 0,38, 95% CI 0,27-0,54) dan pada kelompok pengguna perikonsepsi dan postkonsepsi insidensinya serupa. Pada ketiga kelompok tersebut hasilnya bermakna secara signifikan, sedangkan pada kelompok *palatoschisis* hasil yang bermakna hanya terlihat pada kelompok pengguna prakonsepsi (aOR 0,52, 95% CI 0,30-0,90).[10]

Penelitian Mendonca VJ[5] menggunakan kuesioner untuk mengumpulkan data suplementasi prenatal, asupan folat dari sumber bahan makanan, dan faktor yang berpotensi sebagai perancu. Analisis regresi logistik dilakukan pada data dari kelompok kasus dan kontrol untuk melihat hubungan antara suplementasi asam folat dan bibir sumbing semua tipe, serta menganalisis secara terpisah untuk *labioschisis* dan/atau *palatoschisis* dan *palatoschisis*, disesuaikan dengan variabel yang bermakna secara signifikan. Suplementasi asam folat tunggal sebanyak 0,4 mg selama setidaknya 3 dari 4 bulan periode perikonsepsi memiliki peran protektif terhadap semua tipe bibir sumbing. Kadar folat makanan yang lebih tinggi ditemukan berkaitan dengan penurunan risiko semua tipe bibir sumbing. Kekurangan dari penelitian ini adalah pengumpulan data hanya 3 bulan, sejak Oktober sampai Desember 2017.

Asam folat banyak terdapat pada sayuran hijau, kacang-kacangan, serta buah. Beberapa contoh sumber bahan makanan beserta kandungan asam folat per 100 g diuraikan sebagai berikut, yaitu edamame (311 mcg), lentil (181 mcg), asparagus (149 mcg), bayam (146 mcg), selada (136 mcg), brokoli (108 mcg), alpukat (81 mcg), mangga (43 mcg), jagung manis (42 mcg), dan jeruk (30 mcg). Selain itu asam folat dapat difortifikasikan ke dalam makanan seperti sereal, spageti, ataupun bagel.[23] Sedangkan untuk suplementasi, terdapat 2 macam sediaan yang beredar di Indonesia, yaitu suplementasi asam folat saja dan suplementasi asam folat kombinasi dengan mikronutrien lain.

Kesimpulan dan Saran

Berdasarkan telaah kritis dari ketiga penelitian tersebut, diperlukan studi longitudinal dengan durasi waktu yang lebih lama, subjek penelitian berskala besar, dengan etnis yang beragam, serta melibatkan faktor-faktor lain yang berpotensi sebagai komponen perancu seperti usia, indeks massa tubuh, paritas, medikasi selama kehamilan (terutama trimester pertama), paparan terhadap pestisida dan rokok, riwayat konsumsi alkohol, riwayat keluarga dengan bibir sumbing, dan asupan makan.

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EFFECTIVENESS OF PROBIOTIC SUPPLEMENT ON *HELICOBACTER PYLORI* INFECTION ERADICATION IN GASTRIC ULCERS

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Abstract

Background: *Helicobacter pylori* colonizes the gastric mucosa in 50% of the human population. *H. pylori* infection causes several upper gastrointestinal tract diseases, such as chronic gastritis, peptic ulcer, duodenal ulcer, and gastric cancer. *H. pylori* is also associated with a high risk of developing gastric adenocarcinoma. The World Health Organization classifies *H. pylori* infection as a class 1 carcinogen. Giving probiotics may improve the immune system and suppress the effects of pathogens. However, mixed results were obtained from the use of various kinds of bacteria and fungi as probiotics.

Objective: To determine the effectiveness of probiotic supplementation against the eradication of *Helicobacter pylori* infection in gastric ulcers.

Methods: Article searches were conducted using advanced searching by combining MesH Terms and abstracts/titles in the Pubmed, Cochrane Library, and Scopus databases. The search found two selected literature to further conduct a critical assessment.

Result: From the results of the literature search, it was found that 2 studies that met the criteria were a clinical trial study from Chang et al. which analyzed the effect of probiotic supplementation and broccoli extract on *H. pylori* eradication and a clinical trial study from Oh et al. comparing the combination of antibiotics and probiotics with antibiotics alone in *H. pylori* eradication. The results of these two studies of *H. pylori* eradication with probiotics got a higher eradication rate, but it was not statistically significant. However, the number of these research subjects was not large enough.

Conclusion: The effectiveness uses of probiotics to eradicate *H. pylori* has not been proven. It will take clinical trials with a sufficient number of subjects and certain probiotic strains to be able to determine the type of strain, dosage, duration of use, and side effects that can be caused.

Keywords: Probiotics, *Helicobacter pylori*, *H. pylori*, gastric ulcer

Introduction

Peptic ulcer disease (PUD), including gastric and duodenal ulcers, is a major health burden in China. The prevalence of PUD in Western countries ranges from 0.1% to 4.7%, with an annual incidence of 0.19% to 0.3%.[1] Peptic ulcer disease is strongly related to chronic *Helicobacter pylori* (*H. pylori*) infection. Data from the developed world has shown that in the first decade of the discovery of *H. pylori*, 95% of duodenal ulcers and 85% of gastric ulcers were associated with *H. pylori* infection and that the lifetime risk of developing PUD was 3–10-times higher in *H. pylori*-positive subjects than in their *H. pylori*-negative counterparts.[2]

H. pylori is a gram-negative microaerophilic bacterium that colonizes the gastric mucosa in 50% of the human population.[3] It is estimated that more than 50% of the world population is infected with *H. pylori*, with a remarkable variation in the prevalence among countries and within different regions of the same country. Interest in *H. pylori* resulted from its association with a variety of gastrointestinal conditions,

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ranging from benign to malignant diseases.[2] It causes several upper gastrointestinal tract diseases, such as chronic gastritis, peptic ulcer, duodenal ulcer, and gastric cancer. *H. pylori* is also associated with a high risk of developing gastric adenocarcinoma. The world health organization classifies *H. pylori* infection as a class 1 carcinogen.[3,4]

The success of antimicrobial therapy depends on adherence to medication, dose, formula, duration, and rate of reinfection.[5] During the eradication of *H. pylori*, the most common problems facing gastroenterologists include (1) antibiotic resistance phenomenon, (2) persistence of bacteria in latent status, (3) degradation of antibiotics in acidic gastric conditions, (4) re-infection, especially in regions with high prevalence, (5) adverse side effects of antibiotics such as diarrhea, nausea, vomit, and abdominal pain, (6) rapid metabolization of antibiotics due to CYP2C19 enzyme, (7) poor compliance of multiple antibiotics.[6]

In recent years, antibiotic resistance (with high divergence) has led to increased therapeutic failure in eradicating *H. pylori* with current regimens. There are several recommended regimens for *H. pylori* eradication. One of them was a combination therapy of proton pump inhibitor, amoxicillin, and clarithromycin or metronidazole. This regimen can be used in cases with low clarithromycin resistance.[5] A study by Savoldi et al.,[7] showed an increase in *H. pylori* resistance in both primary and secondary regimens. According to the World Health Organization (WHO) report, the rate of resistance to clarithromycin and metronidazole ranged from 14–34% and 20–38%, respectively. The therapeutic regimens with less than 80% efficacy are considered as treatment failure. Recently, adjuvant therapy with probiotics has received much attention as a new strategy to increase the success of anti-*H. pylori* therapy.[6]

Probiotics are defined as live microorganisms which, when in adequate amounts, can provide benefits to the host.[8] Probiotics have been used as a preventive and therapeutic agent in several gastrointestinal diseases, such as diarrhea, irritable bowel syndrome, and inflammatory bowel disease. Giving probiotics will improve the immune system and suppress the effects of pathogens. In an in vitro study, we found the inhibitory effect of probiotics on the expression of genes encoding virulence factors. Some probiotics such as *Lactococcus lactis*, *Lactobacillus reuteri*, and *Lactobacillus bulgaricus* produce peptide and nonpeptide antipathogens that suppress the development and adhesion of *H. pylori*.[9,10]

Probiotics have various mechanisms to eradicate or restrict *H. pylori* growth within the stomach of humans, including (1) inhibition of the colonization of *H. pylori* via

conquering gastric epithelial receptors or co-aggregation mechanism, (2) anti-*H. pylori* activity throughout the production of bacteriocins, organic acids, as well as biosurfactants, (3) supportive role in intestinal tissues by promoting mucin synthesis, (4) modulation of immune system response, (5) induction of antigen-specific antibodies, and (6) reduction of stomach inflammation.[6]

Defenses mechanisms against *H. pylori* infection, which are subdivided into two main mechanisms, including physiological barriers and the immune system. Upon entrance of *H. pylori* into the stomach, both innate and specific immunity enter the area of infection (lamina propria). Consumption of probiotics has several advantages in strengthening and stimulating the immune system versus this pathogen. Antibacterial activities of probiotics, direct and indirect, are helpful for human health. Therapeutic effects of these bacteria in the gastric tract include immune modulation via interaction with Toll-Like Receptors (TLRs) and anti-*H. pylori* activity, co-aggregation of invasive bacteria, decrease pH by secretion of short-chain fatty acids, support epithelial barrier integrity, mucin production, as well as promoting immune cells to inhibit gastric inflammatory response, particularly Interleukin-8 production, and induction of immunoglobulin secretions.[6]

Clinical Question

A 40-year-old male patient came to the hospital complaining of nausea, frequent burping, bloating and burning sensation in the epigastric that interrupted activities. The symptoms appear several times and usually get better after eating. But now the complaints persist and feel worsening. He is a field worker who often skips meals and regularly drinks coffee. He often consumes herbal medicine whenever he feels tired after work. The patient's blood pressure was 140/100 mmHg, pulse 80 times per minute, breath 20 times per minute. The body weight was 70 kg, height 154 cm, BMI 29,5 kg/m^2. In addition, the patient was also subjected to a blood examination of Hemoglobin 11 g/dL, leukocytes 15,400/µL and platelets 354,000/µL. There is a history of diabetes mellitus for a couple of years. He was diagnosed with gastric ulcer caused by *Helicobacter pylori* infection and treated with a combination of proton pump inhibitor, amoxicillin and clarithromycin. The patient asked whether probiotic consumption can be beneficial to improve his condition or not.

Methods

The article searches were conducted using basic and advanced searching methods by combining Pubmed, Cochrane Library, and

Scopus databases. The search was carried out on December 19, 2021. Keywords were entered in the MeSH Terms and title/abstract categories. The articles included in the search were systematic reviews, meta-analyses, and randomized controlled trials within the last 5 years. Studies on animals, studies that were not fully available, and studies other than in English were not included in the search. Titles and abstracts were reviewed, articles that did not meet the eligibility criteria and PICO were excluded, and duplication screening was carried out. A critical study was carried out using tools from the Center for Evidence-Based Medicine, Oxford Center for Evidence-Based Medicine.

Research Results

The search results yielded 72 articles from Pubmed database, 7 articles from Cochrane Library, and 46 articles from Scopus. After the search results were obtained, a screening of duplicated articles was conducted using the Mendeley program. A subsequent screening test was carried out by comparing the title and abstract to the suitability of the PICO. Eligibility criteria such as full text and limitations on the publication of articles within the last 5 years were applied before conducting a critical review of the articles obtained. After screening duplication and selecting articles according to eligibility criteria, 2 literature from Chang et al.,[11] and Oh et al.,[12] were found to be relevant and could be analyzed to answer clinical questions **(Figure 1)**.

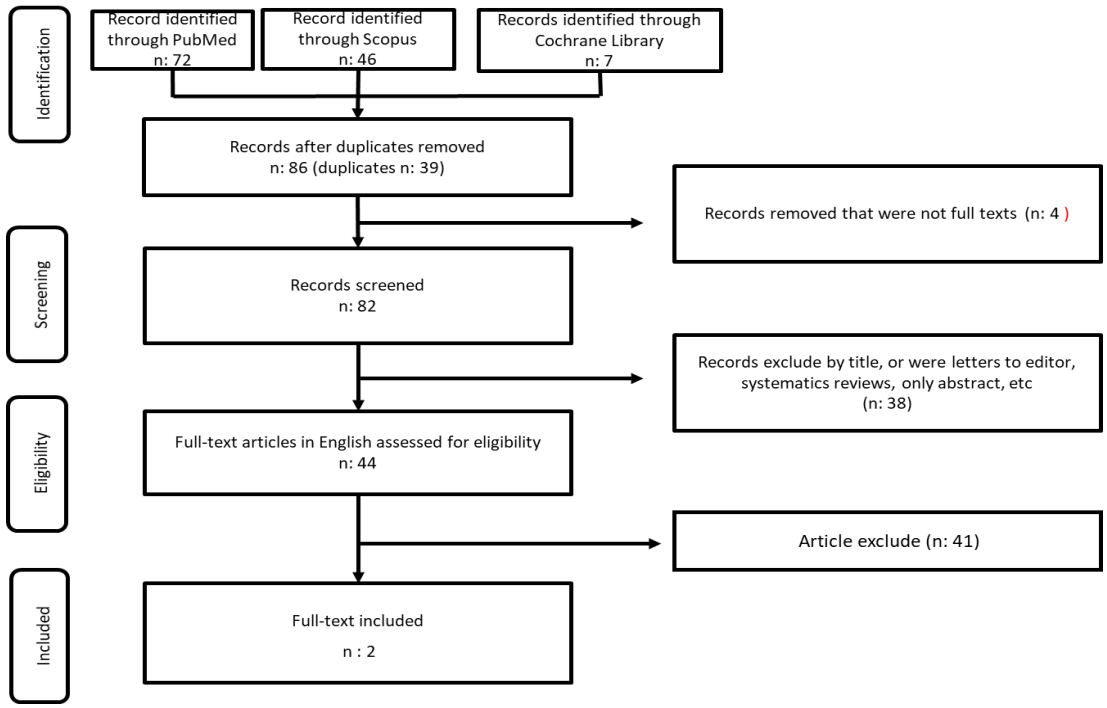

Figure 1. PRISMA's Flow Chart

Discussion

The gastric mucosa is well protected against bacterial infection. Mucous membranes are one of the first lines of defense to protect humans against environmental pathogens; excessive secretion of mucins and large glycoproteins effectively cover the surface of gastrointestinal tracts and prevent the colonization of infectious agents, especially *H. pylori*.[6]

After ingestion, *H. pylori* must survive the bactericidal activity of the gastric lumen and enter the mucus layer. *H. pylori* is highly adapted to special conditions in the stomach. It possesses flagella, which enables colonization of the gastric epithelium. Moreover, the bacteria produce the enzyme urease, which hydrolyzes urea into carbon dioxide and ammonia and elevates the pH in the surroundings of the bacteria. The enzyme activity is highest at low pH. The *H. pylori* bacteria usually causes chronic infection due to a complex balance between host factors and virulence bacterial factors. Among several bacterial factors, one of the main factors, which drive Th17 inflammation, represents the secreted peptidyl-prolyl cis, trans isomerase.[13] Recent studies have shown that this bacterium inhibits the expression of several mucins genes, such as MUC1 and MUC5. In vitro studies show that some probiotics, for example, *L. rhamnosus* and *L. plantarum*, induce the expression of MUC2 and MUC3 genes (the most important mucins in the gastrointestinal tract), leading to inhibition of *H. pylori* colonization. Interestingly, the study showed that consumption of *L. johnsonii* thickens the mucosal layer, which in turn prevents bacterial colonization.[6]

Probiotics can inhibit *H. pylori* by several immunological and non-immunological mechanisms. Probiotics are capable of modifying the immunologic response of the host. Neutrophils, lymphocytes, plasma cells, and macrophages are involved in the inflammatory response to *H. pylori*. The consequences are increased levels of pro-inflammatory cytokines, such as IL-1β, IL-2, IL-6, IL-8 and tumor necrosis factor α in the gastric mucosa. Probiotics like *L. salivarius* WB 1004 have *in vitro* reduced IL-8 secretion by gastric epithelial cells. It looks like that, at least in vitro, *L. acidophilus* can improve *H. pylori*-induced gastric inflammation by inactivating the Smad7 and NFκB pathways.[13]

Furthermore, the study demonstrated that *L. bulgaricus* inhibited the activation of the TLR4 signaling pathway and IL-8 production induced by *H. pylori* lipopolysaccharide in SGC-7901 cells. Gastric inflammation can be controlled to

some level by different strains of *Lactobacilli* through inactivating JAK2 through JAK–STAT pathways and through the higher expression of the SOCS protein family. *H. pylori* also induce humoral response of gastric mucosa, which may contribute to gastric mucosal damage. *Lactobacilli* were able to increase the local IgA concentration and decrease specific anti-*H. pylori* IgG antibodies in animal models. [13]

Among non-immunological mechanisms, probiotics are capable of influencing bacterial growth by secreting antibacterial substances such as lactic acid, short-chain fatty acids, hydrogen peroxide and bacteriocins. The metabolites can diminish the number of spiral bacteria. Lactic acid has probably an additional effect on *H. pylori* by lowering the pH and inhibiting the urease. *L. acidophilus* CRL 639 secret an autolysin, a proteinaceous compound released after cell lysis, which has some antibacterial activity. Substances similar to isocoumarin antibiotics are produced by *B. subtilis,* and those can also kill *H. pylori* bacteria. *L. reuteri* ATCC 55730 produces a unique substance called reuterina, which suppresses the growth of spiral bacteria. [13]

Chang et al. [11] conducted a study on 183 patients with *H. pylori* infection who received the conventional eradication regimen compared with additional probiotics and sulforaphane supplementation of broccoli extract. The results measured the rate of eradication and side effects of treatment. A population study was randomly divided into 3 groups, namely the group that received conventional therapy only, conventional therapy with additional probiotics, and with sulforaphane addition. The results showed a similar eradication rate in each group, namely group A = 89.2%, B = 86.8% and C = 96.3%). The frequency of occurrence of side effects was also not significantly different (A vs B p = 0.574; A vs C; p = 1.00). There were no statistically significant results in this study.[11]

There are several limitations; first, the small number of subjects in each group, conducted in one study center, and limitations in taking subjects during the study period. In this study, supplementation of probiotics and sulforaphane did not significantly increase the rate of eradication or side effects. Further studies with a large number of subjects and the selection of other probiotic strains are needed to study the effect of probiotics on the eradication of *H. pylori*.[11]

In Oh et al. study,[12] 23 subjects with *H. pylori* infection were randomly divided into two groups, the antibiotic group and the probiotic group. The intervention was carried out for two weeks, and then a stool examination was carried out to obtain the *H. pylori* eradication rate from each group. It was found that the eradication rate in the probiotic group was higher than the antibiotic group,

namely 100% and 90%, respectively. However, this result is not statistically significant because the number of research subjects is small.[12]

This study also did not get a sufficient number of subjects to get meaningful results. In addition, the lifestyle of the subjects, such as alcohol consumption and smoking, changes in gut microbiota before and after the intervention were also different. Nutrient intake factors also play an important role in changes in the gut microbiota. In previous studies, it was reported that the positive effect of probiotics in the eradication of *H. pylori* was quite high using several strains such as *Lactobacillus acidophilus*, *Lactobacillus casei DN-114001*, *Lactobacillus gasseri*, and *Bifidobacterium infantis 2036*.[12]

Conclusions

Based on the result of the critical review, the effectiveness of using probiotics for eradication of *H. Pylori* has not been proven. So, probiotics cannot be recommended as *H. Pylori* eradication regimen. Further studies are needed to obtain better results. The research duration should be longer with a sufficient number of subjects using certain probiotic strains to determine the strains type, dosage, duration of use, and side effects that can be caused.

Competing Interest

The authors have no conflict of interest in this study.

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PROFIL ANTROPOMETRIK, VITAMIN D, B12, FOLAT, DAN FERITIN PASIEN OBES PRABEDAH BARIATRIK DI POLIKLINIK GIZI RUMAH SAKIT SUMBER WARAS

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Abstract

Obese patients, especially patients with severe obesity and requiring bariatric surgery, have a high prevalence of nutrient deficiencies. This study aims to determine some of the basic characteristics of patients undergoing bariatric surgery so that they can be used as supporting data for post-bariatric surgery nutrition medical therapy, particularly in the provision of food sources and micronutrient supplementation which can be deficient due to anatomic and physiological alterations after the surgery. The study was conducted on 55 preoperative bariatric patients by assessing age, gender, and degree of obesity based on body mass index (BMI), serum vitamin D and B12 levels, erythrocyte folic acid, and serum ferritin of subjects. The study is descriptive with a cross-sectional design. Subjects were taken by consecutive sampling. The results showed that the mean age of preoperative bariatric patients was 36 ± 7.1 years; most (85.5%) were women. Most subjects (34.5%) had BMI of 35¬–39.9 kg/m2. Vitamin D deficiency was present in most (75.6%) of the study subjects, but most had serum vitamin B12 levels, erythrocyte folic acid levels, and serum ferritin levels within normal limits. This study shows that the basic profile of patients undergoing bariatric surgery is primarily late adults, classified as severe obese and having vitamin D deficiency.

Keywords: Obesity, Prebariatric, Serum Vitamin D, Serum Vitamin B12, Erythrocyte Folic Acid, and Serum Ferritin

Abstrak

Pasien obesitas, terutama pasien dengan derajat obesitas berat dan membutuhkan tindakan bariatrik memiliki prevalensi defisiensi nutrien yang tinggi. Penelitian ini bertujuan mengetahui beberapa karakteristik dasar pasien yang akan menjalani bedah bariatrik, sehingga dapat menjadi data pendukung terapi medik gizi pascabedah bariatrik, terutama dalam pemberian makanan sumber dan suplementasi mikronutrien yang dapat mengalami defisiensi akibat perubahan anatomi dan fisiologis pascabedah. Penelitian dilakukan pada 55 orang pasien prabedah bariatrik sebagai subyek penelitian. Parameter yang dinilai adalah usia, jenis kelamin, derajat obesitas berdasarkan indeks massa tubuh (IMT), kadar vitamin D dan B12 serum, asam folat eritrosit, dan feritin serum subjek. Penelitian bersifat dekriptif dengan rancangan cross sectional. Pengambilan subjek penelitian dilakukan dengan cara consecutive sampling. Hasil penelitian menunjukkan rerata usia pasien prabedah bariatrik 36 ± 7,1 tahun. Sebagian besar (85,5%) pasien perempuan. Indeks massa tubuh subjek yang terbanyak (34,5%) adalah 35,0–39,9 kg/m2. Defisiensi vitamin D terdapat pada sebagian besar (75,6%) subjek penelitian. Sebagian besar mempunyai kadar vitamin B12 serum, kadar asam folat eritrosit, dan kadar feritin serum dalam batas normal. Penelitian ini menunjukkan profil dasar pasien yang akan menjalani bedah bariatrik sebagian besar berusia dewasa akhir, tergolong obesitas derajat berat, dan memiliki defisiensi vitamin D.

Kata kunci: Obesitas, Prabariatrik, Vitamin D Serum, Vitamin B12 Serum, Asam Folat Eritrosit, dan Feritin Serum.

Pendahuluan

Data World Health Organization (WHO) menunjukkan kejadian obesitas di seluruh dunia saat ini meningkat hampir tiga kali lipat dibandingkan dengan tahun 1975. Pada tahun 2016, lebih dari 1,9 miliar orang usia 18 tahun ke atas mengalami kelebihan berat badan, 650 juta orang di antaranya mengalami obesitas.[1] Peningkatan prevalensi obesitas ini sejalan dengan data di

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Indonesia.[2] Bila dibandingkan dengan data Riset Kesehatan Dasar (Riskesdas) Indonesia tahun 2013, data Riskesdas tahun 2018 menunjukkan peningkatan prevalensi obesitas pada populasi dewasa sebesar 7% menjadi 21,8%. [2, 3]

Untuk mengatasi akar penyebab obesitas, pasien obes membutuhkan tata laksana yang bersifat individual. Sebagian pasien cukup melakukan perubahan perilaku seperti pengaturan asupan makanan dan aktivitas fisik, serta intervensi psikologis, namun pada sebagian pasien dengan kondisi tertentu dibutuhkan terapi tambahan seperti pemberian obat dan pembedahan. Terapi obat diberikan sebagai tambahan tata laksana obesitas untuk individu dengan IMT ≥30 kg/m^2 atau individu dengan IMT ≥27 kg/m^2 yang memiliki komplikasi terkait dengan massa lemak tubuh yang berlebihan. Bedah bariatrik secara global dipertimbangkan untuk dilakukan pada individu dengan IMT ≥40 kg/m^2 atau IMT ≥35 kg/m^2 yang memiliki sedikitnya satu komorbid terkait obesitas.[4]

Pada pasien obes didapatkan perubahan kadar beberapa nutrien[5] antara lain kadar vitamin D[6,7], vitamin B_{12}[8], asam folat[9], dan zat besi.[10] Studi meta analisis Vimaleswaran dkk.[11] menunjukkan kenaikan IMT 1 kg/m^2 menyebabkan penurunan kadar 25(OH)D sebesar 1,15%. Arshad dkk.[10]dalam studinya pada 1.252 pasien obesitas menemukan prevalensi anemia defisiensi zat besi dan vitamin B_{12} berturut-turut sebesar 9,8% dan 20,9%. Studi lain oleh Mlodzik-Cyzewska dkk.[12] menunjukkan dibandingkan dengan kontrol, subjek penelitian dengan berat badan lebih dan obes memiliki kadar asam folat 8,5% lebih rendah. Defisiensi nutrien ini semakin tinggi prevalensinya pada pasien dengan derajat obesitas yang berat dan membutuhkan tindakan bariatrik. Studi observasi prospektif oleh Lee dkk.[13] pada pasien prabariatrik di Singapura menemukan defisiensi asam folat, vitamin B_{12}, feritin, dan vitamin D, berturut-turut pada 31%, 9,5%, 29,3%, dan 83,1% subjek penelitian.

Bedah bariatrik dapat menurunkan rata-rata sebesar 60–75% kelebihan berat badan dengan penurunan berat badan yang maksimal terjadi antara 18–24 bulan pascabedah.[14] Penurunan berat badan pascabariatrik dapat dicapai dan dipertahankan melalui berbagai mekanisme antara lain induksi rasa kenyang, malabsorpsi, perubahan mikrobiota usus, dan perubahan metabolisme empedu. Mekanisme ini juga dapat berpengaruh terhadap terjadinya defisiensi mikronutrien pascabariatrik.[15] Penelitian terdahulu menunjukkan kadar hemoglobin, vitamin B_{12}, dan feritin prabedah yang rendah berkaitan dengan penurunan mikronutrien pascabedah. Selain itu, ditemukan bahwa

keadaan defisiensi vitamin D sebelum tindakan bariatrik dapat memprediksi terjadinya defisiensi satu tahun pascabedah.[16]

Saat ini, data mengenai profil pasien obes di Indonesia, terutama pasien dengan obesitas derajat berat, masih terbatas. Penelitian ini dilakukan untuk mendapatkan profil antropometrik, kadar vitamin D, B_{12} serum, asam folat eritrosit, dan feritin serum pasien obes prabedah bariatrik di RS Sumber Waras, Jakarta Barat. Tersedianya data profil prabariatrik diharapkan dapat menjadi dasar tata laksana pasien yang baik, termasuk terapi medik gizi, untuk mencegah salah satu efek samping terbanyak yaitu defisiensi mikronutrien pascabedah bariatrik.

Metode Penelitian

Desain dan lokasi penelitian

Penelitian ini menggunakan rancangan potong lintang deskriptif dengan metode pengambilan sampel non probabilitas, *consecutive sampling*. Pengambilan data penelitian dilakukan pada bulan September hingga Desember 2021 dan sudah mendapat persetujuan dari Komite Etik dan Penelitian Kesehatan RS Sumber Waras, Jakarta Barat (nomor 031/RSSW/KoM.EP/EC/VIII/2021)

Subjek dan prosedur pemilihan subjek

Subjek penelitian adalah pasien Poliklinik Gizi RS Sumber Waras, Jakarta Barat pada tahun 2018–2021. Kriteria inklusi penelitian adalah laki-laki dan perempuan berusia 18–59 tahun, didiagnosis obesitas (IMT ≥25 kg/m^2) oleh Tim Dokter Spesialis Gizi Klinik (Sp.GK), dan berencana menjalani bedah bariatrik. Sementara kriteria eksklusi penelitian adalah data rekam medis pasien yang tidak lengkap. Terdapat sejumlah 67 subjek pada awal penelitian, namun 12 subjek dieksklusi karena tidak memenuhi kriteria penelitian sehingga subjek yang dianalisis berjumlah 55 subjek penelitian.

Data penelitian

Penelitian ini menggunakan data sekunder dari rekam medis pasien yang meliputi data karakteristik dasar (usia, jenis kelamin), data antropometri, dan data hasil pemeriksaan laboratorium (kadar vitamin D dan B_{12} serum, asam folat eritrosit, dan feritin serum). Data antropometri berupa berat badan dan tinggi badan digunakan untuk menghitung IMT. Nilai IMT dikategorikan menjadi 4 kelompok yaitu IMT 30–34,9 kg/m^2, IMT 35–39,9 kg/m^2, IMT 40–44,9 kg/m^2, dan IMT >45 kg/m^2. Kadar vitamin D serum dikategorikan menjadi 3 kelompok, yaitu defisien (<20 ng/mL), insufisien (20–30 ng/mL), dan normal (>30 ng/mL).[17] Kadar vitamin B_{12} serum dikategorikan menjadi defisien (<201 pg/mL), normal (201–1.606 pg/mL), dan hiper (>1.606 pg/mL). Kadar asam folat eritrosit dikategorikan menjadi

defisien (<655 ng/mL), normal (655–3.249 ng/mL), dan hiper (>3.249 ng/mL). Kadar feritin serum dikategorikan menjadi defisien (<10 ng/mL), normal (10–1.000 ng/mL), dan hiper (>1000 ng/mL).

Analisis statistik

Data karakteristik dasar, antropometri, dan data hasil pemeriksaan laboratorium dianalisis secara deskriptif. Uji Kolmogorov-Smirnov dan Shapiro-Wilk digunakan untuk menentukan distribusi variabel. Data kategori dilaporkan dalam bentuk n (%), sementara data kontinyu dilaporkan dalam bentuk rerata ± simpang baku (SB) untuk variabel dengan distribusi normal dan dalam bentuk median (minimum-maksimum) untuk variabel yang distribusinya tidak normal.

Hasil penelitian

Sebanyak 55 subjek penelitian dengan obesitas prabedah bariatrik yang akan menjalani pembedahan, terdapat 47 (85,5%) subjek perempuan dan 8 (14,5%) subjek laki-laki, dengan rerata usia sebesar 36,0 ± 7,1 tahun. IMT terbanyak terdapat pada rentangan IMT 35-39,9 kg/m^2 yaitu 19 subjek (34,5%) dan nilai median IMT seluruh subjek penelitian adalah 37,9 (31,2–72,0) kg/m2 (Tabel 1).

Tabel 1. Karakteristik dasar subjek penelitian (total subjek = 55)

Variabel	Rerata ± SB atau median (min-maks)	n (%)
Usia	36,0 ± 7,1	
IMT	37,9 (31,2-72,0)	
IMT 30-34,9 kg/m^2		13 (23,6)
IMT 35-39,9 kg/m^2		19 (34,5)
IMT 40-44,9 kg/m^2		11 (20,0)
IMT >45 kg/m^2		12 (21,8)
Jenis kelamin		
Perempuan		47 (85,5)
Laki-laki		8 (14,5)

Jumlah subjek penelitian pada tiap hasil pemeriksaan kadar mikronutrien tidak sama. Data kadar vitamin D serum diperoleh dari 41 subjek penelitian dengan nilai median 13,7 (6,6–35,6) ng/mL, dimana 1 (2,4%) subjek masuk kategori normal, 9 (21,9%) subjek insufisien, dan terbanyak yaitu 31 (75,6%) subjek termasuk kategori defisien. Data kadar vitamin B_{12} serum didapat dari 39 subjek dengan median sebesar 528,0 (191,0–2.000,0) pg/mL. Data kadar asam folat eritrosit didapat dari 31 subjek penelitian dengan median sebesar 998,9 (574,6–2.203,5) ng/mL. Dari 35 subjek penelitian diperoleh data kadar feritin serum dengan nilai median 73,9 (2,7–636,0) ng/mL.Sebagian besar subjek penelitian memiliki kadar vitamin B_{12}, asam folat, dan feritin yang normal, yaitu berturut-turut 36

subjek (92,3%), 28 subjek (90,3%), dan 31 subjek (88,6%) (Tabel 2).

Tabel 2. Kadar vitamin D dan B_{12} serum, asam folat eritrosit, dan feritin serum

Variabel	Jumlah subjek	Median (min-maks)	n (%)
Vitamin D (ng/ml)	41	13,7 (6,6-35,6)	
Defisien (< 20 ng/mL)			31 (75,6)
Insufisien (20-30 ng/mL)			9 (21,9)
Normal (> 30 ng/mL)			1 (2,4)
Vitamin B_{12} (pg/ml)	39	528,0 (191,0-2.000,0)	
Defisien (< 201 pg/mL)			1 (2,6)
Normal (201-1.606 pg/mL)			36 (92,3)
Hiper (>1.606 pg/mL)			2 (5,1)
Asam folat (ng/ml)	31	998,9 (574,6-2.203,5)	
Defisien (< 655 ng/mL)			3 (9,7)
Normal (655-3.249 ng/mL)			28 (90,3)
Hiper (>3.249 ng/mL)			0 (0)
Feritin (ng/ml)	35	73,9 (2,7-636,0)	
Defisien (< 10 ng/mL)			4 (11,4)
Normal (10-1.000 ng/mL)			31 (88,6)
Hiper (>1.000 ng/mL)			0 (0)

Diskusi

Penelitian ini menggambarkan bahwa subjek penelitian yang akan menjalani pembedahan bariatrik, mempunyai rerata usia 36 tahun. Data dari The International Federation for the Surgery of Obesity (IFSO) tahun 2018 menunjukkan usia rata-rata saat operasi adalah 42 tahun (kisaran antar kuartil: 33–51 tahun) dengan kecenderungan pasien di negara-negara Asia menjalani operasi pada usia lebih muda dibandingkan dengan pasien di negara Barat.[18] Sebagian besar subjek penelitian adalah perempuan, yaitu sebanyak 85,5%. Hal ini sesuai dengan penelitian Rachmi dkk.[19] di Indonesia yang mendapatkan pada populasi remaja dan dewasa, prevalensi berat badan lebih dan obesitas lebih banyak pada perempuan. Data ini juga sejalan dengan data demografik dasar dari IFSO tahun 2018 yang menunjukkan prevalensi pasien bariatrik perempuan lebih banyak daripada laki-laki, yaitu sebesar 73,7%. [18] Prevalensi yang lebih tinggi pada perempuan dibandingkan dengan laki-laki tersebut kemungkinan salah satunya berkaitan dengan masalah psikologis citra tubuh yang lebih banyak dialami perempuan. Kondisi ini menyebabkan lebih banyak perempuan yang menjalani prosedur penurunan berat badan daripada laki-laki.[20]

Seluruh subjek penelitian ini memiliki IMT ≥30 kg/m^2, sehingga tergolong kategori obes II berdasarkan kriteria populasi Asia Pasifik. Subjek terbanyak mempunyai IMT 35–39,9 kg/m^2, yaitu 34,5%, diikuti sebesar 23,6% dengan IMT 30–34,9 kg/m^2 (Tabel 1). Median IMT penelitian ini lebih rendah dibandingkan dengan penelitian Toh

dkk.[21] pada populasi Asia multi etnik di Singapura, dimana rerata IMT prabedah adalah 43 ± 7,9 kg/m^2, 40,9 ± 9,9 kg/m^2, dan 40,3 ± 9,1 kg/m^2, berturut-turut untuk tindakan *laparoscopic sleeve gastrectomy* (LSG), *Roux-en Y gastric Bypass (*RYGP*)*, dan *mini gastric bypass*.

Secara global, pasien memenuhi syarat menjalani operasi bariatrik bila memiliki IMT antara 35–40 kg/m^2 dan komplikasi terkait obesitas seperti diabetes mellitus (DM), *obstructive sleep apnea*, atau faktor risiko kardiovaskular lainnya, atau pada pasien dengan IMT >40 kg/m^2, walaupun tidak terdapat komorbiditas terkait obesitas.[22] Populasi Asia memiliki keunikan dibandingkan dengan populasi Kaukasia. Pada populasi Asia timbulnya komplikasi terkait obesitas sudah terjadi pada IMT yang lebih rendah. Hal ini berkaitan dengan persentase lemak tubuh yang lebih tinggi dan kecenderungan terjadi adipositas abdomen yang meningkatkan risiko hipertensi, dislipidemia, DM, dan sindrom metabolik. Prevalensi DM tipe 2 di Asia mirip dengan negara-negara Barat meskipun rerata IMT di Asia lebih rendah. WHO membuat kriteria tersendiri untuk berat badan lebih dan obesitas di Asia dan Asia-Pacific Bariatric Surgery Group (ABPSG) juga membuat modifikasi indikasi operasi bariatrik. Di Asia, operasi bariatrik dianjurkan untuk pasien dengan BMI >37 kg/m^2 atau >32 kg/m^2 dengan DM saja atau dua kondisi komorbid signifikan lainnya terkait obesitas.[23] Sebagian subjek dengan IMT >30 kg/m^2 pada penelitian ini diindikasikan menjalani bedah bariatrik, karena memiliki lebih dari satu komorbid serta telah menjalani diet medis terkontrol dan terapi medikamentosa di bawah pengawasan dokter yang berkompeten, namun tidak berhasil.

Saat ini, operasi bariatrik dianggap sebagai terapi penurunan berat badan yang efektif bagi pasien obesitas morbid.[24] Jenis tindakan utama operasi bariatrik yang sering dilakukan antara lain *laparascopic adjustable gastric banding*, LSG, RYGB, *biliopancreatic diversion* (BPD). [22] Tindakan operasi pada tata laksana obesitas menunjukkan penurunan berat badan dan komorbiditas yang lebih besar, serta kelangsungan hidup yang lebih panjang dibandingkan dengan intervensi non bedah.[24] Namun, sering terjadi defisiensi makronutrien dan mikronutrien pada sebagian besar prosedur bariatrik, terlebih pada dasarnya pasien obesitas morbid memiliki kecenderungan mengalami defisiensi nutrien yang lebih prominen dibandingkan dengan pasien non obes.[25] Hal ini menyebabkan pentingnya dilakukan penilaian dan koreksi nutrien yang defisien, baik pra maupun pascabedah bariatrik.[25]

Kadar Vitamin D Serum

Sejumlah 41 subjek pada penelitian ini (n = 55) memiliki data kadar vitamin D serum dan didapatkan median kadar vitamin D serum 13,7 (rentangan 6,6–35,6) ng/mL. Sebanyak 75,6% subjek mengalami defisiensi vitamin D, 21,9% insufisiensi, dan 2,4% mempunyai kadar vitamin D dalam batas normal. Gambaran defisiensi vitamin D pada subjek prabedah bariatrik juga diperlihatkan pada berbagai penelitian. Penelitian Hannah dkk.[26] dengan desain kohort retrospektif selama 20 tahun dilakukan pada 1.256 pasien prabedah bariatrik. Pemeriksaan kadar vitamin D pada 1.071 subjek menunjukkan sekitar 50% subjek mengalami defisiensi dan insufisiensi dengan kadar bervariasi, tergantung pada musim, dengan kadar rerata 31,45 ± 13,22 ng/mL. Penelitian Vivan dkk.[27] menunjukkan gambaran serupa, yaitu 291 subjek prabedah bariatrik mempunyai kadar rerata vitamin D 19,2 ± 7,6 ng/mL dan sebanyak 55,3% mengalami defisiensi dengan kadar 25(OH)D serum ≤19,9 ng/mL, serta 37,1% insufisiensi (kadar vitamin D 20–29,9 ng/mL). Penelitian ini juga memperlihatkankan defisiensi vitamin D makin berat pada subjek dengan IMT yang lebih tinggi. Penelitian kohort oleh Chan dkk.[28] pada 134 subjek yang akan menjalani bedah bariatrik menunjukkan sejumlah 64% subjek mempunyai kadar vitamin D rendah, yaitu berturut-turut 34% dan 30% mengalami defisiensi dan insufisiensi, dengan kadar rerata vitamin D 24,9 ng/mL.

Kadar vitamin D subjek prabedah bariatrik di RS Sumber Waras, Jakarta, lebih rendah dibandingkan dengan ketiga penelitian di atas. Hasil penelitian ini menunjukkan wilayah tropis di mana cukup sinar matahari seperti di Indonesia, tidak menjamin kecukupan kadar vitamin D pada subjek penelitian prabedah bariatrik, dan besar sampel penelitian ini jauh lebih kecil dibandingkan dengan dua laporan hasil penelitian tersebut. Berbagai faktor dapat menyebabkan defisiensi vitamin D antara lain malnutrisi, malabsorpsi (seperti penyakit *celiac*, *cystic fibrosis*, inflamasi usus kronis, atau pascareseksi usus halus), dan kurang pajanan sinar matahari (dipengaruhi oleh etnik, warna kulit, letak geografis, musim, dan usia).[29] Faktor risiko defisiensi vitamin D lainnya adalah obesitas. Berbagai penelitian menunjukkan hubungan antara IMT dan massa lemak yang tinggi dengan defisiensi vitamin D.[30-32] Mekanisme hubungan ini adalah terjadi sekuestrasi vitamin D oleh jaringan lemak pada subjek obes. Selain itu subjek obes umumnya kurang terpajan sinar matahari akibat kurang melakukan aktivitas fisik.[29]

Hasil penelitian ini menggambarkan pentingnya dilakukan pemeriksaan kadar vitamin D serum pasien yang akan menjalani bedah bariatrik, berkaitan dengan risiko

defisiensi yang mungkin terjadi pada pasien obesitas. Pemeriksaan kadar vitamin D serum ini dapat menjadi dasar terapi medik gizi pasien prabedah bariatrik, khususnya pemberian suplementasi mikronutrien dan dosis yang sesuai dengan kondisi klinis, sehingga pasien memiliki kadar vitamin D yang optimal, pada pra dan pascabedah batriatrik.

Kadar Vitamin B_{12} Serum

Sejumlah 39 subjek dari 55 subjek penelitian memiliki data vitamin B_{12} prabedah bariatrik. Penelitian ini menggambarkan nilai median kadar vitamin B_{12} pada subjek penelitian prabariatrik adalah 528,0 (191,0–2000,0) pg/mL. Sebagian besar subjek penelitian, yaitu 92,3% memiliki kadar vitamin B_{12} dalam batas normal, 2,6% mengalami defisiensi, dan sebanyak 5,1% dengan kadar vitamin B_{12} di atas normal. Gambaran ini sejalan dengan penelitian Antoine dkk.[33] yang menilai kadar vitamin B_{12} pada pasien bedah bariatric. Subjek dibagi menjadi dua kelompok tindakan yaitu *laparoscopic gastric bypass* (LGB) dan LSG. Pada kedua kelompok terlihat rerata kadar vitamin B_{12} plasma prabariatrik, berturut-turut 268,0 ± 318,7 dan 257,0 ± 153,3 (pmol/L), yaitu berada dalam batas normal berdasarkan referensi kadar vitamin B_{12} pada penelitian tersebut. Hasil penelitian ini berbeda dengan penelitian *cross-sectional* Baltaci dkk.[8] yang menilai kadar vitamin B_{12} subjek obes dengan resistensi insulin dan sindrom metabolik. Para peneliti mendapatkan subjek obes dan berat badan lebih mempunyai rerata kadar vitamin B_{12} yang tergolong defisiensi dan lebih rendah dibandingkan dengan subjek sehat.

Vitamin B_{12} berperan sebagai koenzim beberapa jalur metabolisme yang penting di dalam tubuh. Absorpsi vitamin B_{12} terjadi di ileum terminal dengan bantuan faktor intrinsik (FI) yang disekresikan oleh sel parietal lambung. Defisiensi vitamin B_{12} dapat disebabkan asupan makanan tidak adekuat, malabsorpsi karena kurang FI, akibat pembedahan, dan cadangan vitamin B_{12} di hati yang kurang.[34]

Pascabariatrik dapat terjadi perubahan metabolisme vitamin B_{12}, sehingga pasien perlu diberikan suplementasi yang tepat. Suplementasi B_{12} setiap minggu terbukti memberikan hasil baik pada sebagian besar subjek untuk mencegah defisiensi pada dua tahun pascabedah.[33] Pemeriksaan kadar vitamin B_{12} prabedah, pemberian makanan sumber B_{12}, suplementasi, dan pemantauan pascabedah merupakan hal penting untuk diperhatikan pada pasien bariatrik.

Kadar Asam Folat Eritrosit

Kadar asam folat yang dinilai adalah kadar asam folat eritrosit. Nilai median kadar asam folat eritrosit pada penelitian ini 998,9 (754,6–2203,5) ng/mL. Sebagian besar (90,3%) subjek penelitian mempunyai kadar asam folat dalam batas normal, sejumlah 9,7% subjek mengalami defisiensi asam folat, dan tidak terdapat pasien yang memiliki kadar asam folat di atas normal. Hasil penelitian ini sesuai dengan penelitian Antoine dkk.[33] yang menilai kadar asam folat pada pasien bedah bariatrik, yaitu subjek yang menjalani bedah bariatrik LGB dan LSG. Rerata kadar asam folat plasma prabariatrik kedua kelompok, berturut-turut 6,6 ± 5,08 ng/mL dan 6,52 ± 3,72 ng/ml dan berada dalam rentang kadar normal, sesuai referensi yang digunakan para peneliti. Penelitian Baltaci dkk.[8] dengan desain *cross sectional* menggambarkan kadar asam folat subjek obes dan berat badan lebih berada dalam rentang normal, yaitu berturut turut 8,8 ± 3,7 dan 8,2 ± 4,3 ng/mL, yang tidak berbeda signifikan dengan subjek sehat.

Kadar Feritin Serum

Data kadar feritin serum 35 subjek penelitian menunjukkan nilai median 73,9 (2,7–636,0) ng/mL. Penelitian ini menggambarkan sebagian besar (88,6%) subjek memiliki kadar feritin normal, dan sejumlah 11,4 % memiliki kadar feritin kurang dari normal. Penelitian Baltaci dkk.[8] menggambarkan kadar feritin pada pasien obes dan berat badan normal berada dalam rentang normal, yaitu berturut-turut adalah 60,1 ± 47,7 dan 38,8 ± 19,9 pg/L. Rerata kadar feritin subjek obes lebih tinggi daripada subjek berat badan lebih, namun tidak berbeda signifikan.[8] Sementara itu, meta analisis Cheng dkk.[35] menunjukkan populasi obesitas memiliki kadar feritin yang lebih tinggi dibandingkan dengan subjek berat badan normal. Perubahan metabolisme zat–besi pada obesitas memiliki ciri-ciri serupa dengan anemia pada inflamasi kronis, yaitu ditandai dengan hipoferemia dan kadar ferritin yang normal hingga tinggi. Hasil ini sejalan dengan studi epidemiologi oleh Zafon dkk.[36] yang menunjukkan peningkatan risiko defisiensi zat besi dan ditemukan kadar feritin yang tinggi pada pasien obes.

Meta analisis Suarez-Ortegon dkk.[37] menggambarkan pengaruh IMT terhadap hubungan antara feritin dengan sindrom metabolik yang melibatkan perubahan pada hati. Hal ini kemungkinan berkaitan dengan peningkatan hepsidin akibat inflamasi kronis yang terjadi pada obesitas.[35] Hepsidin adalah hormon yang secara primer diproduksi di hati dan berfungsi sebagai regulator utama homeostasis zat besi dalam tubuh. Hepsidin menginduksi internalisasi dan degradasi ferroportin-1 dalam enterosit, hepatosit, dan makrofag usus dua belas jari. Kondisi ini menyebabkan penghambatan absorpsi zat

besi dalam usus dan pelepasan cadangan zat besi dari hati dan sistem retikuloendotelial, serta peningkatan risiko terjadinya anemia.[35]

Kesimpulan dan Saran

Hasil penelitian menunjukkan rerata usia pasien prabedah bariatrik 36 ± 7,1 tahun dan sebagian besar (85,5%) perempuan. Penelitian ini menggambarkan IMT subjek yang terbanyak (34,5%) adalah 35,0–39,9 kg/m^2. Defisiensi vitamin D terdapat pada sebagian besar (75,6%) subjek penelitian, namun sebagian besar mempunyai kadar vitamin B_{12} serum, kadar asam folat eritrosit, dan kadar feritin serum dalam batas normal. Penelitian lanjutan perlu dilakukan untuk memperoleh gambaran perubahan berat badan dan komposisi tubuh, serta perubahan kadar mikronutrien pada pasien bariatrik.

Konflik Kepentingan

Para penulis mendeklarasikan bahwa tidak terdapat konflik kepentingan apa pun terkait studi pada naskah ini.

Kontribusi Penulis

Penulis 1 – pembuatan proposal penelitian, pengumpulan data, penulisan manuskrip
Penulis 2 – pengumpulan data, penulisan manuskrip
Penulis 3 – pengumpulan data, penulisan manuskrip
Penulis 4 – pengumpulan data, penulisan manuskrip
Penulis 5 – pengumpulan data, penulisan manuskrip
Penulis 6 – pembuatan proposal penelitian, penulisan manuskrip
Penulis 7 – pengumpulan data, analisis data, penulisan manuskrip

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HUBUNGAN PHASE ANGLE DENGAN TINGKAT KEPARAHAN INFARK MIOKARD

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Abstract

Background : Phase angle (PhA) is an indicator of cellular integrity that may be associated with severity of myocardial infarction (MI) as reflected by troponin levels, which are markers of myocyte injury.
Objective : to analyze association between PhA with the severity of MI.
Method : An observational study, involving 40 MI patients who met the inclusion and exclusion criteria. The severity of MI was measured by troponin I levels, PhA was obtained from bioelectrical impedance analysis, and comorbid data were extracted from medical record. Chi square test were used to analyze association between phase angle and some comorbidities with the severity of MI.
Results : Majority of the subjects were male (82.5%), the mean age was 56.1 years old, and mean BMI was 25.56 kg/m2. Dyslipidemia was the most prevalent comorbid (92.5%) and 62,5% of subjects had 2 or more comorbidities. The results of chi square test of PhA, comorbidity, number of comorbidities, BMI, age, and sex on troponin I levels were not significant (p>0.05).
Conclusion : PhA was not associated with the severity of MI..
Keywords : BIA, cardiovascular comorbidities, myocardial infarction severity, phase angle

Abstrak

Latar belakang : Phase angle (PhA) merupakan indikator integritas seluler yang mungkin berhubungan dengan tingkat keparahan infark miokard (IM) yang tercermin dari petanda cedera miosit yaitu kadar troponin.
Tujuan : Menganalisis hubungan PhA dengan tingkat keparahan IM.
Metode : Penelitian observasional, melibatkan 40 subjek dengan IM yang memenuhi kriteria inklusi dan eksklusi. Tingkat keparahan IM diukur dari kadar troponin I, PhA didapatkan dari bioelectrical impedance analysis, dan data komorbid diambil dari rekam medis pasien. Uji kai kuadrat digunakan untuk melihat hubungan phase angle dan beberapa komorbid dengan tingkat keparahan IM.
Hasil : Mayoritas subyek penelitian berjenis kelamin laki-laki (82,5%), rerata usia 56,1 tahun, dan rerata IMT 25,56 kg/m2. Dislipidemia merupakan jenis komorbid yang paling banyak diderita (92,5%) dan 62,5% subyek penelitian memiliki 2 atau lebih komorbid. Hasil analisis bivariat hubungan PhA, jenis komorbid, jumlah komorbid, usia, IMT, dan jenis kelamin terhadap kadar troponin I adalah tidak signifikan (p>0,05).
Kesimpulan : PhA tidak berhubungan dengan tingkat keparahan IM
Key words: cleft lip, folic acid supplementation, preconception

Pendahuluan

Penyakit kardiovaskular menyebabkan sekitar sepertiga kematian di seluruh dunia dan di antara penyakit kardiovaskular, *ischemic heart disease* (IHD) menempati urutan tertinggi. IHD bermanifestasi secara klinis sebagai infark miokard (IM) dan iskemik kardiomiopati. Data Global Burden of Disease tahun 2017 memperkirakan IHD mempengaruhi sekitar 126 juta orang (1.655 per 100.000), yang merupakan sekitar 1,72% dari populasi dunia. Sembilan juta kematian disebabkan oleh IHD secara global. Laki-laki lebih sering terkena dibandingkan perempuan, insiden biasanya dimulai pada dekade

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keempat dan meningkat seiring bertambahnya usia. Prevalensi IHD di Indonesia berdasarkan Riskesdas 2013 adalah sebesar 1,5%, dan 85,2% IHD terjadi pada usia produktif. [1–3] *Low-grade chronic inflammation* berperan penting dalam patogenesis aterosklerosis dan dapat menyebabkan cedera seluler. Pembuluh darah koroner yang tersumbat menyebabkan ketidaksesuaian suplai oksigen yang menghasilkan nekrosis dan kematian sel. Troponin serum adalah petanda yang sangat sensitif dari cedera miokard, diperlukan untuk menegakkan diagnosis IM, dan kadarnya dapat menunjukkan tingkat keparahan kerusakan miokard.[4,5] Faktor risiko yang telah dikenal berkontribusi terhadap IHD antara lain hipertensi, diabetes, obesitas, dislipidemia, dan merokok. Berdasarkan studi INTERHEART, hampir 90% *cardiovascular diases* (CVD) dapat dicegah dengan perubahan gaya hidup. Semakin tinggi faktor risiko yang ada, semakin buruk prognosis CVD. Tingkat keparahan CVD mungkin berbanding lurus dengan jumlah, durasi, dan derajat faktor risiko yang ada.[6]

Phase angle (PhA) merupakan indikator integritas dan kesehatan seluler, yang didasarkan pada perubahan resistensi dan reaktansi saat arus bolak-balik melewati jaringan yang dievaluasi. PhA diukur dengan *bioelectrical impedance analysis* (BIA) yang merupakan metode aman, mudah, relatif murah, dan non-invasif. PhA yang rendah merupakan prediktor independen dari *all-cause mortality* pada gagal jantung kronis dan PhA yang tinggi berhubungan dengan risiko kejadian CVD pertama yang lebih rendah. Pada dua dekade terakhir, banyak dilakukan penelitian terhadap PhA, namun belum pernah dilakukan penelitan PhA khusus pada pasien IM. Troponin merupakan petanda cedera miosit yang dilepaskan ke dalam sirkulasi ketika terjadi kerusakan pada sel jantung. Membran miosit yang pecah, menyebabkan isi intraseluler, termasuk troponin tumpah ke ruang ekstraseluler. Oleh karena itu, PhA yang merupakan indikator integritas seluler mungkin berhubungan dengan tingkat keparahan IM yang tercermin dari kadar troponin.[5,7–9] Penelitian ini bertujuan menganalisis hubungan PhA dengan tingkat keparahan IM.

Metode

Penelitian observasional dengan ruang lingkup penelitian di bidang Gizi Klinis, dilakukan di RSUP dr.Kariadi pada bulan Juni 2022. Subjek penelitian adalah pasien rawat inap dengan diagnosis IM di ICU di RSUP Dr. Kariadi Semarang dengan kriteria inklusi diagnosis IM, usia ≥ 18 tahun dan data di rekam medis lengkap. Kriteria eksklusi pada penelitian ini diantaranya edema anasarka, ascites derajat berat, dan

hamil. Variabel bebas dalam penelitian ini adalah PhA sedangkan variabel terikat adalah kadar troponin I. Variabel perancu yang dikontrol antara lain DM, hipertensi, dislipidemia, IMT, usia, jenis kelamin.

PhA dihitung dari *resistance* (R) dan *reactance* (Xc) sebagai tangen busur (Xc/R) x 180°/ π yang diukur dengan BIA SECA mBCA 525, dikelompokkan menjadi <5,7° dan ≥5,7°. Tingkat keparahan infark miokard ditunjukkan melalui kadar troponin I yang diambil pada 24 jam pertama, dikelompokkan menjadi ≥10 µg/l dan <10 µg/l. Data penyakit komorbid DM, dislipidemia, hipertensi, IMT, usia, dan jenis kelamin diambil dari data rekam medis pasien. Penentuan besar sampel dihitung berdasarkan *rule of thumb* dan didapatkan besar sampel minimal 30 orang. Subyek penelitian dipilih secara *consecutive sampling*. Data yang terkumpul selanjutnya diubah dalam bentuk angka yang dimasukkan ke dalam program analistik statistika komputer. Analisis data meliputi uji deskriptif dan uji hipotesis dengan uji kai kuadrat. Selanjutnya dilakukan analisis multivariat dengan uji regresi logistik dengan tingkat keparahan IM sebagai variabel terikat, PhA sebagai variabel bebas dan jenis kelamin & IMT sebagai variabel perancu. Penelitian dilakukan setelah memperoleh keterangan layak etik dari Komisi Etik Penelitian RSUP Dr. Kariadi, dengan nomor surat 1175/EC/KEPK-RSDK/2022.

Hasil

Penelitian dilakukan pada 40 pasien dengan infark miokard (Tabel 1). Mayoritas subyek berjenis kelamin laki-laki, yaitu 33 dari 40 subyek. Rerata usia pada subyek penelitian ini adalah 56,1 tahun, dengan usia termuda 33 tahun dan usia tertua adalah 75 tahun, dan rerata IMT adalah 25,56 kg/m^2, di mana 27 subyek (67,5%) dari keseluruhan sampel mengalami *overweight* dan obesitas. Sebanyak 2 dari 40 orang (5%) tidak memiliki satupun dari 3 penyakit komorbid yang diteliti, dan mayoritas subyek yaitu sebanyak 20 orang (50%) memiliki 2 komorbid. Tingkat keparahan IM dalam penelitian ini ditunjukkan melalui kadar troponin I, di mana rentang nilai normal untuk troponin I adalah 0,015-0,038 µg/l. Seluruh subyek dalam penelitian ini memiliki kadar troponin I di atas nilai normal yang menunjukkan adanya infark miokard. Kadar troponin I ≥ 10 µg/l menunjukkan infark miokard sedang hingga berat yang didapati pada 19 subyek penelitian dan < 10 µg/l menunjukkan infark miokard ringan yang didapati pada 21 subyek penelitian.

Data yang dilakukan analisis bivariat dengan uji kai kuadrat meliputi *phase angle*, dislipidemia, diabetes, hipertensi, jumlah komorbid, jenis kelamin, IMT, dan usia

terhadap kadar troponin I (Tabel 2). Pada uji kai kudrat tidak didapatkan nilai yang signifikan antara variabel bebas dengan terikat (semua p>0,05). Selanjutnya, analisis regresi logistik dilakukan pada data dengan nilai p<0,25 yaitu *phase angle*, jenis kelamin, dan IMT terhadap kadar troponin I (Tabel 3). Nilai p pada uji regresi logistik variabel *phase angle*, jenis kelamin, dan IMT adalah >0,05 sehingga disimpulkan pada penelitian ini tidak didapatkan nilai yang signifkan antara variabel-variabel bebas dengan terikat.

Tabel 1. Karakteristik subyek penelitian

Karakteristik Subyek	Rerata ± SB	Jumlah (%)
Phase angle (°)	5,7 ± 1,00	
< 5,7°		17 (42,5)
≥ 5,7°		23 (57,5)
Kadar Troponin I (µg/l)	18,3 ± 18,59	
≥ 10 µg/l		19 (47,5)
< 10 µg/l		21 (52,5)
Usia (tahun)	56,1 ± 9,82	
≥ 60		15 (37,5)
< 60		25 (62,5)
Jenis kelamin		
Laki-laki		33 (82,5)
Perempuan		7 (17,5)
IMT (kg/m^2)	25,5 ± 3,85	
≥ 23 kg/m^2		27 (67,5)
< 23 kg/m^2		13 (32,5)
Jumlah komorbid		
tanpa komorbid		2 (5,0)
1 komorbid		13 (32,5)
2 komorbid		20 (50,0)
3 komorbid		5 (12,5)
Jenis komorbid		
Hipertensi		17 (42,5)
Diabetes melitus		14 (35,0)
Dislipidemia		37 (92,5)

Tabel 2. Hasil analisis kai kuadrat

		Kadar Troponin I				χ^2	df	p
		≥10µg/l		<10µg/l				
		n	%	n	%			
Phase Angle	< 5,7°	10	58,8	7	41,2	1,52	1	0,218
	≥ 5,7°	9	39,1	14	60,9			
Diabetes	ya	8	57,1	6	42,9	0,803	1	0,370
	tidak	11	42,3	15	57,7			
Dislipidemia	ya	18	48,6	19	51,4	0,261	1	0,538
	tidak	1	33,3	2	66,7			
Hipertensi	ya	9	52,9	8	47,1	0,351	1	0,554
	tidak	10	43,5	13	56,5			
Jenis Kelamin	laki-laki	14	42,4	19	57,6	1,948	1	0,164
	perempuan	5	71,4	2	28,6			
Jumlah Komorbid	≥ 2	13	52,0	12	48,0	0,541	1	0,462
	< 2	6	40,0	9	60,0			
IMT (kg/m^2)	≥ 23	15	55,6	12	44,4	2,162	1	0,141
	< 23	4	30,8	9	69,2			
Usia	≥ 60	8	53,3	7	46,7	0,327	1	0,567
	< 60	11	44,0	14	56,0			

Tabel 3. Hasil analisis multivariat regresi logistik

	B	**S.E>**	**Wald**	**df**	**Nilai p**	**OR**	**IK95%**	
							Min	Mak
PhA	-0,871	0,740	1,388	1	0,239	0,418	0,098	1,783
Jenis kelamin	1,227	0,986	1,549	1	0,213	3,412	0,494	23,577
IMT	-1,431	0,816	3,079	1	0,079	0,239	0,048	1,182
Constant	0,446	1,123	0,158	1	0,691	1,562		

Pembahasan

Karakteristik jenis kelamin, IMT, dan usia pada subyek penelitian ini menunjukkan hasil yang tidak jauh berbeda dari penelitian yang sebelumnya pernah dilakukan di RS dr. Kariadi dengan subyek pasien IM yang dirawat pada tahun 2013-2018, yaitu 72,9% subyek berjenis kelamin laki-laki, 55,5% subyek memiliki IMT ≥ 23 kg/m^2, dan 56% subyek berusia < 60 tahun. Karakteristik ini juga sejalan dengan hasil ulasan sistematis dan meta-analisis di Iran yang menyimpulkan bahwa usia rerata terjadinya IM pertama kali pada penduduk Iran adalah 59,3 tahun, di mana onset untuk laki-laki lebih muda dibandingkan dengan perempuan.[10,11]

Karakteristik penyakit komorbid pada penelitian yang sebelumnya dilakukan di RS dr.Kariadi berbeda dari penelitian ini khususnya pada komorbid dislipidemia, pada penelitian tersebut hanya 35,4% subyek yang menderita dislipidemia.[10] Dislipidemia merupakan jenis komorbid yang paling

banyak diderita oleh subyek pada penelitian ini, yakni 37 dari 40 subyek (92,5%). Prevalensi dislipidemia di wilayah Asia Pasifik memang makin meningkat seiring dengan peningkatan CVD dan dapat dipengaruhi oleh etnis, usia, jenis kelamin, wilayah tempat tinggal, dan status sosial ekonomi.[12]

Rerata PhA pada penelitian ini adalah 5,7° dan mayoritas subyek penelitian memiliki nilai PhA ≥5,7°. Sebanyak 53,6% subyek dengan kadar troponin I ≥ 10 µg/l memiliki nilai PhA <5,7. Namun, hasil analisis bivariat PhA terhadap kadar troponin I tidak signifikan, sehingga disimpulkan bahwa PhA tidak berhubungan dengan tingkat keparahan IM. Sampai saat penelitian ini dilakukan, belum ada studi lain yang meneliti mengenai hubungan PhA dengan tingkat keparahan IM. Namun, studi yang telah ada menunjukkan bahwa PhA merupakan petanda yang berguna untuk sarkopenia, malnutrisi, dan kakeksia pada pasien rawat inap dengan penyakit kardiovaskular dan PhA yang tinggi berhubungan dengan risiko kejadian CVD pertama yang lebih rendah. Selain itu, PhA <4,2° merupakan prediktor independen dari *all-cause mortality* pada gagal jantung kronis dan pasien dengan PhA ≥ 5,7° dikatakan memiliki *survival* yang lebih baik. [8,13,14]

Pada penelitian ini tidak didapatkan hubungan antara komorbid, jumlah komorbid, usia, jenis kelamin, serta IMT terhadap tingkat keparahan IM. Hasil ini sejalan dengan studi kohort retrospektif pada 104 pasien STEMI yang menjalani *Coronary Angiogram* atau *Coronary Intervention* di Dubai. Studi tersebut menunjukkan tidak ada perbedaan signifikan antara jumlah faktor risiko CVD dengan tingkat keparahan STEMI yang dilihat dari jumlah arteri koroner yang terdampak, baik *single-vessel* ataupun *multivessel*. Namun, studi tersebut membuktikan bahwa faktor risiko yang insidental atau *under-diagnosed* atau tidak diobati secara adekuat berdampak pada tingkat keparahan CAD.[15] Hasil yang berbeda ditunjukkan oleh studi pada 160 pasien yang dirawat karena serangan *acute coronary syndrome* (ACS) pertama di Polandia yang bertujuan menyelidiki efek sindrom metabolik terhadap tingkat keparahan CAD dan risiko kardiovaskular. Studi tersebut menyimpulkan bahwa tingkat keparahan angiografi CAD berkorelasi positif dengan usia, IMT, dan *homeostatic model assessment for insulin resistance* (HOMA IR).[16]

Perbedaan hasil dengan studi lain mungkin dipengaruhi oleh pemilihan petanda tingkat keparahan IM yang digunakan. Tingkat keparahan IM dapat dilihat melalui gambaran elektrokadiogram (EKG), petanda laboratorium, dan *coronary angiography* (CAG). Pada infark miokard akut, perubahan

EKG bergantung pada waktu sehingga waktu antara onset gejala dan perekaman EKG mempengaruhi kemampuan untuk menangkap elevasi segmen ST pada EKG. Indikator keparahan lainnya, seperti *creatine kinase*, troponin dan perkembangan gelombang Q pada EKG, mencerminkan perjalanan infark dan mungkin dipengaruhi oleh pengobatan, terutama reperfusi. Evaluasi tingkat keparahan infark dari nilai petanda laboratorium dapat dipengaruhi oleh kesalahan pengukuran, variasi waktu pengambilan, dan frekuensi pengukuran. Selain itu, CAG telah lama menjadi standar emas untuk evaluasi *coronary artery disease* (CAD), namun karena penilaian angiografi didasarkan pada visualisasi lumen pembuluh darah maka lesi kompleks (seperti lesi difus, lesi bifurkasi, dan lesi seperti celah) sulit divisualisasikan sehingga tidak ideal untuk dievaluasi dengan CAG.[17,18]

Simpulan dan Saran

Subyek pada penelitian ini mayoritas berjenis kelamin laki-laki (82,5%), memilliki rerata usia 56,1 tahun, dan rerata IMT 25,56 kg/m^2. Dislipidemia merupakan jenis komorbid yang paling banyak diderita (92,5%) dan mayoritas subyek penelitian (50%) memiliki 2 komorbid. *Phase angle* tidak berhubungan dengan tingkat keparahan infark miokard.

Penelitian selanjutnya mungkin dapat menggunakan jumlah sampel yang lebih besar dan menggunakan petanda tingkat keparahan infark miokard yang lain seperti EKG dan *coronary angiography*. Pengumpulan data tambahan seperti riwayat infark miokard atau penyakit CVD lain sebelumnya, riwayat dalam keluarga, kebiasaan merokok, aktivitas fisik, dan riwayat asupan dapat memperkaya penelitian selanjutnya.

Konflik Kepentingan

Para penulis mendeklarasikan bahwa tidak terdapat konflik kepentingan apapun terkait studi pada naskah ini.

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REDUCED BODY MASS INDEX BUT NOT FAT MASS IN ANTHRACYCLINE-BASED CHEMOTHERAPY OF LOCALLY ADVANCED BREAST CANCER PATIENTS

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Abstract

Background: *Breast cancer is a cancer disease with the highest proportion of new cases and the proportion of deaths it causes is quite high at 6.9%. Cancer patients who use anthracycline-based chemotherapy experience loss of body weight, muscle, body cell mass, distribution of extracellular fluid expansion and reduced intracellular air. This study was to determine the change of the Body Mass index (BMI) and body composition of patients with locally advanced breast cancer (stage IIIA, IIIB and IIIC) who had undergone anthracycline-based chemotherapy.*
Methods: *This anthracycline-based observational analytical study of pre and post chemotherapy was conducted with a cross-sectional approach. Subjects were measured height by microtoise; weight, body composition, daily calorie intake (DCI) and basal metabolic rate (BMR) as measured by Bioelectrical Impendance Analysis (BIA).*
Results: *47 locally advanced breast cancer patients underwent anthracycline-based chemotherapy. Based on the Wilcoxon statistical test, 6 variables with a 95% confidence level ($p<0.05$) showed a decrease in the value 5 variables, namely BMI, total body water (TBW), visceral fat, skeletal muscle mass and skeletal bone mass. Meanwhile, body fat showed a p value=0.224. The changes of variable confounding, DCI decrease ($p=0.004$), but BMR increase not significantly ($p=0.795$).*
Conclusion: *There is an effect of chemotherapy on nutritional status of BMI, TBW, visceral fat, skeletal muscle mass and bone mass in patients with locally advanced breast cancer who underwent anthracycline-based chemotherapy, which may the result of the calorie intake decreased, but not on body fat.*
Keywords: *anthracycline-based chemotherapy, bioelectrical impedance analysis, BMI, body composition, daily calorie intake.*

Introduction

Breast cancer is the most common malignancy in women in developed countries and the second leading cause after cervical cancer in developing countries and constituted 29% of all cancers diagnosed each year. According to GLOBOCAN data in 2020, it is known that breast cancer is a cancer disease with the highest percentage of new cases, which is 11.7% and the percentage of deaths from breast cancer is 6.9%, noted that 16.7% of Indonesia's population, or as many as 58,256 people suffered from breast cancer.[1,2,3]

Breast cancer therapy can be classified into surgery, radiotherapy, and hormonal therapy. Chemotherapy is a treatment process using drugs that aims to destroy or slow the growth of cancer cells. Side effects vary

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depending on the drug regimen given. According to the National Cancer Institute, side effects of anthracycline-based chemotherapy include nausea, vomiting, diarrhea, stomatitis, alopecia, susceptibility to infection, thrombocytopenia, neuropathy, myalgia. Cancer patients do not experience overall weight loss but also loss of musce and body cell mass (BCM), and changes in fluid distribution with extracellular expansion and reduced intracellular air. Managing nutritional needs based solely on weight can be misleading, as it does not reflect body composition.[1,4,7]

The Bioelectrical Impedance Analysis (BIA) is an objective, easy-to-use, and technical tool that can be used to measure changes in body composition. This examination is quite easy and inexpensive to apply to patients undergoing outpatient or inpatient treatment. The purpose of this study is to analyse the effect of chemotherapy on body composition of locally advanced breast cancer patients who have undergone anthracycline-based chemotherapy.

Materials and Methods

This research is a cohort study of pre and post chemotherapy to determine changes in BMI and nutritional status. The subjects of the study were local advanced breast cancer patients who would undergo treatment in the form of anthracycline-based chemotherapy at the Polyclinic of Oncology Surgery, Dr. Hasan Sadikin Hospital Bandung between August 2021 to May 2022. The sample size of the study was set at a total of 47 patients, calculated using a sample size determination in health studies issued by WHO.

The inclusion criteria were: women at least 18 years old when they were first diagnosed; suffered from stage IIIA, IIIB, or IIIC breast cancer based on AJCC 2002 breast cancer staging criteria; underwent anthracycline-based chemotherapy (FAC regimen) used doxocorubicin 6 cycle doses of 60mg/LPT, cyclophosphamide doses of 600 mg/LPT, and 5 Fluoro Uracil doses of 600 mg/LPT for the first time at RSUP Dr. Hasan Sadikin Bandung; and willing to participate in the study. The exclusion criteria were subjects with a history or currently had cancer other than breast cancer in the last 5 years and subjects with Diabetes Mellitus, pregnancy and other chronic diseases.

Body composition assessment include body fat (BF), visceral fat, total body weight (TBW), skeletal muscle mass (SMM), skeletal bone mass (SBM), basal metabolic rate (BMR), and daily calorie intake (DCI) was collected by using Tanita BC-730. BMR and DCI assessed as variable confounding. Nutritional status assessed

by body mass index (BMI) according to WHO criteria.

The statistical analysis to determine the correlation of chemotherapy with nutritional status BMI and body composition used the Wilcoxon non-parametric with 95% confidence interval level. P value ≤0.05 is statistically significant or meaningful, and p value >0.05 is insignificant or statistically insignificant.

Research Results

Characteristic of 47 research subjects are presented in Table 1. The range age of the study was 26 until 79 years. The most stage obtained in this study was stage IIIC 57.4%. There was a preliminary examination obtained body weight with a median of 59 kg. This study also calculated the height in subjects with a Median of 155 cm. For the BMI results, the study obtained a median of 24.7 and a BMI range of 14.3 to 39.5. This showed that the mean BMI in the study subjects was overweight.

Table 1. Characteristic of Research Subjects

Variable	Amount (n=47)
Age (years)	
Mean	49.4
Median	48
Range (min-max)	26-79
Stages of breast cancer	
Stage III A	7 (14.9%)
Stage III B	13 (27.7%)
Stage III C	27 (57.4%)
Weight (kg)	
Mean	60.2
Median±Std	59 kg ±13.42
Range	30-96
Height (cm)	
Mean	155.1
Median±Std	155 cm ± 6.38
Range	136-170
BMI (kg/m^2)	
Mean	25.4
Median±Std	24.7 ± 4.91
Range	14.3-39.5

Notes: BMI=body mass index

Table 2. Changes of Body Mass Index, Total Body Weight, Body Fat, Skeletal Muscle Mass, Visceral Fat Level, Skeletal Bone Mass after Anthracycline Chemotherapy

Variable	Chemotherapy		P-value
	Before n=47	After n= 47	
Body Mass Index			
Median±Std	24,70±4,91	23,10±4,63	**< 0.01***
Range (min-max)	14.30-39,50	13,10-36,80	
Total Body Weight			
Median±Std	47,00%±8,00	45,00%±4,98	**< 0.01***
Range (min-max)	34.00%-73,00%	36,00%-54,00%	
Body Fat			
Median±Std	35,00%±7,86	34,00%±7,91	**0.224****
Range (min-max)	13,00%-53,00%	11,00%-49,00%	
Skeletal Muscle Mass			
Median±Std	60.07%±11.09	54.40%±9,72	**< 0.01***
Range (min-max)	30.06%-80,57%	21.12%-74,94%	
Visceral Fat Level			
Median±Std	7,00±2,53	6,00±2,30	**< 0.01***
Range (min-max)	1,00-14,50	2,00-13,00	
Skeletal Bone Mass			
Median±Std	2,00 kg±0,38	2,00 kg±0,35	**0.025***
Range (min-max)	0,90 kg-3,60 kg	0,90 kg-2,90 kg	

P value was tested using Wilcoxon test, *p≤ 0.01 means very significant, **p> 0.05 means insignificant

Changes of body mass index, total body weight, body fat, skeletal muscle mass, visceral fat level, skeletal bone mass after anthracycline chemotherapy presented in Table 2. Based on the results above, there were an effect of chemotherapy on BMI and body composition (TBW, body fat, visceral fat, skeletal muscle mass and skeletal bone mass) in locally advanced breast cancer patients undergoing anthracycline-based chemotherapy, except for body fat.

The changes of DCI and BMR as variable confounding after anthracycline chemotherapy presented in Table 3. There was a change in DCI after the administration of anthracycline chemotherapy, significantly (p=0.004). In contrast, there was increased of BMR but not statistically significant (p=0.795).

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Table 3. Changes of Daily Calorie Intake and Basal Metabolic Rate after Anthracycline Chemotherapy

Variable	Chemotherapy		P value
	Before N=47	After N= 47	
Daily Calorie Intake			
Median±Std	1,510kkal±399,8	1,235kkal±280,5	**< 0.01***
Range (min-max)	649kkal-2569kkal	878kkal-2178kkal	
Basal Metabolic Rate			
Median±Std	4,356±788	4,458±838,1	**0.795****
Range (min-max)	2714-6312	2567-6138	

P value was tested using Wilcoxon test, *p≤ 0.01 means very significant, **p> 0.05 means insignificant

Discussion

This study was conducted to determine the effect of anthracycline chemotherapy on nutritional status BMI and body composition. The results showed that there was an influence of anthracycline chemotherapy on body composition in several parameters. We measured several parameters of body composition such as total body water, skeletal muscle mass, skeletal mass, body fat and visceral fat level. Body composition assessed in our study subjects decreased statistically significantly compared to before getting anthracycline chemotherapy. This is in accordance with research conducted by Cotogni et al. which the nutritional status in cancer patients who received chemotherapy was decreases in total body water and body fat. Cotogni et al. said the main reason was because the toxicity of chemotherapy caused a decrease in appetite in people with chemotherapy.

Shachar et al. shows that cancer patients who were given chemotherapy such as anthracyclines and taxans would result in a decrease in body fat levels and a decrease in skeletal bone mass and skeletal muscle with no significant weight loss. Similar with our study, there was a decrease in the skeletal muscle mass and skeletal bone mass caused by the chemotherapy process. Justa et al. in 2019 stated that after chemotherapy, there was a decrease in lean mass body composition but an increase in fat period. Accordance with our study, body fat did not change significantly, but other body compositions decreased statistically significant. Taufik et al. stated that there were changes in body composition that could be calculated by BIA in chronic severe disease patients. There

was a decrease in body mass such as skeletal bone mass, skeletal muscle mass and also a decrease in total body water. This condition was caused by the burden of chronic severe diseases that resulted in an increase in metabolism that broke down energy stores in the body (skeletal bone mass, skeletal muscle mass), this might also appear in breast cancer patients.

Talima et al. showed changes of BMI in breast cancer patients who had been given chemotherapy in Egypt. In this study, one of the causes of weight loss was the toxicity of chemotherapy itself. Most of the studies suggest that there was an incidence of weight change in breast cancer patients. Most agreed that this was caused by the toxicity of chemotherapy which resulted in a decrease in appetite, a decrease in intake directly and the presence of an imbalance of the metabolism system in the body of a cancer survivor. Custodio et al. stated that chemotherapy would have an effect on impaired consumption of micro and macro nutrients which would result in disturbances in nutritional status.

The research conducted by Van De Berg et al., obtained different results from our study. Van De Berg et al. found that body composition improved during the chemotherapy period such as an increase in total body water, skeletal muscle mass and skeletal bone mass. This was likely due to the ability of chemotherapy drugs to retain fluids which resulted in an increase in body weight. The same thing was conveyed by Vivosky et al. which found that patients who received chemotherapy experienced an increase in body weight, some of the possible causes due to a decrease in physical activity in breast cancer patients with decrease in body metabolism which resulted in an increase in body weight.

In our study, variable confounding such as basal metabolic rate and daily calorie intake was also taken. The changes in body composition not only occurred due to anthracycline chemotherapy but also due to a decrease in daily calorie intake. Custodio et al. also stated that there was a decrease in calorie intake, and nutrition in the form of macro and micronutrients in patients who were carried out chemotherapy. This stated that the possibility of decreased appetite as the effect of toxicity and anthracycline was the caused a decrease in calorie intake, this is in line with our study. Basal metabolic rate did not change in our study which stated that there was no significant metabolic change to make BMR as a confounding variable. However, it turned out that our study showed a significant decrease BMI due to the administration of anthracycline chemotherapy.

In our study, the decrease in BMI was accompanied in detail with a decrease in body composition, except fat mass, whereas, BMI has been used to indicate obesity, or fat accumulation, so, the decrease in BMI is more due to the composition of fat-free mass, and not fat mass. BMI measurements cannot detect in detail changes in body composition.

Conclusion

There was an effect of chemotherapy on nutritional status of BMI and body composition (TBW, visceral fat level, skeletal muscle mass and skeletal bone mass) in patients with locally advanced breast cancer who underwent anthracycline-based chemotherapy, except for body fat.

Competing Interest

The authors declare that there are no competing interests related to the study.

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