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EDITORIAL

How COVID-19 pandemic affected nutrition behaviors

Pittara Pansawira

Indonesian Nutrition Association (INA) / Perhimpunan Nutrisi Indonesia

Coronavirus disease (COVID-19) had started as a global pandemic and public health emergency back in year 2020. Starting in year 2023, which was a little more than three years afterwards, World Health Organization (WHO) removed COVID-19's public health emergency status.[1] During the past three years, the pandemic, quarantine, and lockdown policy had changed many aspects in life, sosio-economic and public health alike. This included nutrition behaviors which significantly affected the global population's nutritional status.

A study to adults and elderly living independently in Amsterdams revealed an increase of nutritional behavior predisposing to overnutrition, such as more snacking and decreased physical activity to those who had not been in quarantine. Whereas those who were in quarantine, behavior changes related to undernutrition, such as eating less, skipping meals, and drinking more alcoholic beverages, were more seen in the study results.[2] An online survey study to lockdown countries e.g Europe, North-Africa, Western Asia, and United States showed a decrease in both frequency and the duration of physical activity, included an increase of time spent in sedentary behavior. The study also revealed a significant increase in consuming unhealthy food, eating out of control, snacking between meals, alcohol binge drinking, and number of main meals per day.[3]

An online study to students in Indonesia showed changes in eating patterns consisted of increased meal portions and snacks. The sedentary behavior was also excalated.[4]

What factors contributed to these changes? As we all aware, confinement influence our daily activities and mental health. Those who usually commute to the office had to work from home thus limiting physical activities. We also saw the increased numbers of anxiety, depression, and boredom which may led to more snackings or skipping meals.

We had learned that the restriction to stay at home had influenced dietary and physical activity. These changes may or may not expected, however, they surely altered global nutritional status. The numbers of overweight and obesity are more prevalent post-pandemic thus may lead to the increase of non-communicable diseases.

We certainly hope that there will be no more pandemic which warrants lockdown in the future, however the future itself is not a certainty. In the present, we will have to tackle many nutritional-related problems in any population. Within the course of time, if a similar pandemic should occur, we might have to compile a public health, nutrition, mental health, and physical activity policy to minimize the problems.

Conflict of interest

The authors declare that there is no conflict of interest related to the study.

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CASE REPORT

Nutritional management of a malnourished cancer patient with high output ileostomy: a case report

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Abstract

High output stoma is a complication that may follow ileostomy formation, with an incidence of 23%. There is no general consensus on the limit of ileostomy production to be defined as high output. However, output of more than 2000 mL/day, can cause fluid and electrolyte imbalance, also malnutrition due to reduced nutrient absorption. Delay in recognition and treatment, especially in cancer patient with high risk of malnutrition, can further deteriorate patient's nutritional status. A 43-year-old malnourished female with ascending colon cancer underwent tumor resection and ileocolostomy surgery. Starting from the third postoperative day, ileostomy effluent drastically increased to 2700 mL/day, causing severe hyponatremia, hypokalemia, and hypomagnesemia. Risk factors of high output stoma identified were routine prokinetic medication use and unresolved malignancy-related retroperitoneal abscess. Moreover, increment of food intake in the first days after surgery, specifically food high in insoluble fiber, was one of the contributing factors. High output stoma was then resolved by abscess drainage, discontinuation of prokinetic agent, and administration of antimotility agent. Hyponatremia and hypomagnesemia improved with correction, whereas hypokalemia needed longer time to resolve. Enteral nutrition was maintained and increased gradually to prevent further malnutrition. Oral hypotonic fluid intake was limited to 1000 mL/day and isotonic solution consumption was advised. High stoma production due to hypersecretory phase after ileostomy was expected, but thorough management would prevent patient's deterioration that was caused by the fluid, electrolyte, and nutritional imbalances.

Keywords: high output stoma, malnutrition, ileostomy, cancer

Introduction

High output stoma as one of surgery complications is still commonly found with incidence of 23%.[1,2] There is no consensus on the definition of high output stoma, ranging from more than 1000 to 2000 mL/day, but clinically ileostomy effluent of more than 2000 mL per day can lead to significant fluid and electrolyte loss. Further it can cause malnutrition, dehydration, electrolyte imbalance, and also renal failure.[3,4] Delay in recognition of high output stoma is one of the common reasons for potentially preventable emergency visits,[5] and for cancer patient with high prevalence of malnutrition, high output stoma could further deteriorate patient's nutritional status. Malnutrition itself is associated with higher rate of postoperative

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complication forming a vicious cycle of malnutrition. Cohort of 918 colorectal patients who underwent resection surgery showed malnutrition based on Global Leadership Initiative on Malnutrition (GLIM) criteria was associated with higher risk of total postoperative complications, either surgical or medical complications [OR 1.497 (1.042-2.152), p=0.029].[6]

There is no guideline on nutritional management of high output stoma readily available. Knowing that patient would enter hypersecretory phase early after surgery, it has yet to be defined on when and on what threshold of effluent volume are best to start therapy. There is also still no consensus on optimal nutritional provision route and type of formula that should be given in such case. This case report elaborates on nutritional management of high output stoma in a malnourished patient.

Case report

A 43-year-old female suffered from ascending colon adenocarcinoma with retroperitoneal infiltration underwent right hemicolectomy for tumor resection. Ileostomy was also performed for fecal diversion, as retroperitoneal abscess was found during surgery. The patient's condition was further complicated by her nutritional status which was severely malnourished. Patient's body mass index was 16.4 kg/m^2. She experienced weight loss of 21% in the last 4 months, with intake of only 35% energy requirement for more than 1 month. There were clinical signs of severe loss of muscle mass and body fat, also decrement of functional capacity. Severe malnutrition according to American Society for Parenteral and Enteral Nutrition (ASPEN) malnutrition criteria was assessed. Ileostomy initial production was 500–700 mL/day for the first two days after surgery. Starting from the third day, ileostomy production drastically increased to more than 2000 mL/day, reaching 2700 mL/day. Simultaneously, severe hyponatremia, hypokalemia, and hypomagnesemia were observed.

Intravenous hydration using normal saline was given to prevent dehydration due to fluid loss. Both intravenous and oral electrolyte correction were given to correct the imbalances, and

loperamide as anti-motility drug was given to reduce the fluid loss from ileostomy effluent. Nutritional therapy was administered by enteral route, with energy target determined using Harris-Benedict formula and stress factor of 1.5, while protein target was 1.5–2 g/kg body weight. Oral hypotonic fluid intake was limited to maximum 1000 mL/day, and isotonic fluid was added to achieve patient's fluid daily need. Identifying and managing the cause of the high output was as important. Metoclopramide given after surgery as prokinetic was discontinued. Unresolved intraabdominal abscess was suspected, therefore abscess drainage was performed. With all the measures taken, ileostomy production gradually decreased, and electrolyte imbalances were corrected (**Figure 1**). Hypokalemia took a longer time to be corrected, while sodium and magnesium level were already in normal range.

Patient was given solid food and oral nutrition supplements (ONS), administered orally. Prior to abscess drainage, patient's average energy intake was 1000 kcal (27 kcal/kg body weight). Then patient's intake increased to 1500 kcal (41 kcal/kg body weight) after the procedure or increased by 40%. Patient lost 2.5 kg in a span of two weeks after surgery, yet upper arm circumference was found to be unchanged. Calculated cumulative fluid balance was 2300 mL, therefore could explain patient's weight loss.

Discussion

It is important to evaluate adaptation of newly formed ileostomy, so that any complications could be managed promptly. Ileostomy usually starts functioning in the first 24 hours, then hypersecretory phase is expected in first days, producing watery stool around 500–2000 mL/day.[7] This initial phase last around 1–2 months.[8] High output stoma is usually observed on postoperative day 2 to 15, with a median of the fourth day. Production volume ranging from 1800 to 5450 mL per day, with a median of 2460 mL.[1] In this case, effluent increment was observed starting on postoperative day 3, reaching 2700 mL/day. Electrolyte imbalance aside, note should be taken on patient's nutritional status. Malnutrition
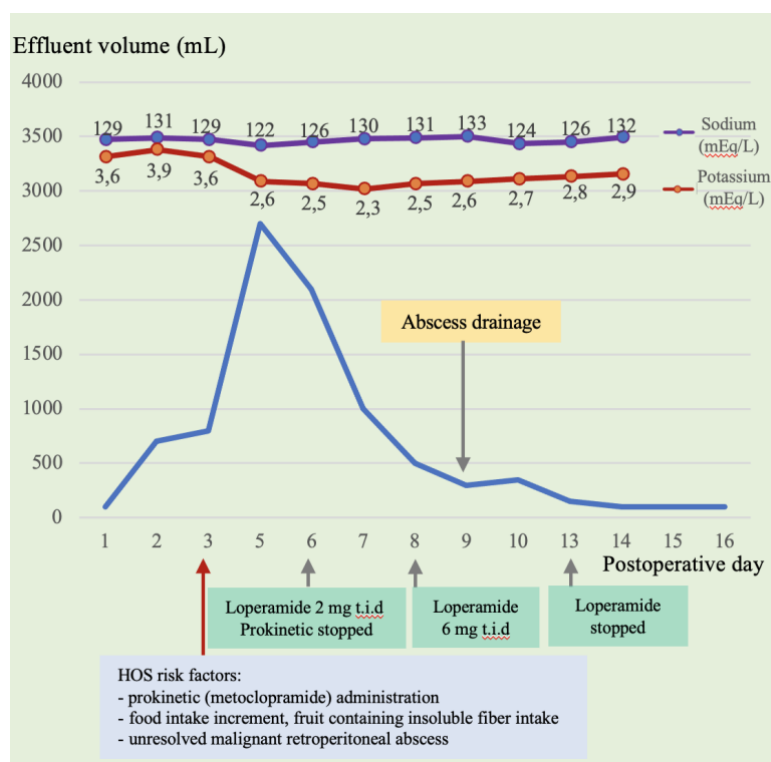
Figure 1. Effluent volume according to postoperative day
compared with sodium and potassium level. HOS: high output stoma

prevalence in colorectal cancer patient ranges from 13 to 45%,[9] and malnutrition is associated with poorer 30-days outcome and infection rate, affecting not only postoperative morbidity and mortality, but also patient's quality of life.[10,11] It is imperative to ensure adequate nutritional provision and prevent nutrient loss from ileostomy effluent, especially for patient with severe malnutrition.

Several factors were identified as the cause of high output stoma in this patient. First, colon cancer infiltrated the retroperitoneal space causing abscess. Inflammation due to intraabdominal infection could contribute to the ileostomy overproduction by decreasing intestinal absorption due to intestinal edema.[1,12] Prokinetic agent could also cause high output stoma.[13] After ileostomy, the patient complained of nausea and bloating, which could be caused by ileal brake upregulation as a form of adaptation after the gut manipulation. Peptide YY secretion is increased after ileal resection, causing longer gastric emptying and slower gut motility to maximize nutrient absorption. Prokinetic agent was used to overcome ileal brake but could hinder chyme and fluid absorption and hence ileostomy production

increment.[14] Loperamide as antidiarrhea agent stimulates μ-opioid receptors in the myenteric plexus, working on high output stoma by slowing intestinal transit time, blocking intestinal calcium channels, and decreasing gut secretion.[15]

Ileostomy production was also influenced by the amount of dietary and fluid consumption.[7] Increment of food and fluid intake was observed after surgery, specifically food high in insoluble fiber were consumed and fluid intake was 1500 – 2000 mL/day. Fruit pulp was found in the ileostomy effluent, raising concern of reduced bowel absorption capacity. The bowel resected was part of ileum from 20 cm oral from ileo-caecal valve and whole right colon, therefore it was predicted digestion and absorption of nutrients had already finished by the time chyme reaching ileostomy. Studies on fiber role in managing high output stoma are scarce and inconclusive. Generally, insoluble fiber consumption was encouraged to thicken stoma production, but in this case insoluble fiber consumption potentially increased effluent production, for that reason patient was advised to reduce insoluble fiber consumption.[16,17]

Ileostomy on ileo-caecal valve level produces 1000–1500 mL fluid a day, containing 200 mEq sodium, 100 mEq chloride, and 10 mEq potassium.[14] Fluid loss of more than 2000 mL per day had caused hyponatremia, hypokalemia, and hypomagnesemia. Sodium and magnesium level responded to treatment, while hypokalemia persisted even with correction and effluent volume decrement. After ileostomy, potassium excretion and sodium retention were increased following the increment of aldosterone level, hence explaining why sodium level responded well to correction while potassium level did not.[14]

Patient's hypotonic fluid consumption was restricted to maximum of 1000 mL per day, and isotonic fluid consumption was advised. Fluid best consumed by high output stoma patient is isotonic solution with sodium concentration at least 90 mmol/L.[18] Along ileum, sodium absorption was through gradient concentration, therefore hypotonic solution, such as water, tea, coffee, alcohol, and juice, would cause sodium efflux from plasma to gut lumen, while hypertonic solution would further increase fluid and sodium loss.[19] Sodium absorption along jejunum was different, because sodium needed glucose to be absorbed. Solution containing glucose and sodium could increase water absorption in jejunum by 60% and sodium by 40%, consequently providing solution that contained both sodium and glucose was recommended for patient with high output stoma.[13] Formula which has been studied for high output stoma management is St. Mark's electrolyte mix, containing 20 g glucose, 2.5 g sodium bicarbonate, and 3.5 g sodium chloride, mixed with 1 L of water.[20] This formula is similar with WHO oral rehydration solution (ORS) ReSoMal®, but 2004 WHO ORS mix, which is readily available nowadays, has osmolarity of 245 mmol/L, lower than plasma osmolarity. Commercial electrolyte solution containing 1.5 g sugar, 2.5 g sodium chloride, 1.5 g potassium chloride, and 2.5 g sodium bicarbonate has also been used in high output management as the only oral source of fluids.[17] While commercial isotonic solution we had unexpectedly had higher osmolarity of 388–392 mmol/L with sodium content of only 21 mmol/L. Further study is needed to ensure which

solution has the best effect in high output stoma management.

There is no consensus on optimal nutritional provision route for high output stoma. Enteral nutrition was continued to be given to preserve gut function and promote adaptation, with a choice of high-calorie and low fiber diet, ensuring better nutrient absorption.[4] Combination of solid food and oral nutritional supplements were given. Energy provision increment was achieved (69–94% target), with mean protein of 1.4 g/kg body weight/day. To ensure absorption while providing adequate protein, low residue high protein formula was chosen. Elemental formula was not given due to concern that hyperosmolar formula could worsen high output stoma. Mean of fat provided was 28%. It is recommended for cancer patient who loses weight to get more energy from fat.[21]

Conclusion and Suggestion

This case report showed a good outcome on nutritional management for patient with high output stoma. High stoma production due to hypersecretory phase after ileostomy was expected, but thorough management would prevent patient's deterioration that was caused by the fluid, electrolyte, and nutritional imbalances. Guideline on optimal nutritional management of high output stoma needs to be developed as it could prevent post ileostomy morbidity.

Conflict of interest

The authors declare that there is no conflict of interest related to the study.

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LITERATURE REVIEW

Effect of oral iron supplementation on functional capacity in heart failure patients

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Abstract

Introduction: Cardiovascular disease is the leading cause of mortality worldwide. Heart failure (HF) accounts for 13.4% of deaths and reduces the quality of life of patients. Iron-deficiency is a common condition found in heart failure patients, often occurs due to decrease in iron intake, absorption, and chronic inflammation. Oral iron supplementation is a low-cost and easy alternative for iron-deficiency management in heart failure patients.

Method: Literature search was conducted using advanced searching in three large databases: PubMed, Cochrane Library, and Google Scholar. MeSH terms, advanced search and eligibility criteria were used for title and abstract screening after removing duplicates. Critical assessment tools and levels of evidence of the final articles are based on the Oxford Center for Evidence-Based Medicine.

Results: Two systematic reviews and meta-analyses and two RCTs met the PICO and eligibility criteria that had been set. Two systematic reviews and meta-analyses found that oral iron supplementation did not improve the functional capacity of heart failure patients, while the two RCTs found an improvement in functional capacity in heart failure patients who received oral iron supplementation.

Conclusion: Based on critical reviews that have been carried out, currently we do not recommend oral iron supplementation in heart failure patients. Further research may potentially provide different recommendations as oral iron therapy evolves.

Keywords: iron , supplement, iron deficiency, iron deficiency anemia, heart failure

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Case Scenario

Mr. AF, 38 years old, has been treated with a diagnosis of heart failure reduced ejection fraction (HFrEF) for the past 5 years, routinely consuming ramipril 2x5 mg, clopidogrel 1x75 mg, and acetylsalicylic acid 1x80 mg. Patient was admitted to the hospital due to difficulty of breathing and low intake. The patient's clinical condition has worsened, making it difficult for him to walk for the past month. During hospitalization, patient underwent laboratory examination and was found to have anemia (Hb 10.8 g/dL), hyponatremia (123 mEq/L), hyperkalemia (5,9 mEq/L), hypoalbuminemia (2,6 g/dL), low serum iron (30,2 mcg/dL), low ferritin (21 ng/mL) and low transferrin (15%). The patient was referred by a cardiologist to a clinical nutrition specialist to provide nutrition therapy and education appropriate for the patient's condition and to inquire whether oral iron supplementation can help improve the patient's functional capacity. When examined by clinical nutrition specialist, patient was bedridden and still experiencing shortness of breath.

Introduction

Cardiovascular disease is the leading cause of mortality in the world. According to data from the World Health Organization in 2019, 17.9 million people worldwide died from cardiovascular disease, equivalent to 32% of all global deaths.[1] Over 75% of these deaths occurred in low- and middle-income countries. In Indonesia, based on data from basic health research in 2018, the prevalence of heart disease is 1.5%.[2] Patients with heart failure often experience iron- deficiency with or without anemia caused by a decrease in serum iron in the body or inadequate iron production to meet the needs of target tissues due to sequestration. The prevalence of anemia in patients with heart failure is estimated to reach 50% in hospitalized patients.[3] The etiology of iron deficiency in heart failure can be classified into three, namely: decreased in iron intake, decreased iron absorption or increased iron loss.[4] Elevated chronic proinflammatory factors, intestinal oedema, and anorexia are some of the factors that can underlie the occurrence of anemia in heart failure.

Iron deficiency anemia can independently increase mortality in heart failure patients by up to two-fold. Decrease oxygen delivery can also affects hemodynamic and neurohormonal conditions, and can exacerbate the already existing heart failure.[3] Iron is known as a nutrient source for pathogens, therefore iron supplementation is generally delayed until infection is treated. Common side effects of oral iron supplementation include gastrointestinal symptoms such as constipation, nausea, and abdominal pain.[5] Testing is often performed to determine the level of iron in the body that includes serum iron, ferritin, transferrin, and total iron-binding capacity (TIBC) tests.[6]

Iron supplementation in heart failure patients with iron deficiency is thought to improve functional capacity. Meta-analysis by Sindone, et al.,[7] found align results with the recommendation from European Society of Cardiology's guideline in 2021 which found that intravenous iron improve functional capacity in patient with heart failure. On the contrary, controversial results were found for oral iron supplements in heart failure patients. Research by Zhou, et al.[8] found that oral iron supplementation did not improve functional capacity, but another study by Suryani, et al.[9] found that oral iron supplementation improved the results of the 6-minute walk test (6MWT) in patients with heart failure.

Clinical question

P	: Heart failure patients
I	: Oral iron supplement
C	: Placebo or intravenous
O	: Functional capacity

Clinical question: could oral iron supplementation improve functional capacity in patients with iron deficiency and heart failure?

Method

Literature search was performed using combination of MeSH terms and Title/Abstract on three large databases: Pubmed, Cochrane Library and advanced search on Google Scholar. Search was carried out on 16th January 2023.
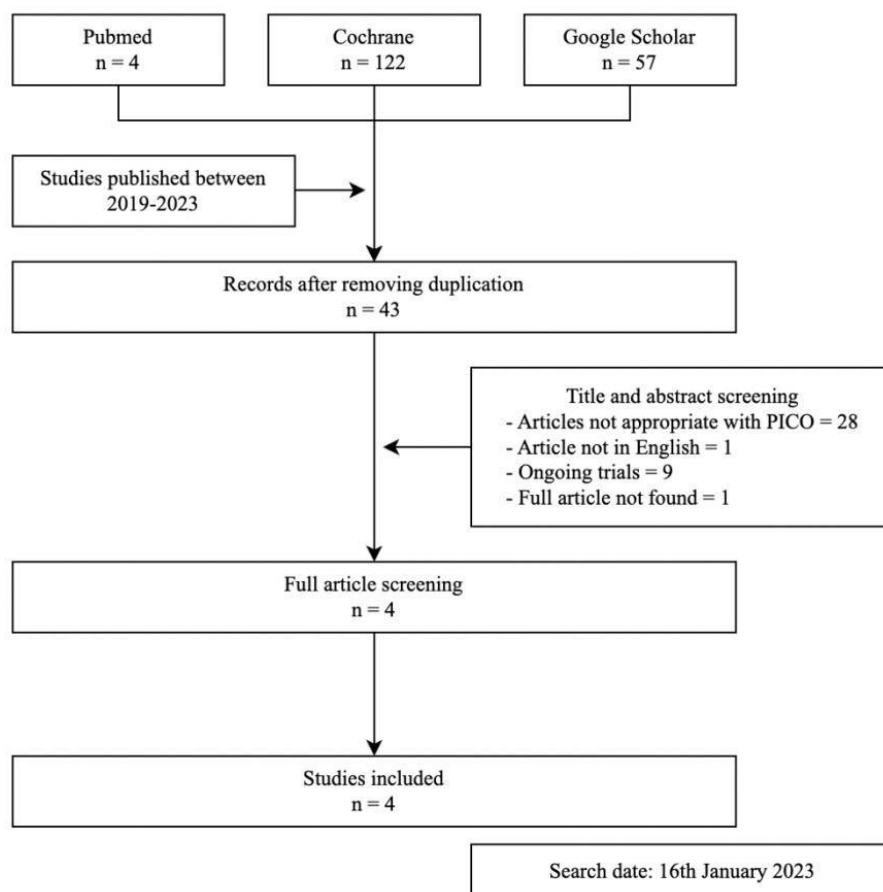
Figure 1 Prisma's flow chart

Table 1 Resources and search strategy

Database	Terminology	Hits	Eligible
PubMed	((oral iron supplement) AND (heart failure)) AND (functional capacity)	2	1
Cochrane	#1 MeSH descriptor: [Iron] explode all trees		
	#2 (iron):ti,ab,kw (Word variations have been searched)		
	#3 MeSH descriptor: [Heart Failure] explode all trees		
	#4 (heart failure):ti,ab,kw (Word variations have been searched)		
	#5 MeSH descriptor: [Administration, Oral] explode all trees	122	2
	#6 (oral):ti,ab,kw (Word variations have been searched)		
	#7 #1 OR #2		
	#8 #3 OR #4		
	#9 #6 AND #7 AND #8		
Google Scholar	allintitle: oral iron heart failure	57	1

Results

The authors found four articles in the Pubmed database, 122 articles in the Cochrane Library, and 57 articles in Google Scholar. Duplicate removal was performed using Excel **Table 1**). The articles were assessed for eligibility based on PICO and eligibility criteria (**Figure 1**), resulting in the selection of four articles. The study characteristics of these articles were listed in **Table 2**. The level of evidence for these articles is presented in **Table 3**, and all the articles were found to be relevant for answering the clinical question (**Table 4**).

Discussion

Iron deficiency with or without anemia are co-morbidities that are often found in patients with heart failure and can reduce functional capacity, quality of life, increase hospitalization rates and mortality. Iron in the body, functions as a raw material for hemoglobin and myoglobin which have an important role in oxygen transportation. Other than that, iron is also an important cofactor for many enzymes and proteins that play a role in oxidative metabolic processes, immune system and various other processes.[13] Oral iron supplementation is available in various forms, among which are often used are ferrous sulphate (20% elemental iron), ferrous fumarate (33% elemental iron), and ferrous gluconate (12% elemental iron).[13] To increase the absorption of supplementation, it is best to take it at least 30 minutes before eating or two hours before taking drugs. These three preparations can cause gastrointestinal disturbances such as nausea, vomiting, diarrhea, constipation, and epigastric pain.[13] Other complaints that may be found are metallic taste and yellow teeth. Some foods or drugs to avoid when taking iron supplementation are milk, calcium, antacids, caffeine and high fiber. Those foods and drugs can reduce iron absorption in the gastrointestinal tract.[13]

There are two types of iron deficiency, namely absolute iron deficiency and functional iron deficiency. Absolute iron deficiency (AID) is defined as reduced iron stores in the bone marrow, liver and spleen, whereas functional iron deficiency (FID) is characterized by normal or increased total body iron storage but cannot be formed into erythroid precursors.[14] The European Society of Cardiology defines iron deficiency as serum ferritin <100 μg/L (AID) or ferritin 100–300 μg/L with transferrin saturation (TSAT) <20% (FID).[4] The etiology of iron deficiency in heart failure can be classified into three, namely: decreased iron intake, decreased iron absorption or increased iron loss.[4] Decreased iron absorption that causes AID can be influenced by conditions such as intestinal oedema, anorexia, or gastrointestinal bleeding due to the use of antiplatelets or anticoagulants. Increased iron loss can be caused by chronic inflammation, increases proinflammatory cytokines and hepcidin. Proinflammatory cytokines in heart failure are produced as a result of intestinal oedema, hypoperfusion and tissue hypoxia. Interleukin-1 (IL-1), interleukin-6 (IL-6) and tumor necrosis factor (TNF) alpha inhibit erythropoietin production in the kidney and suppress the proliferation of erythroid progenitor cells in the bone marrow.[4] IL-6 is also involved in increasing the acute phase protein hepcidin in the liver that plays a role in suppressing ferroportin activity. Reduce ferroportin activity cause a decrease in iron absorption in the duodenum and also reduces the release of stored iron from the reticuloendothelial system.[4]

A systematic review and meta-analysis study conducted by Song, et al.,[10] stated that oral iron supplementation did not improve functional capacity in heart failure patients assessed by 6MWT examination (MD=59.6, CI 95%, -17.89 to 137.08, p=0.13). A systematic review and meta-analysis study by Tan, et al.,[11] also yielded similar results (MD=13.92 m, 95% CI: -47.33 to 19.5, p=0.41). The high heterogeneity (I2=92%, p heterogeneity<0.000001 and I2=75%, p heterogeneity<0.02) in both studies indicate that the results of the RCTs included in both systematic review and meta-analyses have very mixed results. Tan, et al.,[11] explained the source of heterogeneity in their study may be due to one study by Jiang, et al,[15] which after eliminated the heterogeneity became low.

Table 2 Study ch aracteristic

No	Author	Study design	Population characteristic	Total participants	Outcome	Key results
1	Song, et al (2022)[10]	*Systematic review dan Meta-analysis RCT*	Patients age 18–75 years old with HF (EF <50, NYHA II-IV), with iron deficiency or anemia (ferritin <100 ng/mL) who wer given oral iron supplementation for 8-26 weeks.	590 (5 study)	Iron status (ferritin dan TSAT), cardiac function and functional capacity (6MWT)	Oral iron supplement did not reduce mortality (RR=0,77, CI 95%, 0,6-1,16, p=0,28), did not improve functional capacity (6MWT, MD 59,6, CI 95%, -17,89 to 137,08, p=0,13), and did not improve iron status significantly (ferritin: MD = 2,70, 95% CI, – 2.41 to 7.81, P=0.30; TSAT: MD= 27.42, 95% CI, – 4.93 to 59.78, P=0.10)
2	Tan, et al (2022)[11]	*Systematic review dan Meta-analysis RCT*	Patients with HFrEF (EF<50%) and serum ferritin <100 ng/mL or serum ferritin <100-200 ng/mL with TSAT <20%	582 (4 study)	Primary outcome: LVEF, *6-minute walking test* (6MWT), ferritin Secondary outcome: NT-proBNP, haemoglobin, quality of life, safety and adverse events	Oral iron supplementation improve LVEF (MD = 1,52%, CI 95%: 0,69 to 2,36, p=0,0003, I^2 = 0%) and ferritin (MD = 1,64, CI 95%:0,26 to 3,02, p=0,02, I^2=98%), but did not significantly improve 6MWT (MD= 13,92 m, CI 95%: -47,33 sampai 19,5, p=0,41, I^2=90%)
3	Suryani, et al (2022)[9]	RCT, double blind	Patients with HFrEF (EF <45%, NYHA functional class II-III), Hb <13 (men), <12 (women), ferritin <100 ng/mL or ferritin 100-300 ng/ml with transferrin <20% and eGFR >30 ml/menit/1,73 m^2 was given oral supplementation of *ferrous sulphate* (FS) 200 mg three times a day for 12 weeks	54	Functional capacity measured by 6MWT	Oral ferrous sulphate improve functional capacity (6MWT, p<0,001, CI -86,8 sampai -33,2) in HFrEF patients.
4	Zdravkovic, et al (2019)[12]	RCT, open label	Patients with CDHF, ferritin <100 μg/L and TSAT <20% were divided into 2 groups. Group I was given oral supplementation of ferrous fumarate 350 mg (115 mg elemental iron) two times a day and ascorbic acid 500 mg once a day. Group II was given oral supplementation of *ferric hydroxide polymaltose complex* 357 mg (100 mg elemental iron) without ascorbic acid. Supplementation was continued for 6 months.	201	Haemoglobin, hematocryte, RBC, ferritin, TSAT, 6MWT, dan LVEF	Oral supplementation with *ferrous fumarate* and *ferric hydroxide* increase haemoglobin (group I:p<0,001, group II: p<0,001), hematocryte (group I:p<0,001, group II: p<0,001), RBC (group I:p<0,001, group II: p<0,001), 6MWT (group I: p<0,0001 dan group II: p<0,001), ferritin (group I: p<001, group II: p<0,001) and TSAT (group I: p<0,001, group II: p<0,001), but did not improve LVEF (group I: p=0,8, group II: p=0,4) after 6 months of supplementation

NYHA, New York Heart Association; CI, confidence interval; MD, median; LVEF, *left ventricular ejection fraction*; RCT, *randomized controlled trial*; 6MWT, *6 minute walking test*; HFrEF, heart failure reserved ejection fraction; CDHF, chronic decompensated heart failure; RBC, red blood cell; TSAT, transferrin saturation; Hb, hemoglobin.

Table 3 Validity criteria

	Study design	Number of patients	Randomization	Similarity treatment and control	Blinding comparable treatment	Domain	Determinant	Measurement of outcomes	Quality of evidence*	Level of evidence**
Song Z, et al (2022)[10]	+	+	+	+	+	+	+	+	Moderate	1A-
Tan N, et al,(2022)[11]	+	+	+	+	+	+	+	+	Moderate to high	1A-
Suryani LD, et al (2022)[9]	+	+	+	+	+	+	+	+	Moderate	1B
Zdravkovic SC, et al (2019)[12]	+	+	+	+	-	+	+	+	Low to moderate	1B

* Quality of evidence according to GRADE guidelines, https://www.ncbi.nlm.nih.gov/pubmed/21208779
**Level of evidence according to Oxford Center of Evidence-based Medicine (CEBM), http://www.cebm.net.
+ clearly mentioned in the article; - not done; ? Not stated clearly
- Systematic review and meta-analysis with troublesome heterogeneity

Table 4 Relevance criteria

Article	Similarity Population	Similarity determinant/intervention/indicators	Similarity outcome
Song Z, et al (2022)[10]	+	+	+
Tan N, et al,(2022)[11]	+	+	+
Suryani LD, et al (2022)[9]	+	+	+
Zdravkovic SC, et al (2019)[12]	+	+	+

The RCT by Suryani, et al.,[9] conducted a study on 54 HFrEF patients (EF <45%, NYHA II-III) by dividing them into two groups. First group comprise of 27 people received ferrous sulphate 200 mg three times daily for 12 weeks, and the remaining 27 people received placebo. The study concluded that there was an improvement in functional capacity as indicated by an improvement in 6MWT (46.23 ± 35 m vs –13.7 ± 46 m, p<0.001, CI -86.6 to -33.2). In addition, there are also an increase in ferritin levels (207.3 ± 104 ng/ml vs 111.7 ± 81.4 ng/ml, p = 0.001, CI –160 to –41.87) and TSAT (29.5 ± 10.4% vs 20 ± 10.6%, p = 0.008, CI –16.3 to –2.6). The author tried to explain the difference in results with other studies that might be caused by the difference of oral iron supplements used. This RCT was conducted at the Harapan Kita National Heart Center Hospital Jakarta, Indonesia so it has the same population characteristic as the patient in this EBCR.

The study by Zdravcovic, et al,[12] compared supplementation of 350 mg of ferrous fumarate twice daily plus 500 mg of ascorbic acid (group I), with supplementation of 357 mg ferric hydroxide polymaltose complex once a day without ascorbic acid (group II) for six months in 201 patients with CDHF with ferritin <100 g/L and TSAT <20%. The results of the study found that both ferrous fumarate and ferric hydroxide polymaltose complex supplementation improved 6MWT examination in CDHF patients after six months of supplementation. The study also found improvements in ferritin levels (group I: p<001, group II: p<0.001) and TSAT (group I: p<0.001, group II: p<0.001). This study also concluded that ferric supplements were better tolerated than ferrous supplements. Major limitation in this study was the lack of control group (not provided with iron supplement).

Based on the critical review from this literature, both systematic review and meta-analysis yielded consistent findings, while the results of the two RCTs were different. The characteristics of patients included in the four articles were similar to those of the case patient, thus the research findings can be applied to patient in this case as well. If possible, iron status examination should be conduct as a screening in heart failure patients due to high prevalence of iron deficiency and their proven association with functional capacity in heart failure patients.

Conclusion

Oral iron supplement is an alternative therapy for iron deficiency in heart failure patients. Based on critical reviews that have been carried out in two systematic reviews and meta-analyses as well as two RCTs in this evidence-based case report, oral iron supplementation does not improve functional capacity in iron deficiency patients with heart failure. Currently, we do not recommend oral iron supplementation for patient in this case and heart failure patients with decrease iron status in general. However, it has been shown that decrease iron stores can affect functional capacity in heart failure patients, therefore routine iron status assessment is advisable. Further research may potentially provide different recommendations as oral iron therapy evolves and improved research data quality is available.

Conflict of interest

The authors declare that there is no conflict of interest related to this article.

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ORIGINAL PAPER

Medical nutrition therapy in hospitalized patients with pemphigus vulgaris

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Abstract

Dysphagia due to involvement of the oral, pharyngolaryngeal, and esophageal mucosa and increased catabolism due to epidermal shedding can contribute to a decline in nutritional status in pemphigus vulgaris (PV) patients. On the other hand, decreased lean body mass is associated with immune system impairment, increased risk of infection, and delayed wound healing in PV patients, therefore, nutritional screening and assessment are necessary. Medical nutritional therapy in PV patients aims to overcome the metabolic response to the insults, prevent further malnutrition, modulate the immune system, and accelerate wound healing process. An aggressive nutritional support to minimize protein loss during the phase of mucocutaneous lesion healing is needed in patients with PV. Aside from macronutrient adequacy, micronutrients including vitamin A supplementation can be considered to accelerate wound healing process. Medical nutritional therapy including provision of adequate macronutrients, micronutrients, addressing dehydration and electrolyte imbalances should be the cornerstone of multidisciplinary treatment in PV patients.

Keywords: malnutrition, medical nutrition therapy, pemphigus vulgaris, micronutrients, wound healing

Background

Pemphigus vulgaris (PV) is one of the most commonly found autoimmune bullous disease, with an incidence of up to 70% of all pemphigus cases.[1,2] Study by Budianti et al.[3] in referral hospital in Indonesia also showed similar results, with pemphigus vulgaris being the most commonly found type of pemphigus (75%). The use of corticosteroids as the main therapy for PV has led to a drastic decrease in PV mortality, from 75% to 30%. However, currently there is a shift in the causes of pemphigus mortality from the direct effects and severity of the disease to long-term complications.[1,2] This is due to the long-term use of steroids, which can cause various complications such as hyperglycemia, osteoporosis, hypertension, edema, adrenal suppression, and delayed wound healing. [4–7]

Involvement of the oral, pharyngolaryngeal, and esophageal mucosa in PV patients can induce dysphagia and contribute to a decline in nutritional status in patients with PV. Increased catabolism due to epidermal shedding, protein loss, inflammatory responses, and physical immobilization can also increase the risk of malnutrition and sarcopenia in pemphigus patients.[8,9] Furthermore, malnutrition can also affect wound healing in pemphigus patients. Decreased lean body mass is associated with immune system impairment, increased risk of infection, and delayed wound healing.[10]

Medical nutritional therapy in PV patients aims to overcome the metabolic response to the insults, prevent further malnutrition, modulate the immune system, and accelerate wound healing process. In addition to adequate macronutrient intake, micronutrient supplementation including vitamin A is associated with the wound healing process. Vitamin A is also associated with modulating the immune system through the effects of proliferation, differentiation, and apoptosis of immune cells, thus playing a role in modulating pemphigus.[11] However, to this day literature on vitamin A supplementation specifically for patients with pemphigus vulgaris is still limited. Therefore, this review article will discuss medical nutritional therapy in patients with pemphigus vulgaris, specifically the role of vitamin A in wound healing in order to achieve optimal clinical outcomes.

Pemphigus Vulgaris

Pemphigus vulgaris is a chronic autoimmune disease that belongs to the group of autoimmune bullous diseases (AIBD). It is initiated by an autoantibody response with the accumulation of immunoglobulin G (IgG) on the skin. Exposure of autoantibodies to autoantigens triggers the formation of immune complexes, which subsequently cause damage to the skin integrity, leading to the formation of blisters and further infiltration of immune cells. Both the innate and adaptive immune systems are involved in the autoimmune response and inflammation in the pathogenesis of AIBD. In patients with PV, there are abnormalities in the ratio and function of T cell subsets in circulation. There is an increase in the levels of Th17 cells that secrete IL-17, which promotes an inflammatory response, and a decrease in Treg cells that inhibit Dsg3-autoreactive T cell proliferation and antibody production which prevent autoimmune disease.[12]

Several external factors can initiate and prolong the course of pemphigus vulgaris, including drugs, viral infections (herpes simplex), physical agents, contact allergens, vaccination, dietary factors, and psychological stressors.[13] Genetic contributions are also associated with the pathogenesis of pemphigus vulgaris, as it can be found in other autoimmune diseases, including autoimmune thyroid disease, type 1 diabetes, and rheumatoid arthritis. Several dietary factors can also induced PV in patients with genetic susceptibility such as allium vegetables, phenols, tannins and cinnamic acid.[14]

The clinical manifestations of pemphigus vulgaris generally start from the oral mucosa and can take several months prior to the appearance of skin lesions. The lesions can then be localized for several months until generalized listers appear.[15] Acute eruptions in the form of generalized bullae that appear from the beginning are rare. Skin bullae are usually flaccid and non-pruritic with erythematous or non-erythematous bases that can quickly develop into bloody erosions. These lesions can be focal or generalized and there is a sensation of burning and pain on the erosions or ruptured bullae. The flexural regions and extremities, which are vulnerable to stress and trauma, are common sites for pemphigus vulgaris.[2,9] Lesions on the oral mucosa often cause pain and can lead to decreased food intake in PV patients.[15]

One of the characteristics of PV lesions is the erosion can spread to previously healthy skin. This phenomenon is called Nikolsky sign and occurs when the bullae rupture and the bulla wall is pulled towards the periphery of the active lesion. [15,16] Unlike lesions caused by viral infections or stomatitis that can heal within a few days, lesions in pemphigus usually cannot heal on their own.[7] The spread of lesions can lead to complications such as infections, which can prolong the healing process.[7,16–18]

The diagnosis of PV can be established through a clinical examination and various diagnostic modalities such as skin and mucous membrane biopsy, immunopathology examination, and serum autoantibody examination. Biopsy examination can reveal suprabasal keratinocyte separation, triggering basal cell layer separation and vesicles that contain separated and round-shaped keratinocytes (acantholytic). Immunopathology examination using immunofluorescence can show the presence of immunoglobulin G and sometimes C3 deposits on skin lesions. Autoantibody examination also usually shows an increase in detected IgG.[15]

The management of PV involves administering glucocorticoids until no new bullae form and Nikolsky sign disappears. The initial systemic corticosteroid therapy with 0,5–1 mg/kgBW/day of prednisone and 1 to 1,5 mg/kgBW/day is recommended in patients with mild PV and patients with more moderate to severe PV, respectively.[15,19] The glucocorticoid dosage should then be gradually tapered down to reach the minimum effective maintenance dose. Patients may also be given other immunosuppressants as steroids sparing-agents. Management also includes wound care, administration of antibiotics to patients with secondary infections, as well as fluid and electrolyte management. Monitoring of PV patients includes improvement in skin lesions and side effects of treatment. Laboratory monitoring also includes pemphigus antibody titers, as well as hematologic and metabolic indicators of glucocorticoid side effects.[15]

Nutritional Problems

The clinical manifestations of pemphigus can involve the oral mucosa, epidermis, or both.[20] The involvement of mucous membranes, especially the oral mucosa and upper gastrointestinal tract such as the esophagus, can affect the patient's ability to eat, including chewing and swallowing, leading to malnutrition and electrolyte imbalances, thereby increasing the severity of the disease. In addition, increased catabolism due to epidermal shedding can also increase the risk of malnutrition and sarcopenia in patients with pemphigus.[8,9] However, studies assessing the incidence of malnutrition and sarcopenia in patients with PV have not yet been found. The increased loss of protein due to extensive mucosal and cutaneous erosion, serous discharge from wounds, and increased catabolism can also lead to hypoalbuminemia in PV patients. Studies[21,22] showed that low albumin levels in pemphigus patients are associated with poor clinical outcomes.

Micronutrients including trace elements levels can also be affected in patients with PV. These could be secondary to poor nutritional intake or chronic inflammation.[14] Inflammation caused by acute or chronic diseases can trigger the redistribution of various micronutrients in circulation to organs, leading to a decrease in plasma micronutrient levels. The effect of inflammation on micronutrients can be short but can also persist in chronic diseases.[23] Severe skin lesions could also result in excessive loss of fluids which leads to dehydration, an imbalance of electrolytes and the loss of water-soluble micronutrients.[8,24]

Furthermore, a study by Moravvej et al.[25] also showed that suboptimal vitamin D status (<30 ng/mL) is commonly found in patients with pemphigus, and the risk of low vitamin D status is higher in patients with pemphigus with a large surface area of lesions and high Pemphigus Area and Activity Scores.

Side Effects of Glucocorticoid

Long-term use of systemic steroids in patients with autoimmune diseases can also increase the risk of hyperglycemia and drug-induced diabetes. High-dose administration of glucocorticoid, whether oral, inhaled, or topical, are associated with hyperglycemia and steroid-induced diabetes. Corticosteroids increase blood glucose levels by increasing hepatic gluconeogenesis and decreasing glucose uptake in peripheral tissues. In addition, acute exposure to corticosteroids can trigger insulin resistance by reducing the ability of adipocytes and hepatocytes to bind to insulin.The risk of hyperglycemia also increases with increasing daily steroid dose and cumulative dose.Glucose uptake and metabolism in peripheral tissues can return to normal when corticosteroid use is discontinued.[4,5]

Due to the increased activity of lipoprotein lipase that hydrolyzes circulating triglycerides such as chylomicrons and very low-density lipoproteins, long term used of glucocorticoids also result in an elevated amount of fatty acids in circulation. These fatty acids can then be distributed to ectopic fat locations and responsible for the occurrence of central adiposity.[6]

The use of immunosuppressants can inhibit several inflammatory mediators involved in the wound healing process, including IL-2, IL-4, IFN-gamma, and TNF alpha, thereby inhibiting T-cell activation. Corticosteroids can also affect

lymphocyte recirculation and trigger lymphocyte death, thereby contribute to delayed wound healing.[7]

Glucocorticoids can also lead to a decrease in bone formation and an increase in bone resorption through several mechanisms. First, glucocorticoids can reduce the differentiation and maturation of osteoblasts, leading to a decrease in the number and function of osteoblasts. In addition, glucocorticoids can induce apoptosis of osteoblasts, further contributing to a decrease in bone formation. Glucocorticoids can also induce apoptosis of osteocytes, which play a role in repairing microdamage to bones, further reducing bone quality. Up to 40% of patients receiving glucocorticoids may experience a decrease in bone mass. The secondary decrease in bone mass due to glucocorticoids can occur even from the beginning of use, and is most significant in the first six months. The initial rate of bone mass reduction can reach 12% in the first year of glucocorticoid use, with an average of 2-3% per year. The daily dose of glucocorticoids can predict the occurrence of fractures, with a dose as low as 2.5 mg of prednisone per day already increasing the risk of fractures, and a dose of more than 7.5 mg per day can increase the risk of fractures up to fivefold.[26]

Nutritional Assessment

Patients with pemphigus vulgaris (PV), especially those with involvement of the oral mucosa and gastrointestinal tract, are at an increased risk of malnutrition. Therefore, nutritional screening and assessment are necessary. Several methods are commonly used to screen for malnutrition in hospitalized patients, including MST, Nutritional Risk Screening (NRS), and Patient Generated Subjective Global Assessment (PG-SGA).[27]

Relying solely on Body Mass Index (BMI) as a way to evaluate nutritional status is considered insufficient for anticipating a decline in muscle mass and physical capabilities. Up to this point, there have been no studies that assess the sensitivity, specificity, and validity of nutritional diagnostic modalities in patients with PV. However, diagnostic modalities such as GLIM can be used as it assesses malnutrition based on

etiological and phenotypic factors, which includes nonvolitional weight loss, low BMI, reduced muscle mass, reduced food intake or assimilation and disease burden or inflammation.[28]

It is also important to identify sarcopenia in chronic PV patients. The diagnosis of sarcopenia can be confirmed if a patient has low quantity and quality of muscle, based on body composition assessment using modalities such as magnetic resonance imaging (MRI), computed tomography (CT) scan, or by using dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA).[29]

Electrolytes laboratory examination is also necessary for PV patients due to the risk of electrolytes disturbances. It is also important to regularly monitor blood sugar and lipid profile as they can serve as metabolic indicators for the adverse effects of glucocorticoids. Considering the need for high protein therapy, kidney function tests should be considered as part of clinical examination to exclude any kidney disorders. Biochemical panel examination, including vitamin D, parathyroid hormone, and serum phosphate, can also be used as an initial step in predicting the occurrence of glucocorticoid-induced osteoporosis.[26]

Medical Nutrition Therapy

The main goal of managing autoimmune diseases such as pemphigus vulgaris is to induce remission, minimize treatment side effects, and improve patients' quality of life.[6] Medical nutritional therapy, as part of a multidisciplinary approach for pemphigus patients, aims to prevent further protein loss, improve nutritional status, optimize fluid and electrolyte balance, accelerate wound healing, and help prevent relapse.[8,30]

When the affected body surface area (BSA) is more than 30% or when at least two mucous membranes are affected, the condition can be categorized as severe. In addition, the response to injury increases metabolic needs and can raise energy requirements up to 250%.[10] In such cases, it is necessary to provide aggressive nutritional support to reduce protein loss and to aid in the healing of mucocutaneous lesions.[8,9]

Indirect calorimetry is the gold standard for determining resting energy expenditure (REE) in hospitalized patients. In situations where the use of indirect calorimetry is not possible, REE calculation can be done using weight-based equations of 30 kcal/kg body weight in malnourished patients. Energy administration needs to be increased gradually, especially in PV patients who have experienced decreased intake for some time due to dysphagia or odynophagia, which puts them at risk of developing refeeding syndrome.[31]

In addition to increased energy requirements, patients with extensive wounds also experience an increased protein requirements, up to 50%, due to significant protein loss. Moreover, protein is also required in the formation and activity of immune cells involved in the wound healing process. A decreased in lean body mass by 10% is associated with impaired immune function and an increased risk of infection. In cases where lean body mass decreases by more than 10%, there is a competition between wound healing process and the body's need to restore lean body mass. Patients who lose more than 30% of their lean body mass will experience delayed wound healing.[10]

Inadequate protein intake can slow down the progression of wound healing, especially from the inflammatory phase to the proliferative phase. In the proliferative and remodeling phases, energy and protein deficiency can also decrease fibroblast activity, slow down angiogenesis, and reduce collagen formation.[10] Therefore, patients with pemphigus vulgaris require more aggressive nutritional support to minimize protein loss during the phase of mucocutaneous lesion healing. Protein intake of up to 2-3 g/kg body weight per day can be considered for pemphigus patients.[8,30]

Adequate carbohydrate and fat intake is also needed to support the inflammatory response, cellular activity, angiogenesis, and collagen deposition in the proliferative phase of wound healing. Specifically, adequate carbohydrate intake is needed for fibroblast production and movement as well as leukocyte activity. Carbohydrates can also stimulate the secretion of hormones and growth factors, including insulin, which plays a role in the anabolic process in the proliferative

phase.[10] Nevertheless, the choice of carbohydrates must still be taken into account because of the possibility of hyperglycemia and diabetes induced steroids in patients receiving steroids. Providing carbohydrates in the amount of 45-60% from high-fiber complex carbohydrates and avoiding simple carbohydrates may be considered in patients receiving long-term steroid therapy.[32]

Fat also plays a structural role in the cell membrane layer during tissue growth in wound healing process.[10] Just like carbohydrates, the selection of fat also needs to be considered in PV patients receiving steroids due to the risk of dyslipidemia and altered lipid metabolism.[6]

Replacing saturated fat with unsaturated fats such as monounsaturated fatty acids (MUFA) can be considered in patients on long-term steroid therapy to help manage hyperglycemia and dyslipidemia.[32] Polyunsaturated fatty acids (PUFAs) such as omega-3 have been shown to have anti-inflammatory effects. Metabolites of omega-3 PUFAs, such as resolvins (Rvs)-1 and Rvs2, have anti-inflammatory effects by inhibiting immune reactions and increasing the levels of Treg cells.[33] However, studies regarding omega-3 fatty acid supplementation doses specifically in patients with pemphigus vulgaris have not yet been found.

Avoiding hot foods and sharp foods such as chips and consuming soft foods can be done in patients with involvement of oral mucosa. Pemphigus vulgaris patients with malnutrition or those at risk of malnutrition who are unable to meet their energy needs through oral intake may benefit from the administration of oral nutrition supplements (ONS) to improve their clinical outcomes. ONS administration can help maintain muscle mass during treatment and significantly reduce post-treatment mortality in malnourished patients.[31] In cases where oral and gastrointestinal mucosal lesions caused a decrease in intake due to dysphagia or odynophagia, the placement of enteral nutrition access such as nasogastric tube (NGT) can be considered.[8,30] Restrictions of several dietary factors should be done cautiously as it could cause malnutrition or worsen the malnutrition.

Resuscitation with intravenous fluids to correct any dehydration should be addressed in the PV patients. Any electrolyte imbalance also needs to

be corrected in the PV patients.[24] Supplementation of micronutrients should be considered in PV patients, especially in those with reduced intake and cannot meet their micronutrient requirements from dietary intake. Vitamin B, including thiamine, riboflavin, pyridoxine, folic acid, pantothenic acid, and cobalamin, are essential factors in enzyme reactions involved in leukocyte formation and anabolic processes of wound healing. Thiamine, riboflavin, pyridoxine, and cobalamin are also needed in collagen synthesis. Therefore, inadequate intake of vitamin B indirectly affects the wound healing process by disrupting antibody production and white blood cell function, thereby increasing the risk of infection complications.[7] Therefore, supplementation with B complex vitamins can also aid in the wound healing process.

Vitamin C is an important cofactor in collagen biosynthesis and can protect endothelium by increasing collagen synthesis, maintaining endothelial vasodilation and barrier function. Vitamin C also plays a role in limiting the inflammatory response and aid in wound healing process.[23] Vitamin C deficiency can disrupt the immune response during the inflammatory phase of wound healing, increase capillary fragility, decrease collagen synthesis and elasticity needed in the proliferative and remodeling phases. Supplementation with 500 mg to 2 grams of vitamin C per day may be considered to aid wound healing. The beneficial effects of vitamin C supplementation can also be enhanced by co-supplementation with zinc. Zinc plays a role in the wound healing process through its role in DNA replication in cells with high proliferation rates, including epithelium and fibroblasts. Zinc is involved in fibroblast proliferation and epithelialization through the stimulation of enzymes. The recommended dose of zinc to accelerate wound healing can reach up to 40 mg per day.[34]

According to the American College of Rheumatology, adult patients who take prednisone at a dose of 2.5 mg or more per day for three months or longer should optimize their vitamin D intake with supplementation of 600-800 IU and calcium intake of 1000-1200 mg per day to prevent glucocorticoid-induced osteoporosis. The Endocrine Society guideline recommends vitamin D supplementation of 1500-2000 IU per day to consistently increase vitamin D levels above 30 ng/mL in patients at risk of vitamin D deficiency. However, studies showed that patients with autoimmune disease require higher dose of supplementation.[35,36]

The expression of the transcription factor FoxP3, which plays a crucial role in the differentiation and effector function of Treg cells, can be enhanced by vitamin D. In addition, T cells activated by vitamin D also exhibit decreased expression of IFNγ, IL-17 and IL-21, indicating suppression of inflammation.[37] Patients with autoimmune disease should have their 25(OH)D levels measured. A high initial dose of vitamin D (50,000 IU capsule once a week for 8 weeks) should be considered if the levels are less than 30 ng/mL followed by a maintenance phase with an initial dose of 800 IU/day is recommended.[38]

Currently, studies on the role of vitamin A in patients with PV have yet been found. However, vitamin A functions as a hormone that can influence the activity of epithelial cells, melanocytes, fibroblasts, and endothelial cells through its action on retinoic acid receptors (RARs). The need for vitamin A can increase sharply in cases of injury or acute stress.[39] Vitamin A is also associated with the modulation of the immune system through the effects of proliferation, differentiation, and apoptosis of immune cells, thus playing a role in modulating pemphigus by reducing Th17 cells and stabilizing regulatory T cells (Tregs).[11] Vitamin A, in the form of retinoic acid, can increase the expression of Foxp3 and act as a key regulator of TGF-β-dependent immune responses. It can also inhibit the production of IL-6, supporting the differentiation of anti-inflammatory Treg cells and inhibiting the expression of IL-17.[40,41]

Vitamin A also has beneficial effects associated with the wound healing process and its deficiency can disrupt the wound healing process. The beneficial mechanism of vitamin A in the wound healing process occurs through several pathways. Vitamin A can stimulate the growth of epithelial cells, fibroblasts, and granulation tissue. Vitamin A also plays a role in the differentiation of

keratinocytes into mature epidermal cells through its interaction with nuclear chromatin and gene expression.[40,42] Vitamin A facilitates the differentiation process of epithelial cells by increasing the number of monocytes and macrophages in the early inflammatory phase of the wound healing process.[34,39] Retinoic acid can also increase the production of extracellular matrix components such as type I collagen and fibronectin.[43]

Furthermore, high doses of corticosteroids can deplete vitamin A storage in the liver. As discussed earlier, corticosteroids can also delay wound healing process. Vitamin A can counteract the anti-inflammatory effects of corticosteroids on wound healing, therefore systemic or topical vitamin A supplementation may be considered in patients with acute or chronic wounds receiving immunosuppressive therapy to accelerate wound healing.[34,39,43]

The Dietary Recommendation Intake (DRI) for vitamin A is 700 mg or 2310 IU per day for women and 900 mg or 3333 IU per day for men. Specific guidelines and recommendations for administering vitamin A to PV patients have not been found. Nevertheless, administering vitamin A at a range of 10,000 to 50,000 IU per day orally or 10,000 IU intramuscularly for 10 days may be considered to accelerate wound healing.[34] Other literature recommends administering 15,000–20,000 IU of vitamin A per day for 14–21 days in patients with chronic steroid use. However, administration of high-dose vitamin A supplementation should only be given to patients with good liver and kidney function to prevent toxicity.[39]

In addition, regular nutritional monitoring is necessary for patients with PV and should include several aspects such as food intake, enteral feeding tolerance, anthropometric measurement, nutritional status, electrolyte and albumin levels, blood glucose levels, the presence of nutritional deficiency symptoms. Regular nutritional monitoring can help identify nutritional problems in PV patients, enabling timely intervention to prevent further complications.

Conclusion

The involvement of oroesophageal mucosa, increased catabolism, and severe skin lesions can all lead to malnutrition, dehydration, electrolyte imbalances and alteration of micronutrients. The used of glucocorticoids as principal therapy can also caused adverse effects including altered macronutrient metabolisms and delayed wound healing. An adequate medical nutrition therapy including macronutrients, micronutrients, addresing dehydration and electrolyte imbalances are needed as part of multidisciplinary treatment of pemphigus patients. Particularly, aside from macronutrient adequacy, micronutrients including vitamin A supplementation can be considered to accelerate wound healing process. Further clinical research is needed to regarding the role of vitamin A supplementation in wound healing, particularly in PV patients.

Conflict of interest

The authors declare that there is no conflict of interest related to the study.

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LITERATURE REVIEW

Malnutrition and lung cavity formation in pulmonary tuberculosis patients

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Abstract

Background: Tuberculosis (TB) is an infectious disease and still major public health threat globally, also one of the leading causes of death worldwide. One of the characteristics found in pulmonary TB patient is lung cavity on their chest radiograph. This is related to many aspects, including slower conversion of sputum cultures, treatment failure and relapse, drug resistance, higher bacillary load, even higher infection transmission rates. Some studies before had found that the lung cavity is affected by many factors, such as elder age, sex, diabetes mellitus, and malnutrition. Meanwhile, malnutrition itself in pulmonary TB patients is found to be related to each other, this article review how malnutrition affects the formation of lung cavity in pulmonary TB patients.

Objective: To observe the relationship between malnutrition and lung cavity formation in pulmonary tuberculosis patients.

Method: In this paper, we provide a literature review. The method to achieve the objective consists of using literature exploration, which was conducted from October 2022-February 2023 by searching the relevant studies from several databases.

Results: Cavity formation in pulmonary TB patients is a complex mechanism from many factors contributing, including the immune system of the host. Studies show that malnutrition in pulmonary TB patients plays important role linked to lung cavity formation since malnutrition affects both innate and cellular immune response in host.

Conclusion: Malnutrition is more predominating in pulmonary TB patients and is related to incidence of lung cavity in pulmonary TB patients, therefore plays role in the severity of the disease in pulmonary TB.

Keywords: nutritional status, malnutrition, lung cavity, pulmonary tuberculosis

Introduction

Tuberculosis (TB) is an infectious disease caused by the bacillus *Mycobacterium tuberculosis*, which spreads when people with TB expel the bacteria into the air (by coughing). This disease usually affects the lungs, known as pulmonary TB, although it can also affect other organs. TB is a major cause of poorer health-outcome and one of the leading causes of death worldwide. Until the Corona Virus Disease-2019 (COVID-19) pandemic, TB was the leading cause of death from a single infectious agent and was the thirteenth leading cause of death globally.[1] Reporting from the Indonesian tuberculosis website managed by

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the Ministry of Health, estimates of pulmonary TB cases in Indonesia in 2022 are around 459,789 cases with an estimated death rate due to TB of 107,000 or 40 per 100,000 population.[2] This is a problem because it is certainly the opposite of one of the targets of the Sustainable Development Goals (SDGs) of the World Health Organization (WHO), namely ending the TB epidemic by 2030.[1]

The appearance of a lung cavity on radiological examination, which accounts for more than 40% of people with pulmonary TB at the time of diagnosis, is one of the most often observed clinical signs of TB.[3] Cavities are a defining feature of TB disease and add to the disease's dismal prognosis. Compared to TB without cavities, pulmonary cavity will result in slower conversion of sputum cultures, subpar clinical results, and increased infection transmission rates.[3,4] This is because cavities are associated with a greater infection rate possibly due to a higher burden of organisms. In addition, between 20–50% of cavitary TB patients have a persistent cavity even after completion of anti-TB treatment due to incomplete healing and formation of fibrotic scar tissue.[4] Presence of a lung cavity is also associated with treatment failure and relapse among pulmonary TB patients.[5] Some studies have found several risk factors associated with the lung cavity, such as older age, gender, diabetes mellitus, and malnutrition.[3,6-9] It has long been known that there is a relationship between TB and malnutrition, malnutrition promotes the development of active TB, and active TB exacerbates malnutrition.[10]

Malnutrition is a state resulting from lack of intake or uptake of nutrition that leads to altered body composition (decreased fat free mass) and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease.[11] The prevalence of malnutrition in patients with TB is estimated to range from 50% to 57%, and malnutrition is associated with a two-fold risk of death.[12,13] Malnutrition may specifically weaken cell-mediated reactions that are crucial for preventing and controlling TB, according to some researches.[9] Malnutrition, which also indicates a nutritional deficiency and is linked to increased pulmonary inflammation, as well as a number of other conditions like chronic energy deficiency, frequent pulmonary inflammation, elevated oxidative stress, and altered body composition, may also play a role in the development of a cavity in pulmonary TB.[14]

Methods

This review was designed as a literature review to analyse the existing data and information about the relationship between malnutrition and lung cavity formation in pulmonary TB patients. Literature was explored from the following databases: PubMed, ScienceDirect, Web of Science and Google Scholar. All databases were searched from October 2022 to February 2023 and literature from the last 10 years of publication was chosen for this review. A combination of these keywords addressing "malnutrition" or "nutritional status", "lung cavity", "cavity formation", and "pulmonary tuberculosis" were used. There were no language restrictions set in the search strategy. Firstly, the titles and abstract of relevant articles were screened and the full articles were read and observed to identify the eligible studies to be included in this review.

Discussion

Cavity formation in pulmonary tuberculosis

Lung cavity has been defined as a process that begins with caseous lung necrosis, resulting in caseous pneumonia. This in turn causes damage to the alveolar, septal, bronchial, and blood vessels, forming a cavity when the area of caseous pneumonia liquefies, whose contents are released during coughing. The cavity consists of a layer of necrosis on top of the granulomas lipid and may be surrounded by a collagen capsule after tissue repair.[15] There is ongoing discussion over how cavities occur in TB. Serial radiological observations revealed that TB cavities develop from pre-existing regions of lung that are too packed, which then erode the nearby airways. Histological findings showing structural similarity between necrotic granulomas and cavity walls lend credence to this notion. These studies also found two additional morphological alterations required

for cavity formation: central necrosis and extracellular matrix depletion.[16] Cavity formation is the transformation of immune-containing lung tissue into a surface layer of lung tissue protected by immune cells from the outside environment. The TB cavity is a complex phenotype that is influenced by biochemical, biophysical, immunological, and microbiological mechanisms, all of which are crucial for cavity creation at different stages.[4]

Tuberculous cavity development is typically referred to as a "post-primary" process since it happens decades or even centuries after the initial "primary" infection. It has been proposed that liquefaction, which occurs when areas of caseous necrosis liquefy and create an environment for fast bacterial growth, is a crucial step in the creation of TB cavities. Although the lipid content of the caseous centre lacks enzymatic activity and is unable to dissolve the three-helix structure of collagen, which gives the lung its tensile strength, the areas of caseous necrosis are rich in lipids. Consequently, the buildup of lipid-rich necrotic material must be a part of a multifaceted disease process. These occurrences could include lipid buildup, cell death, DNA lysis of dying host cells, and extracellular matrix damage.[17]

Other study also supports this theory by stating that in the process of cavity formation, host lipids and mycobacterial antigens accumulate in the alveoli but only small number of bacteria are present then sudden necrosis related to a delayed-type hypersensitivity reaction against mycobacterial antigens occurs. The lipid-rich necrotic material in granulomas does not have the enzymatic activity to degrade collagen and consequently, its build-up is only one component of cavity formation. Extracellular matrix breakdown takes place and involves matrix metalloproteinase (MMPs). Indeed, increased concentrations of MMPs have been found in TB cavities along with other study before, also neutrophils have also been found in cavities.[17,18]

Factors contributing to cavity formation

Based on the epidemiologic triad, there are three main components that contribute to cavity

formation in pulmonary TB patients; host, agent, and environment.[19] The formation of cavity lesions in pulmonary TB patients is closely related to the host's defense response. The innate immunity plays a major role in the host's response to *M. tuberculosis*. Macrophages are the first line of defense and their response can either control the infection or favor its development. While there is extensive data describing the role of the innate immune response in pulmonary TB, there is still more work to be done to better understand its role leading to lung cavity. Necrosis is associated with cavitation in many processes, such as squamous cell carcinoma and pyogenic lung abscess. Similarly, the relative tendency toward cell necrosis over apoptosis during the inflammatory response to *M. tuberculosis* infection is a likely factor affecting cavitation. Therefore, cell-signalling pathways that favor necrosis over apoptosis could also bias the inflammatory response toward cavity formation.[4]

In addition to those findings, type-1 immune dominance during TB was shown by the predominance of CD4+ and CD8+ T cells responsive to *M. tuberculosis* antigens by rapid gamma interferon (IFN-γ) and alpha tumor necrosis factor (TNF-α) synthesis. These cells were found in both radiologically involved in pulmonary sites but were conspicuously reduced in areas of cavity formation. Study indicates that proportions of TNF-α and IFN-γ producing cells within both the CD4+ and CD8+ subsets were significantly reduced in TB patients with cavities. However, the IFN-γ and TNF-α responses of both CD4+ and CD8+ T lymphocytes from TB patients were remarkably impaired in those individuals with lung cavities. Cavitation has also been reported to be associated with local neutrophilia and relative lymphopenia. Studies show that TB patients with cavities had higher absolute numbers of neutrophils than did patients with infiltrates. The accumulation of neutrophils together with these impaired *M. tuberculosis* specific lymphocyte responses probably plays an important role in the pathogenesis of cavitary TB.[20]

Secondly, pathogenic factors may also contribute to the process of lung cavity formation where research is still being carried out to look for

these factors. Recently genetic variability and strain differences in *M. tuberculosis* have been considered and thought to have contributed to the pathogenesis of the disease. A few factors responsible for the genetic variation among *M. tuberculosis* complex (MTBC) members have been identified. For instance, the small genetic variation in MTBC could be due to disparity in the location and copy number of an insertion (IS) sequence specific (IS6110) form of *M. bovis* and *M. tuberculosis*. Variation in MTBC could also be due to short DNA sequences known as region of difference (RD).[21] Another study was also found that there were branched-evolved sub-clones with a genetic distance between them of 10 ~ 14 SNPs in cavity lesions of pulmonary TB patient.[22]

From environment factors, study found that smoking was associated with more extensive lung disease and lung cavity.[19,23] This finding was related to impairment of the ability of THP-1 cells and primary human alveolar macrophages in controlling *M. tuberculosis* infection caused by nicotine. One mechanism by which nicotine impairs macrophage control of *M. tuberculosis* is via inhibition of autophagy as nicotine induces NF-κB activation.[24] Another study supported this finding by indicating that the pulmonary immune compartment of smokers compared with nonsmokers is replete with high numbers of alveolar macrophages that demonstrate specific immune impairments that would weaken the host immune response to *M. tuberculosis* infection.[25] Nicotine also has the capacity to inhibit production of proinflammatory cytokines, like TNF-α, IFN-γ, and IL-1β, that necessary for host defense against microbes.[24] It was also found in previous study where *M. tuberculosis* infection of nonsmokers' alveolar macrophages induces a significant increase in TNF-α, IFN-γ, and IL-1β compared with uninfected cells. This increase in key cytokines was not seen in alveolar macrophages from smokers after *M. tuberculosis* infection.[25] Furthermore, nicotine can also promote phenotypic expression of other Th cell types, specifically promote Th2 adaptive immune response, that can deleteriously impact host immunity against *M. tuberculosis*.[24]

Malnutrition and lung cavity formation in pulmonary tuberculosis

Nutritional status is one of the most important determinants of resistance to infection. It is generally known that immune system impairment is linked to dietary deficiencies. Infection can cause nutritional stress and weight loss, which can affect immune function and nutritional status while malnutrition reduces cell-mediated immunity and increases susceptibility to infection.[26] In 2013, WHO issued its first guidelines on nutritional care and nutritional support for patients with TB. In this guideline, WHO emphasizes that all patients with active TB receive individual nutritional assessment and management, including dietary counselling and nutritional interventions, to improve nutritional status so that it is hoped that it can prevent TB treatment failure.[27] Malnutrition without disease and disease-related malnutrition has established may coexist in TB patients, once an active disease has developed. The latter is frequently triggered by a combination of appetite loss, malabsorption, and/or catabolism triggered by inflammation. Chronic malnutrition is characterized by a reduced body mass index (BMI). According to studies, malnutrition affects 50% to 57% of TB patients.[28]

Study from Boston University about effect of malnutrition on radiographic findings in pulmonary tuberculosis found that those with severe malnutrition were more likely to have lung cavity (OR 3.4, 95%CI: 1.2-9.8) from univariate analysis and in adjusted multivariable analysis, subjects with severe malnutrition were more likely to have lung cavity (adjusted OR 4.6, 95%CI: 1.5-14.1, p=0.03) than those with normal BMI, controlling for smoking. These findings were also supported by data from Kazakhstan where lower BMI is found to be one of the factors associated with fibro-cavernous TB identified by the presence of lung cavity. The binary logistic regression showed that lower BMI (unadjusted OR 6.3271, 95%CI: 2.6746-14.9673, p<0.0001) was associated with fibro-cavernous TB; and multivariate logistic regression analysis confirmed that lower BMI (adjusted OR 5.719, 95%CI: 2.049-15.965, p=0.001) was significantly

associated with fibro-cavernous TB.[29] It is likely that malnutrition has an immunomodulatory effect because it has been found to be linked to more severe radiographic illness. The term nutritionally acquired immune deficiency syndrome refers to the primary cause of acquired immunodeficiency, which is malnutrition. Effective innate and adaptive immune response, typified by a potent T-helper 1 response and granuloma formation, is required for *M. tuberculosis* containment. Malnutrition has been associated to increase T-helper 2 and T-regulatory cells while decreasing T-helper 1. This also may be due to activation of inflammatory process in particular, the presence of nutritional deficiencies and is associated with increased lung inflammation in malnutrition. In the event that these combined impacts on the immune system change the aetiology of TB in the setting of malnutrition and lead to more lung cavity.[9,29]

Another study conducted by Kim, et al[14] with mean BMI 21.8 (18.2-25.4) kg/m^2 showed that from univariate analysis, BMI (unadjusted OR 0.90, 95%CI: 0.84-0.96, p=0.002) was significantly associated with cavitary TB. Moreover, from its multivariate analysis, BMI (adjusted OR 0.88, 95%CI: 0.81-0.97) was significantly associated with cavitary TB after adjusting for age, sex, BMI, previous history of TB, smoking, comorbidities, initial AFB smear, NAAT, and bilateral involvement in chest x-ray.[14] These findings were also supported by study conducted by Koo, et al[30] showed that BMI was significantly associated with the presence of cavities (OR 0.824, 95%CI: 0.67-1.01).[30] There have been reports that BMI is inversely associated with the risk of TB. This means obesity presented a protective effect, while a lower BMI was associated with the development of TB and higher TB-related mortality. In their study population, it is found that lower BMI was related to the presence of lung cavity and leading to poor compliance to treatment in pulmonary TB patients. The host's immunity and the preponderance of T-helper-2 CD4+ cells in the alveoli are linked to lung cavity formation in TB patients. A lower BMI is correlated with higher pulmonary inflammation and free neutrophil elastase activity in the lungs and is indicative of a dietary insufficiency. The development of a cavity in pulmonary TB may be influenced by a number of circumstances linked to a reduced BMI, including chronic energy shortage, recurrent pulmonary inflammation, increased oxidative stress, and changed in body composition.[14,30]

Besides BMI, another component defining malnutrition is biochemical marker, such as albumin and neutrophil/lymphocyte ratio (NLR). The study investigated the association between pre-treatment immunonutritional status and lung cavity in patients with pulmonary TB in Japan has another supporting result. Compared with patients in the non-cavitary TB group, patients in the cavitary TB group had significantly higher neutrophil and platelet count, with marginally low lymphocyte count and serum albumin level. Regarding NLR, prognostic nutritional index (PNI), platelet to lymphocyte ratio (PLR), and BMI, the cavitary TB group had significantly higher NLR and PLR than the non-cavitary TB group (p=0.005 and p=0.009, respectively). In univariate analyses, low serum albumin (<3 g/dL), high neutrophil count ($\geq$6000/mm^3), low lymphocyte count (<1000/mm^3), high NLR ($\geq$5), and high PLR ($\geq$200) were associated with lung cavity. Further in the multivariate analysis, statistically significant associations were observed between lung cavity and high NLR and low serum albumin level (p=0.014 and p=0.025, respectively). An increase in neutrophils, as the main cells engaged in inflammation and the host's defense against bacterial infection, has been linked to a decrease in lymphocyte count. A lower lymphocyte count, which is indicated by an increased NLR, may lead to a weaker lymphocyte-mediated immune response. It is also conceivable that changes in the relative proportions of circulating lymphocytes could affect the development of lung cavity because macrophages and T lymphocytes play crucial roles in lung cavity in pulmonary TB patients. The results of the present study indicated that malnutrition and increased severity of inflammation might be associated with lung cavity in pulmonary TB patients.[31]

Conclusion

Malnutrition is a condition resulting from lack of intake or uptake of nutrition that leads to altered body composition and body cell mass leading to diminished physical and mental function and impaired clinical outcome from disease. In pulmonary TB patients, there are two types of malnutrition that can be taken place: malnutrition without disease and disease-related malnutrition. Malnutrition itself can be described from body composition using BMI and biochemical marker using NLR and albumin. According to some studies, lower BMI and changing in immunonutritional status, indicating malnutrition condition, is more predominating in pulmonary TB patients with cavity. Malnutrition needs to be treated since it is linked to increased cavitation and the severity of the disease in pulmonary TB. All viable strategies should be assessed and tailored to the needs of the nation as we work toward the End TB goals in 2030 as stated by WHO.

Conflict of Interest

The authors declare that there is no conflict of interest regarding this article.

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ORIGINAL PAPER

Correlation of energy intake and physical activity with visceral fat in obese office workers

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Abstract

Background: Obesity is a global health problem with a continuing trend of increasing population. A positive energy balance, where energy intake is more remarkable than energy expenditure, will cause fat accumulation. Obesity due to the expansion of fat, especially visceral fat, is a risk factor for noncommunicable diseases. Office employees can become obese with a high-calorie diet and a sedentary lifestyle. This study aims to determine the correlation between energy intake and physical activity with visceral fat in obese office workers.

Methods: This cross-sectional study was conducted on obese office staff at RSCM. Energy intake was assessed with 3 x 24-h food recalls. Physical activity was assessed with the GPAQ questionnaire, and visceral fat was considered with multifrequency BIA.

Results: A total of 66 study subjects with an average age of 41 years were women and included in the category of obesity degree I. Almost all subjects had abnormal visceral fat volume with a median of 2.95 L (1.3 – 8.5 L). Most have more energy intake, with an average intake of 2196 ± 467 kcal. Most had moderate physical activity with a median value of 1850 MET (120 – 4680 MET). There was a moderate correlation between energy intake and visceral fat (r=0.554, p<0.001) and a weak correlation between physical activity and visceral fat (r=-324, P=0.008).

Conclusion: There was a moderate correlation between energy intake and visceral fat and a weak correlation between physical activity and visceral fat.

Keywords: obese, workers, visceral fat, energy intake, physical activity, 24-h food recall, GPAQ

Introduction

Obesity is a public health problem worldwide and a severe problem in developing countries.[1] Obesity occurs due to excess accumulation of body fat. Visceral fat accumulation is associated with central obesity. Increased visceral fat will result in insulin resistance, which is the basis of abnormalities in

metabolic syndrome.[2] Metabolic syndrome due to visceral fat is a risk factor for non-communicable diseases, such as cardiovascular disease, hypertension, and diabetes mellitus.[3] The World Health Organization (WHO) states that noncommunicable diseases acquired from metabolic syndrome are the most significant cause of death worldwide, which causes 41 million deaths each year or 71% of causes of death globally.[4]

Fat accumulation in obesity results from energy imbalance when energy intake from food or diet is higher than energy expenditure. Energy expenditure consists of basal metabolism,

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thermogenesis, and physical activity.[5] Positive energy balance that occurs continuously will lead to obesity and fat accumulation, especially abdominal or central obesity.[6] Research conducted by Widiantini et al. of office employees with a State Civil Apparatus status of 1,119 employees, 48.3% were obese, where office employees had a lifestyle with a high-calorie diet and a sedentary lifestyle. In this study, physical activity was found to have a significant relationship with obesity with a value of p = 0.000, but there was no significant relationship between energy intake and obesity.[7] This differs from the results of a study conducted by Christina et al.,[8] which shows a significant relationship between energy intake and obesity in-office employees. Strategies for preventing and managing central obesity with a negative energy balance are associated with decreased visceral fat. Still, whether physical activity has a role or diet is hypocaloric is unclear. [9]

Methods

Study population and design

A cross-sectional study was conducted on office workers in dr. Cipto Mangunkusumo Hospital, Jakarta, Indonesia, from August 2022 to September 2022. Subjects were recruited using consecutive sampling, with the inclusion criteria being older than 18 years old and a body mass index (BMI) $\geq$ 25 kg/m^2. Subjects who cannot be checked for body composition (pacemaker, prosthesis, unable to stand, oedema), pregnant, taking drugs that can inhibit the absorption of nutrients and physical disabilities are excluded. This study's primary outcome was the correlation between energy intake and physical activity with visceral fat in an obese office worker.

Data collection

Subjects were interviewed for age, sex, ethnicity, and smoking status. Weight measurement was taken using an electronic scale (SECA) with a precision of 0.1 kg, and height measurement was taken using a stadiometer. Body mass index (BMI) was calculated as weight in kilograms per height in

meters squared (kg/m^2). Visceral fat was assessed with Multifrequency bioelectrical impedance analysis (BIA) under SECA Body Composition Analyzer 525. SECA Analytics 115 software will read the subject's body composition. Food intake was analyzed using a 3x24-hours food recall. Food book photos were used to visualize the food intake and gave aid in the food portion size estimation. The food intake data was put into Nutrisurvey using the United States Department of Agriculture (USDA) database. Physical activity was assessed using the Global physical activity questionnaire (GPAQ).

Ethical approval

Ethical permission was obtained from Committee for Ethics in Research, Faculty of Medicine Universitas Indonesia (No. KET-977/UN2.F1/ETIK/PPM.00.02/2021 and protocol number 21-10-1069).

Statistical analysis

Data were analyzed using Windows's Statistical Package for the Social Sciences (SPSS) version 26. Normal data distribution was assessed if the p-value >0.05 using the Kolmogorov-Smirnov test. Mean and standard deviation was used to describe normally distributed data, and median with minimum-maximum values was used otherwise. Pearson or Spearman correlation tests were used to analyze the correlation between variables, with a p-value <0.05 considered significant. A linear regression test was used to ascertain the variables.

Results

A total of 66 participants were enrolled in this study. The total number of RSCM employees in 2022 is 5,148 people. The mean age of the research subjects was 41 years. The subjects came from the Javanese tribe (60.6%). There were 17 people (25.8%) who had smoking habits. The results of the anthropometric distribution showed that the

Table 1. Characteristics of the study participants

Characteristics	n = 66
Age (year)	$41,97 \pm 9,57$*
Sex (n, %)	
Male	30 (45,5%)
Female	36 (54,5%)
Weight (kg)	74,1 (58,5 – 129,4) †
Height (cm)	$160,3 \pm 8,3$*
Smoking (n,%)	
No	49 (74,2%)
Yes	17 (25,8%)
BMI (kg/m^2)	29,5 (25 – 48,5) †
Obese class I (n, %)	35 (53%)
Obese class II (n,%)	31 (47%)
Visceral fat (L)	2,95 (1,3 – 8,5) †
Normal (n, %)	5 (7,6%)
Upnormal (n, %)	61 (92,4%)
Physical activity score (MET)	1850 (120 – 4680) †
Light	18 (27,3%)
Medium	33 (50%)
Vigorous	15 (22,7%)
Energy intake (kcal)	2196 ± 467*
Insufficient	4 (6%)
Sufficient	17 (26%)
Excessive	45 (65%)
Protein (g/kg)	1 (0,5 – 1,8)†
Fat (%)	34 ± 4*
Carbohydrate	54 ± 5*

median value of BMI was 29.5 kg/m2; 35 people (53%) had grade I obesity nutritional status, and the rest had grade II. The results of the distribution of visceral fat values were 2.95 L. Sixty-one subjects (92.4%) had abnormal (increased) visceral fat, and the rest were normal. Subjects' physical activity values showed a median of 1850 MET, and most had moderate physical activity. Characteristics of the participants can be seen in **Table 1** above.

The correlation between energy intake and physical activity with visceral fat is presented in **Table 2**. There was a statistically significant correlation using the Rank Spearman correlation test.

Table 2. Correlation between energy intake and physical activity with visceral fat

Variable	Visceral fat	
	Correlation coefficient	P value
Energy intake	0,554	<0,001
Visceral fat	-0,324	0,008

*statistically significant (*p<0.05)*

Discussion

Participants were mostly female, 41 years old, and obese grade I. Prevalence study on American women, 65% of them are obese at the age of 40 to 59 years, and 73.8% are obese after entering the age of 60 years.[10] Women who enter perimenopause, namely aged 40-59 years, there will be a decrease in ovarian function which results in a reduction of energy expenditure, and if energy intake is not reduced, it will result in an increase in fat mass and redistribution of abdominal fat.[11]

There were 17 subjects (25.8%) who had smoking habits. Obesity and smoking have the pathogenesis of inflammatory disorders with almost the same characteristics, so they mutually increase oxidative stress. Chronic exposure to toxic substances and inhaled particulate matter from second-hand smoke is an important effector of oxidative stress during smoking. In obesity, especially characterized by metabolic disorders, greater accumulation of fatty acids in adipose tissue alters the metabolic profile of cells, increasing free fatty acids, which activate stress signals, inflammatory processes, and the production of inflammatory mediators. Molecular signalling, smoke-induced inflammation, and obesity involve increased oxidative stress, followed by activation of innate immune responses, particularly affecting adipose tissue in obesity and airway epithelial cells in smokers, which have important roles in the pathogenesis of the disease.[12]

The subject's median BMI was 29.5 kg/m2, with the lowest BMI of 25 kg/m2 and the highest BMI of 48.5 kg/m2. The number of subjects with obese class I was 35 people (53%). The study by Kunyahamu et al.[13] showed a fairly high prevalence of obesity among health workers, reaching 54.2%. An increase in a person's BMI will increase the risk of suffering from DM and cardiovascular disease.[14] In the last two years, the government has implemented work-from-home regulations (WFH) to prevent transmission of COVID-19 during a pandemic. Coskun study et al. show an increase in the average BMI from 24 kg/m2 before the pandemic to 24.9 kg/m2 during the pandemic, as well as an increase in the amount of time doing sedentary activities from 7.7 hours/day before the pandemic to 10.6 hours /day during the pandemic.[15] The median value of the subject's visceral fat volume was 2.95 L, with a range of values from 1.3 to 8.5 L. In this study, 61 subjects (92.4%) had increased or abnormal visceral fat volume. Westphal et al.[16] study assessed body composition using the BIA SECA 252 and obtained an average Asian ethnic visceral fat volume of 1.9 ± 1.1 L.

Subjects had less energy intake by 6% but had a nutritional status of obesity. Various factors could cause this, including because the subject reported food intake that was less than actual food intake (flat slope syndrome) or lower energy expenditure that resulted in a positive energy balance which made the subject become obese.[17] Sixty-five percent of the subjects in this study had excess energy intake, and the subjects had a habit of eating foods with high-calorie density at breakfast, lunch, and dinner. At breakfast and lunch, the subjects bought food around the RSCM environment, so a strategy is needed in community settings to regulate the intake of employees at RSCM. According to a study by Onufrak et al.[18] the food available at work had low dietary quality providing unhealthy food in vending machines, canteens, and catering available at work.

One factor that has been known to trigger obesity is unhealthy food with a high energy density of food, namely the energy content of more than 225 – 275 kcal per 100 g of food. Fast food causes obesity (obesogenic) because it has a high energy density and a composition that contains high levels of saturated fatty acids and trans fats, processed starch, and added sugar.[6] Health promotion programs to promote healthy behaviour, such as nutritional counselling, setting up smoking-free area policies in the workplace, insurance, and work environment support in providing healthy food choices in canteens or cafeterias, have proven effective in changing healthy behaviour among employees.[18]

The median value of the subject's physical activity was 1850 MET with a minimum value of 120 MET and a maximum value of 4680 MET. 18 subjects (27.3%) were included in the light physical activity category, 33 subjects (50%) were categorized in moderate physical activity, 15 subjects (22.7%) were included in the heavy physical activity category. In the study conducted by Saridi et al. on the subject of health workers in a Middle Eastern country, it was known that 37.8% of administrative employees had light physical activity, 48.6% had moderate physical activity, 13.5% did vigorous physical activity.[19]

According to existing literature, physical activity and nutrition interventions involving counselling, education, and group work activities showed significant changes in sedentary behaviour and eating habits, improving physical and mental

health, thereby reducing health care costs and employee absenteeism.[20] There was a significant moderate correlation between energy intake and visceral fat (r=0.554, p<0,001); this was consistent with a study in India in a population of women with a BMI of more than 24.9 kg/m2 (r=0.451, p≤0.05).[21] There was a significant correlation between energy intake and visceral fat. Still, it has a moderate correlation strength in this study. The population of women aged 40–50 years can experience a decrease in estrogen, which affects BMR. [11] BMR has a significant relationship with visceral fat (r=0.332, p=0.018).[22]

Each excess energy from food intake of 1% per day is estimated to cause an increase of 10 kg of fat mass in a decade.[23] There was a significant weak correlation between energy intake and visceral fat (r=-0.324, p=0,008); this was consistent with Lagzdina and Rumaka[24] study found a weak negative correlation between physical activity and visceral fat with a value of r = -0.379. The results of this study follow previous research conducted by Rosa and Riamawati[25] on office employees, namely that there is a significant relationship between physical activity and the incidence of central obesity, which is a physical manifestation of high levels of visceral fat (p=0.028; OR=5.40). This differs from the research conducted by Kurniasanti[26] which found a non-significant relationship between physical activity and visceral fat (p>0.05). One of the systematic studies by Andos et al.[27] reported that individuals and the social environment had a relationship to sedentary behaviour. Based on cross-sectional studies and longitudinal studies, smoking habits, drinking alcohol, and short sleep periods affect physical activity carried out during free time.

Conclusion

There was a significant moderate correlation between energy intake and visceral fat and a significant low correlation between physical activity and visceral fat in obese office workers. This study aligns with the guidelines for managing obesity: energy intake and physical activity have a role in reducing body weight and fat mass. Currently, obesity therapy management

emphasizes comprehensive lifestyle change interventions, primarily by reducing energy intake, eating a healthy diet with balanced nutrition, and increasing physical activity.[28]

Conflict of Interest

The authors have no conflict of interest in this study. No educational grant is provided to the authors.

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ORIGINAL PAPER

The relationship of vitamin A, C, and E intake with premature aging of facial skin in female market traders

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Abstract

Background: Women's market traders are jobs that are often exposed to free radicals, including air pollution, cigarette smoke, sun exposure and have a high workload that causes stress. Antioxidants can protect the skin from free radicals and can inhibit the process of premature aging of facial skin which are found in vegetables and fruits such as vitamins A, C, E.

Objective: To determine the relationship between intake of vitamins A, C, and E with premature aging of market traders in the form of wrinkles around the face.

Methods: Observational research with cross sectional method. The sampling technique is multi-stage cluster sampling. This research was conducted at Beringharjo Market with a total sample of 172 respondents with inclusion criteria namely female traders, aged 26–45 years, workers in the market area. The exclusion criteria are tourists/market visitors, women who are pregnant and breastfeeding. The research variables for intake of vitamins A, C, and E used the SQ-FFQ (Semi-Quantitative Food Frequency Questionnaire) questionnaire with the interview method. In measuring the number of wrinkles on facial skin using photoaging through facial shooting using a Sony A7R3 camera with a 24-70 lens that is analyzed by a dermatologist (skin expert). Data analysis technique using multiple logistic regression analysis. This analysis uses SPSS software version 22.0.

Results: In the multiple logistic regression test, p = 0.037 (p <0.05) means that there is a relationship between vitamin A intake and premature aging of facial skin. On vitamin C intake, p = 0.436 (p> 0.05), meaning that there is no relationship between vitamin C intake and premature aging of facial skin. And on vitamin E intake, p = 0.171 (p> 0.05) there is no relationship between vitamin E intake and premature aging of facial skin.

Conclusion: Intake of vitamin A has a significant relationship with the occurrence of premature aging of the face, but vitamins C and E do not have a significant relationship with the occurrence of premature aging of the facial skin

Keywords: premature aging, intake, vitamin A, vitamin C, vitamin E

Introduction

The skin is the outermost organ that is directly exposed to a pro-oxidative environment and is equipped with a complex system of antioxidants and enzymes, including a redox-active antioxidant network. There are several measures to slow down aging, including exercising and consuming enough food low in calories and fat, lots of vegetables and fruit, and enough protein.[1] Aging of the skin is a natural occurrence that affects everyone. The natural process of aging in humans begins about the third decade of life, and the symptoms grow more noticeable as one gets older. Premature aging, often known as skin aging, can affect anyone.[2]

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Antioxidants are potentially an important group of pharmacological agents that can prevent and reduce the severity of skin damage caused by numerous factors, including UV rays and skin aging. A new formulation method can increase the protection of the skin against sun damage using topical vitamins C and E, achieving much greater protection than was previously possible with ingestion.[3]

The body has antioxidants as the body's defense mechanism to neutralize free radicals that are formed. The mechanism of damage caused by free radicals is quite complex through a chain reaction until oxidative stress occurs which causes cell damage. This knowledge of free radicals leads us to the role of free radicals in skin disorders. The addition of antioxidants in the diet or directly applied to the skin topically to prevent the formation of free radicals is theoretically beneficial. This encourages many pharmaceuticals to produce various antioxidants in the diet or directly applied to the skin topically. Antioxidants work synergistically to stabilize free radicals that play a role in photo aging, carcinogenesis, and immunosuppression.[4]

Women's market traders are jobs that are often exposed to free radicals, including air pollution, cigarette smoke, exposure to sunlight and high physical and mental workload causing work stress. Higher stress levels are often found in women. This is because women's brains have a negative awareness of conflict and stress. Antioxidants can protect the skin from free radicals and can inhibit the process of premature aging of facial skin found in vegetables and fruit. There are three kinds of the mechanism of action of antioxidants on free radicals, namely, (1) Primary antioxidants capable of reducing dismutase (SOD), glutathione peroxidase, and stable catalase. For example, superoxide can convert superoxide radicals into molecules turning them into more products. (2) Water antioxidants form new free radicals by breaking the chain and secondary reactions that play a role in binding free radicals and preventing the amplification of radical compounds. For example, vitamins A (beta-carotene), C, and E and phytochemical compounds. (3) Tertiary antioxidants play a role in bio molecular

mechanisms, such as repairing cell and tissue damage caused by free radicals.[5] Research proves that the effective use of antioxidants is by giving them together according to the antioxidant network.[4] The combination of antioxidants that are reported to give the best results is a combination of vitamins C and E. According Indonesian Recommended Daily Intake (RDA) by Ministry of Health Regulation 2019, the required vitamin adequacy rate in a day is 600 RE for vitamin A, 75 mg for vitamin C, and 15 mcg for vitamin E.[6] Adequate physical activity, in addition to ensuring the adequacy of vitamins delivered appropriately, can aid in the process of adapting or adjusting to the changes encountered, as well as preserving the body's cell turnover to prolong life.[1] According to the above definition, the problem studied in this study is "is there a relationship between vitamin A, C, and E intake and the occurrence of fast facial aging process?" The findings of this study are expected to be used as educational material for the public about the necessity of leading a healthy lifestyle in order to prevent the rate of premature face skin aging.

Methods

This research is an observational type with cross sectional method. This research took place in the Yogyakarta area at Beringharjo market traders which are in the city center as a center for tourist souvenirs. This study used a multi-stage cluster sampling method with a total sample of 172 respondents with inclusion criteria, namely female traders, workers in the market area, aged 26-45 years. And the exclusion criteria are tourists/market visitors, pregnant and lactating women.

The sampling process is obtained in a two-level stage. In this study, the total population was 211,331 women of childbearing age in Yogyakarta and the target population was 6,627 market traders at Beringharjo Market. Then, in Beringhajo Market, it is divided into 4 market blocks. The 4 market blocks consist of the west block (1,678 traders), the middle block (582 traders), the east and north blocks (2,544 traders). The 4 blocks were randomly selected based on research criteria, so

that 172 samples were obtained consisting of the west block (55 traders), the middle block (25 traders), the east block (52 traders) and the north block (40 traders). To collect data on intake of vitamins A, C, and E using the SQ-FFQ (*Semi-Quantitative Food Frequency Questionnaire*) questionnaire with the interview method. In measuring the number of wrinkles on facial skin using photoaging through facial shooting using a Sony A7R3 camera with a 24-70 lens that is analyzed by a dermatologist (skin expert). Data analysis technique using multiple logistic regression analysis. This analysis uses SPSS software version 22.0. Furthermore, this research has received ethical approval from the Research Ethics Committee, Faculty of Medicine, Universitas Sebelas Maret, ethically approved with No. 91/UN27.06.6.1/KEP/EC/2021.

Results

The respondents in this study were women aged 26–45 years. The age is classified by the 2009 Ministry of Health, namely early adulthood (26–35 years) and late adulthood (36–45 years). Based on **Table 1**, the average age of most respondents aged 36-45 years as many as 126 people (73.25%).

With an average high school education of 93 people (54.06%), and an average income of < IDR 1,500,000 for 106 people (61.62%) and most of the respondents did not do facial treatment for as many as 141 people (81.97%).

Table 1 Characteristics of subject

Category	Total	
	n	%
Age		
- 26–35 years	46	26.74
- 36–45 years	126	73.25
Education		
- no school	3	1.74
- not completed elementary school	2	1.16
- elementary school	30	17.44
- junior high school	29	16.86
- senior high school	93	54.06
- vocational school 1 (diploma 1)	1	0.58
- vocational school 3 (diploma 3)	10	5.81
- undergraduate degree	4	2.32
Income		
- < IDR 1,500,000	106	61.62
- > IDR 1.500.000 – 2,500,000	55	31.97
- > IDR 2,500,000 – 3,500,000	5	2.90
- > IDR 3,500,000 - 5,000,000	6	3.48
- > IDR 5,000,000	0	0
Facial treatment		
- Yes (use skin care products)	31	18.02
- No (without skincare products)	141	81.97

Based on **Table 2**, it is known that intake of vitamin A 600 RE is 44.76%, intake of vitamin A 600 RE is 55.23%. Intake of 75 mg of vitamin C was 40.69%, intake of 75 mg of vitamin C was 59.30%. As for the intake of vitamin E 15 mg as much as 100%. Results Based on multiple logistic regression there is a relationship between vitamin A intake and premature aging of facial skin p-value of 0.037 (p <0.05). There is no significant relationship between vitamin C intake and premature facial skin aging in female market traders at Beringharjoh p-value (0.436) > 0.05. There is no significant relationship between vitamin E intake and premature skin aging in female market traders at Beringharjo p-value (0.171) > 0.05.

Table 2. Multivariate analysis of the relationship of vitamin A, C, and E with premature aging of facial skin

Consumption	Total		Premature Aging
	n	%	p-value
Vit A			
≥ 600 RE	77	44.96	0.037
≤ 600 RE	95	55.23	
Vit C			
≥ 75 mg	70	40.69	0.436
≤ 75 mg	102	59.30	
Vit E			
≥ 15 mg	0	0	0.171
≤ 15 mg	172	100	

Discussion

Based on the results above, vitamin A intake has a significant relationship with the occurrence of premature aging of the face, but vitamins C and E do not have a significant relationship with the occurrence of premature aging of the facial skin. Retinol and other vitamin A preparations such as are said to have antiaging effects.[7] Other studies that are in line with this study state that the content of vitamin A in carrots used in mask preparations can overcome various kinds of problems on facial skin, especially facial skin with acne.[8] The antioxidant content in carrots is very high so it can prevent dry skin on the face due to air pollution. Vitamin A (retinol) and its derivatives (retinaldehyde and tretinoin) are a group of agents that also have antioxidant effects. They can induce collagen biosynthesis and reduce the expression of MMP 1 (collagenase 1). Retinol, at present, is the substance most commonly used as an anti-aging compound and, compared to tretinoin, causes less skin irritation. It has been shown that retinol has a positive effect not only on extrinsic but also on intrinsic skin aging and has a strong positive effect on collagen metabolism.[9] Vitamin A has a role as an antioxidant by donating electrons from its atoms to free radicals to bond with unpaired electrons (single) from free radicals without becoming new free radicals. In addition, vitamin A also functions to maintain cell membrane stability against free radicals.[10]

Under normal conditions, the addition of antioxidants in the diet or directly applied to the skin topically to prevent the formation of free radicals is not necessary. However, excessive UV exposure will cause antioxidants in the stratum corneum to be susceptible to depletion. In addition, the aging process can also reduce the levels of antioxidants formed.[4] Free radicals are to fault for cellular and tissue damage as grow older. Free radicals are the primary cause of aging, which is thought to be the only significant process influenced by genetic and environmental variables; oxygen free radicals are responsible for cellular and tissue damage (due to their higher reactivity). Humans have a complex antioxidant system that includes both enzyme-based and non-enzymatic antioxidants that work together to protect cells and organ systems from free radical damage. Glutathione peroxidase, catalase, and superoxide dismutase are examples of enzyme antioxidants. Vitamin E, vitamin C, thiol antioxidants (glutathione, thioredoxin, and lipoic acid), melatonin, carotenoids, natural flavonoids, and others are examples of non-enzymatic antioxidants.[11]

Vitamin A is an active ingredient needed by the body in maintaining a healthy body through the cell cycle mechanism.[11] Vitamin C as an antioxidant works to catch free radicals in the skin. The three main functions of vitamin C in the skin are a strong antioxidant that protects the skin against the negative effects of external factors such as pollution, sun, climate, air conditioning, cigarette smoke, etc., stimulates the formation and increased

production of skin collagen, which will maintain skin elasticity, flexibility, and smoothness, and brightens the skin.[12] In the discussion, the new formulation method can increase the protection of the skin against UV damage using topical vitamin C and E stabilized by ferulic acid.[3] Ferulic acid has many uses for human skin, namely anti-inflammatory, anticancer, photoprotective agent (sunscreen), delaying the photoaging process of the skin, and brightening component. The most active component of vitamin E is alpha-tocopherol. Vitamin E has an important function as an antioxidant. An antioxidant can ward off free radical attacks that will damage cells, preventing the body from being damaged by free radical attacks.[3]

Based on the above theory, this is inversely proportional to the results of research conducted where the intake of vitamins C and E has no direct significant relationship to the occurrence of premature aging of the facial skin This is influenced by the low income of these traders, making it difficult for traders to suffice and complement the needs of the foodstuffs they consume. This can be seen from the average trader income < IDR 1,500,000 as much as 61.62%. Based on the results of this study, it was found that the consumption level of vitamin C intake in market traders was on average less than the daily requirement, namely as much as 59.30% and as much as 100% of vitamin E. The lack of consumption of vitamin C and E intake is due to the lack of purchasing power of traders in buying fruits for consumption. In addition, the lack of knowledge of respondents in terms of knowing which types of food ingredients contain high levels of vitamins C and E as well as the number of vitamins needed in the body. In general, the function of vitamins is as an antioxidant.

The education level of the respondents in this study averaged 54.06% high school graduation. The lack of education and outreach to market traders regarding the importance of consuming vitamin intake, especially vitamins C and E, makes these vitamin intakes less consumed. In addition, there are still several types of food ingredients whose nutritional value of micronutrients is not detected in analyzing vitamin intake, which makes it difficult for this study to determine the amount of these nutrient intakes. The results of this study are almost the same as previous studies which shows that there is no correlation between vitamin E levels in serum and the degree of severity of acne vulgaris.[13] The low income of market traders makes it difficult for market traders to buy foodstuffs high in vitamin E, in the form of vegetable oils, nuts, seeds, meat and milk as well as vitamin E supplements or topical preparations used as components of skin products.

The age factor is revealed to play a function in the premature aging of the face in this study. Premature facial aging is most common between the ages of 35 and 45. This occurs as a result of a lack of facial maintenance. There were 31 people who did face treatments (18.08%) and 141 people who did not (81.97%). One of the key necessities of modern women who will support their activities is skin and facial care. Every woman aspires to have a flawless appearance, not only in terms of clothing but also in terms of face and bodily beauty, which is a top priority in terms of appearance. Because a woman's confidence will be improved by her appearance.[14] The appearance and performance of traders is the attractiveness of the strategy of market traders in promoting and selling their wares. However, the high cost of performing facial skin care is one of the reasons people rarely get treatment, especially for market traders.[15]

The aging process is significantly influenced by nutrition, which benefits both physical and cognitive function [16]. The total daily requirement for vitamin A for those aged 19 to 64 is 600 RE, 75 mg of vitamin C, and 15 mcg of vitamin E, according to the 2019 Nutrient Adequacy Rate (RDA).[6] However, many respondents' intake levels in this study still fell short of what is considered to be an adequate threshold for these substances. The average respondent in this study consumed chicken meat and carrot vegetables. so that vitamin A intake is sufficient. Respondents rarely buy and consume fruit because respondents prioritize staple foods and side dishes compared to vegetables and fruit. Additionally, according to the study's findings, many respondents still do not receive face treatments. The respondents' average income level, which is rather low, has an impact on this.

Therefore, one of the reasons the outcomes of this study are not significant is because of their findings. Repeated facial expressions, the impact of heat, sleeping posture, gravity, way of life, such as smoking, pollution, and exposure to sunshine, particularly UV rays, are additional external variables that contribute to skin aging.[17]

This study only looked at the food intake in the sample, so it did not describe the direct effects of consuming foods sourced from vitamins A, C and E. In addition, this study only looked at the subjective results of photoaging without biochemical tests such as (SOD, glutathione, vitamins A, C, E) from blood and other clinical trials. Meanwhile, in a study conducted in Thailand, they developed a combination of anti-aging skin multi-herbs which they gave to participants for 60 days. Results from a randomized, double-blind, placebo-relief trial showed that the emulsion containing the extract combination significantly improved skin hydration and skin elasticity which contributed to an increase in skin wrinkling after 60 days compared to the emulsion base.[18]

Conclusion

In conclusion, the intake of vitamin A has a significant relationship with the occurrence of premature aging of the face, but vitamins C and E do not have a significant relationship with the occurrence of premature aging of the facial skin.

Conflict of interest

The authors declare that there is no conflict of interest related to this article.

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ORIGINAL PAPER

Prevalence of hypertension and obesity among non-academic staff in a Nigerian University

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Abstract

Background: The aim of achieving a healthy society has motivated and led many researchers to understand the prevalence of diseases to create awareness and assess interventions' effectiveness.
Objective: This study determines the prevalence of hypertension and obesity among the non-academic staff of the Federal University of Agriculture, Abeokuta.
Methods: The study design was descriptive and cross-sectional. 300 Non-academic staff of the institution were randomly selected and data were obtained on their sociodemographic and socioeconomic characteristics, predisposing risk factors of hypertension, anthropometry, and blood pressure measurements using a structured self-administered questionnaire and standard procedures. Data were analyzed and presented using descriptive and inferential statistics. Statistical significance was established at p<0.05.
Results: The mean age was 42±8.0years**,** there were more female respondents (56.0%) than male respondents (44.0%) and 76.0% of the respondents were married. Results further revealed a high prevalence of overweight and obesity (52%), pre-hypertension and hypertension (40%), and risk of abdominal obesity (84%).
Conclusion: Non-academic staff are an essential component of the workforce and workplace intervention is essential to reduce the work nature risk factor of Obesity and Hypertension to prolong lives, and boost productivity and economic growth.

Keywords: prevalence, hypertension, obesity, university

Introduction

According to World Health Organization (WHO), the global burden of hypertension and other non-communicable diseases (NCDs) is rapidly increasing and the African continent seems to be the most affected region in the world. World Health Organization reported that Africa has the highest prevalence of hypertension (27%) and the number of adults with hypertension increased from 594 million in 1975 to 1.13 billion in 2015, with the highest prevalence in low- and middle-income countries (LMICs).[1,2] The prevalence of hypertension in Nigeria forms a significant part of the total burden in Africa because of the large population of the country currently estimated to be over 170 million.[3] High blood pressure, commonly referred to as a silent killer is a risk factor for stroke, ischemic heart disease, heart failure, and chronic kidney diseases.[4] The World Health Organization (WHO) defines hypertension as systolic blood pressure (SBP) ≥140mmHg and/or diastolic blood pressure (DBP) ≥90mmHg.[2]

On the other hand, overweight and obesity are the leading cause of preventable illness and death in the world today including Nigeria,[5] and poses a

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significant risk leading to chronic health conditions, thus increasing the overall disease burden.[6] Overweight and obesity are the fifth largest risk for global deaths, and one-third of the world's adult population is either overweight or obese.[7,8] Overweight and obesity are increasing worldwide at an alarming rate. According to WHO, about 2 billion adults (36%) are overweight, and 650 million (13%) are considered to be affected by obesity in 2016. Obesity is diagnosed as body mass index (BMI) ≥30.0 kg/m2 and overweight as a BMI range of 25kg/m2 to 29.9kg/m2.[8-11]

Several studies have reported links between overweight, obesity, and hypertension.[12-14] According to Saydah et al.,[12] 35.7% of obese individuals had hypertension in the National Health and Nutrition Examination Survey (NHANES) 1999–2010. There is an increase in the frequency of hypertension with a BMI elevated from the lower limit to the upper limit of normal.[14] Williams et al.,[13] opined that a healthy BMI and waist circumference values reduce blood pressure and cardiovascular risk. There are different mechanisms by which increased weight leads to increased blood pressure, hence, controlling and preventing weight gain and obesity may prevent the development of related co-morbidities including hypertension.[14]

Obesity and overweight pose numerous psychological, social and economic threats.[15] Anoshirike et al.,[5] reported increased risk of temporary work loss such as sick leave and reduced productivity while at work as risk factors of overweight and obesity. In addition to the social and psychological burden of obesity, obesity could result in chronic health conditions such as hypertension, type 2 diabetes mellitus, cardiovascular diseases, cancer, gallstones, and respiratory system problems.[6,16] Agha and Agha[17] also opined that excessive fat accumulation in the body may impair health conditions leading to significant long-term health consequences including the development of diabetes, coronary heart disease, and osteoarthritis as well as increased risk of certain cancers.

Omer[10] in an in-depth review identified the contributing factors of overweight and obesity to include; energy imbalance, reduced physical activity, low socioeconomic status, etc. Anoshirike et al.,[5] also reported that being overweight can be caused by unhealthy eating patterns, such as high consumption of sugar-sweetened soft drinks, snacks, and sweets, low consumption of fruit and vegetable, and habit of skipping breakfast. Hruby and Hu[18] opined that the surge in the prevalence of obesity in low- and middle-income countries (LMIC) has generally been a result of rapid industrialization and the adaptation of sedentary lifestyles as they improve economically.

Problem statement and justification

There are major disparities in the burden of hypertension among low-, middle- and high-income countries and even racially.[19] The WHO African Region has the highest prevalence of hypertension (27%). This increase is mainly due to a rise in hypertension risk factors in those populations including overweight and obesity.[2]

The upsurge of overweight and obesity among the adult workforce has become a global public health concern, and is accompanied by a higher risk of type II diabetes, coronary heart disease, and stroke which leads to substantial healthcare costs, reduced work productivity, and losses due to inability to work.[5,20,21] Among University staff in Nigeria, there is a continued increase in the prevalence of obesity, which may be attributed to the nature of their work, yet poor knowledge of the condition is reported among non-academic employees or workers in a Nigerian university setting.[22,23] In suggesting evidence-based context for government and other health policy planners on strategies to reduce this burden in low-resource settings like Nigeria, it is important to have detailed up-to-date information on the prevalence of hypertension to match this with available resources. This study will, hence, provide information on the prevalence of hypertension and obesity among the non-academic staff of the Federal University of Agriculture, Abeokuta.

Materials and methods

Study area and location

The study was carried out in Abeokuta, which is the state capital of Ogun state in southwest Nigeria. It is situated on the east bank of the Ogun River, near a group of rocky outcrops in a wooded savanna.[24] The study location was within the Federal University of Agriculture, Abeokuta (FUNAAB), a unique and leading institution, and also one of the three specialized Universities of Agriculture in Nigeria. It was established on January 1, 1988, with the triple mandate of teaching, research, and extension guiding its educational and community-based operations.[25]

Study design

This study is cross-sectional and descriptive in design.

Study population

The study was carried out among the non-academic staff of the Federal University of Agriculture, Abeokuta.

Sample size determination

The total number of non-academic staff at the Federal University of Agriculture, Abeokuta was known (1,833). The sample size was calculated using Andrew Fisher's formula, and the estimated sample size was 272 which was increased to 300 for possible dropout.[26] Therefore, 300 respondents were recruited for the study.

Sampling technique and procedure

The total number of non-academic staff of the Federal University of Agriculture, Abeokuta was determined which was 1,833. A simple random sampling was used to select 300 respondents from various departments and units of the institution.

Inclusion and exclusion criteria

Full-time non-academic workers who are healthy and free of obvious disabilities were included whereas pregnant women were excluded from the study.

Data collection

Data on socio-demographic and socio-economic including age, gender, ethnicity, gender, education level, and marital status were obtained using a semi-structured self-administered questionnaire. Anthropometry data such as body weight, height, waist circumference, and hip circumference were measured using standard procedures by trained anthropometrists.[27-28]

Anthropometric measurements were taken twice, and average values were used for data analysis. The Body Mass Index (BMI) was estimated as weight in kilograms divided by height square in m^2 and classified using the WHO standard.[29] Blood pressure measurement comprising of both systolic and diastolic readings was obtained after a minimum of 5 minutes of quiet sitting/rest using a calibrated digital sphygmomanometer with respondents in a sitting position, the feet flat on the floor and the arm placed at the same level as the heart, measurements were taken twice, the average was recorded and classified using a standard procedure.[2,11,30]

Physical activity was assessed using self-reported data on physical activity during an entire week, and classified into high, low, and moderate activity levels.[11,31] Predisposing risk factors of obesity and hypertension were assessed from the list of risk factors of hypertension described by Abdullahi and Jegede.[32]

Data analysis

All statistical analysis with descriptive statistics was carried out using statistical package software (SPSS version 20). Data were summarized using frequency, percentage, mean and standard deviation. The Chi-square test was used to test for a statistically significant association between the dependent and independent variables at $p < 0.05$.

Informed consent

The study involved data collection using structured questionnaire and anthropometry assessment, hence, permission to conduct the study was obtained from the Department of Nutrition and Dietetics, the Federal University of Agriculture, Abeokuta. Respondent's consents were sought before data collection and respondent's information was kept confidential and used strictly for research purpose.

Results

Socio-demographic and socio-economic characteristics of the respondents

Table 1 below described the socio-demographic and socio-economic background of the respondents. The mean age was 42±8.0years and more than half (58.0%) of the respondents were aged 41-60 years. The gender distribution shows that there were more female respondents (56.0%) than male respondents (44.0%). More than three-quarters (80%) of the respondents were Christian and 76.0% of the respondents were married. Only 20% of the respondents earned more than #100, 000 monthly whereas the majority (88.0%) of the respondents had tertiary education. More than half (58.0%) of the respondent's parents were self-employed.

Anthropometric characteristics of the respondent

The anthropometric characteristics of the respondents are depicted in **Table 2** below. The assessment revealed that 48.0% of the respondents were of normal weight while 52% were overweight and obese. The result further revealed that a large percentage (84.0%) of the respondents were at risk of abdominal obesity, while only 16.0% showed no risk of abdominal obesity.

Medical history and risk factors of obesity and hypertension among respondents

Table 3 below described the medical history and predisposing risk factors of obesity and hypertension among the respondents. The result showed that a vast majority (84.0%, 86.0%) of the respondents had no previous medical history of diabetes and hyperlipidemia respectively whereas 42.0% and 40.0% had a medical history of obesity and hypertension respectively. Less than half (20.0%) of the respondents drank alcohol and 4.0% smoked. More than half (64.0%) of the respondents reported that they engage in one or more physical activities regularly.

Blood pressure measurement of the respondent

Figure 1 below described the blood pressure measurement of the respondents. The majority (60.0%) of the respondent had normal blood pressure, while 38.0% and 2.0% were in the pre-hypertension stage and stage 1 hypertension respectively.

Physical activity level of respondents

Figure 2 below described the physical activity level of the respondents. The majority (66%) of the respondent had moderate physical activity, while 24.3% and 9.7% had low and high activities level respectively.

Relationship between physical activity level and anthropometric measurements of the respondents

Table 4 below showed the relationship between physical activity level and anthropometric measurements of the respondents. The result revealed that there is a significant difference between the physical activity level and Body mass index of the respondents at p=0.001, whereas physical activity level and respondents' blood pressure measurements were not statistically significant (i.e. p>0.05).

Table 1. Socio-demographic and socioeconomic characteristics of respondents (n=300)

Variable	Frequency	Percentage
Age of the Respondents		
20-30years	66	22.0
31-40years	60	20.0
41-50 years	84	28.0
51-60years	90	30.0
Mean Age of the Respondents		**42±8.0years**
Gender of the Respondents		
Male	132	44.0
Female	168	56.0
Marital Status		
Single	60	20.0
Married	228	76.0
Divorced	12	4.0
Religion of the respondent		
Islam	54	18.0
Christianity	240	80.0
Others	6	2.0
Ethnicity of the respondent		
Yoruba	270	90.0
Igbo	12	4.0
Others	18	6.0
Monthly income of respondents		
<#50,000	108	36.0
#50000-100000	132	44.0
#100001-200000	48	16.0
>#200,000	12	4.0
Educational qualification		
SSCE	36	12.0
NCE	72	24.0
OND	66	22.0
BSc. and above	126	42.0
Occupation of parents		
Civil servant	102	34.0
Self-employed	174	58.0
Others	24	8.0

Table 2. Anthropometric characteristics of the respondent (n=300)

Variable	Frequency	Percentage
BMI		
Normal weight	144	48.0
Overweight	96	32.0
Obese	60	20.0
WHR		
No Risk of Abdominal Obesity	48	16.0
At risk of Abdominal Obesity	252	84.0

BMI- Body mass index
WHR- Waist-Hip ratio

Table 3. Medical history and predisposing risk factors of obesity among respondents (n=300)

Variable	Frequency	Percentage
Do you have a previous medical history of diabetes		
Yes	48	16.0
No	252	84.0
Do you have a previous medical history of obesity		
Yes	126	42.0
No	174	58.0
Do you have a previous history of hyperlipidemia		
Yes	42	14.0
No	258	86.0
Do you have a previous medical history of hypertension		
Yes	120	40
No	180	60
Do you drink alcohol		
Yes	60	20.0
No	240	80.0
Do you smoke		
Yes	12	4.0
No	288	96.0
Do you regularly engage in one or more physical activities		
Yes	108	36.0
No	192	64.0

Table 4. Relationship between physical activity level and anthropometric measurement

Variable	R	R^2	P-value
PAL*Weight	-0.1	0.1	0.11
PAL*BMI	0.2	0.4	**0.001***
PAL*WHR	-0.1	0.1	0.075
PAL*DIASTOLIC	0.5	0.25	0.357
PAL*SYSTOLIC	-0.8	0.16	0.896

PAL- Physical Activity Level
BMI- Body Mass Index
WHR- Waist-Hip Ratio
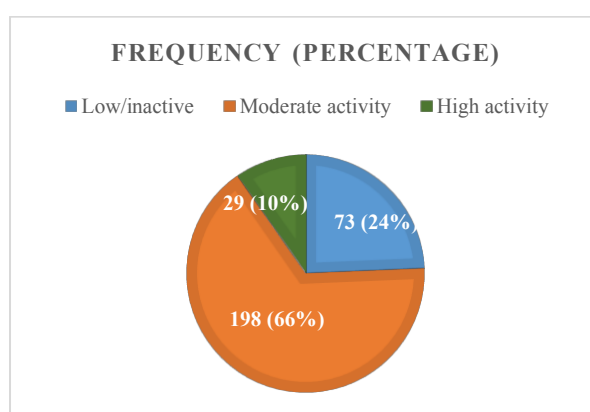
Figure 1. Blood pressure measurement of the respondents
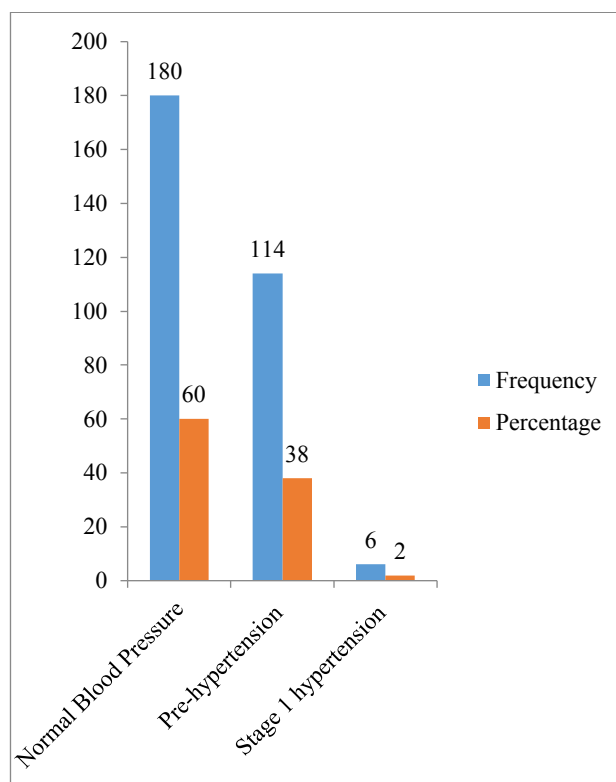
Figure 2. Physical activity level of respondents

Discussion

The increased burden of hypertension and non-communicable diseases among low-income and lower-middle-income countries with the highest prevalence in Africa is a global phenomenon, and has made their prevention an essential component of a global public health initiative.[9,33] Despite the reported prevalence of hypertension in Africa, earlier research reported that poor and undesirable health-seeking behaviors are still prevalent among Nigerians.[34] Adekoya and Sodeinde[35] also stated that Nigerians have inadequate awareness and knowledge of blood pressure, and there is increased practice of risky behavior that predisposes individuals to obesity and hypertension. Hence, this study provides information on the prevalence of hypertension and obesity among the non-academic staff of the Federal University of Agriculture, Abeokuta.

The mean age of respondents in this study agreed with Adedoyin et al.,[30] in a study conducted in Obafemi Awolowo University, Ile Ife, Osun State where the mean age of Non-Academic Staff was 45.6±10.9years. This suggests that the majority of non-academic staff in Nigerian Universities are in the middle adulthood stage. According to the Statista Research Department report of 2018/2019, there are more male non-academic personnel in Nigerian Universities; this study however contradicts the report as there were more female respondents than male respondents.[36] This increased participation of women in the workforce can improve women's empowerment. The majority of the respondents in this study were married. This implies that there are more married workers among non-academic staff. This can improve family income and the nutritional status of households. The result agreed with the study of Abdullahi and Jegede[32] in a study conducted among university staff in Oyo State where majorities (86.0%) of the respondents were married.

Adekoya and Sodeinde[35] in a literature review identified obesity as the major contributory factor of hypertension. The risk of hypertension is substantially increased by being overweight and obese.[14] In a study conducted in Osun State, a

strong significant relationship was established between body mass index, waist circumference, and blood pressure.[30] This study found a high prevalence of overweight and obesity, a high risk of abdominal obesity, and a high prevalence of pre-hypertension and hypertension among the respondents. This could result from a sedentary lifestyle and poor dietary practices among non-academic staff in Nigerian Universities. This high prevalence can pose a threat to health, productivity, and economic development. Dun et al.,[11] in a study conducted in an urbanized community in China reported a high prevalence (40.4%) of overweight and obesity among the respondents establishing that there is a high burden of hypertension, obesity, and overweight in urban areas which can be linked to physical inactivity. A similar study in Osun State reported the prevalence of hypertension among university staff as 34.9%.[30]

The predisposing risk factors of hypertension have been linked with lifestyle choices including physical inactivity, alcohol consumption, smoking, poor diet, obesity, etc.[1,34] However, Adekoya and Sodeinde[35] opined that having a family history of hypertension and obesity are essential risk factors for the condition. This study result showed 42.0% and 40.0% had a medical history of obesity and hypertension respectively. This could be a risk factor for the prevalence of pre-hypertension and hypertension of 40% recorded in this study.

Physical activity is one of the important lifestyle modifications commonly recommended in the prevention and management of hypertension.[33] Williams et al.,[13] also supported that addressing physical activity has proven benefits for blood pressure reduction. The World Health Organization guideline for physical activity and sedentary behavior emphasizes on reduction in sitting time and recommends a weekly physical activity level of moderate intensity for 150 minutes or vigorous intensity for 75 minutes which is essential for achieving optimum health.[37] Despite this recommendation, 24% of the respondents in this study had a sedentary lifestyle. This sedentary lifestyle can be attributed to the nature of their work which has been reported to be a risk factor for Obesity and Hypertension.[30] The physical activity level was estimated using a self-reported

information from the respondents, prior knowledge of high or moderate activity level by the respondents might influence the results. This limitation should be considered in the interpretation of this study result.

Conclusion and recommendation

This study has revealed that the prevalence of obesity, pre-hypertension, and hypertension among non-academic staff is high. A work-based intervention including screening, seminars, and health and lifestyle promotion measures should be encouraged to reduce the burden of obesity and hypertension among non-academic staff in Nigerian Universities.

Declaration of Interest

The authors declare that there is no conflict of interest.

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ORIGINAL PAPER

The effect of intermittent fasting 5:2 on IL-6 levels in obese male employees in Jakarta

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Abstract

Background: Obesity is a condition of excessive fat accumulation in adipose tissue. This condition causes endothelial damage, increase macrophage infiltration, and inflammation in adipose tissue. Inflammation happens due to the increase of interleukin-6 (IL-6) as a proinflammatory cytokine which responsible for the occurrence of chronic diseases. Intermittent fasting is a potentially effective method for losing weight and suggested can reduce levels of proinflammatory cytokines.
Objective: The aim of this study is to determine the effect of 5:2 intermittent fasting on IL-6 cytokine levels in obese employees in Jakarta.
Methods: This study used a cross-sectional method conducted on 50 healthy male employees aged 19–52 years with a body mass index (BMI) ≥25 kg/m2. Subjects were divided into two groups, the 5:2 intermittent fasting group and the non-fasting group. Intermittent fasting 5:2 was observed every Monday and Thursday for eight weeks. IL-6 levels were obtained through examination using an enzyme-linked immunosorbent assay (ELISA) method. Statistical analysis was performed by Mann Whitney and Kruskal Wallis test.
Results: The results showed that the median of IL-6 levels decreased in fasting group from 5,10 (1.06–9.81) pg/mL to 4.64 (1.00–13.39) pg/mL and increased in non-fasting group from 3.65 (1.17–38.70) pg /mL to 6.35 (2.44–19.86) pg/mL, but the change was not significant.
Conclusion: Intermittent fasting 5:2 tend to decrease IL-6 levels in obese male employees in Jakarta although the change of IL-6 level was not significant.
Keywords: obesity, male employees, interleukine-6, intermittent fasting 5:2

Introduction

Based on data from the World Health Organization, 650 million people in the world are included in the obese group.[1] In Indonesia, obesity is a nutritional problem that continues to increase. The obesity rate in Indonesia tends to increase every year, from 10.5% in 2007 and 14.8% in 2013 to 21.8% in 2018.[2] Data from the 2013 Riskesdas found that obesity is more common in people with high economic levels, for example office workers.[3] A study showed that out of 174 office workers in Jakarta, 59% were in the less physically active category and 19% did not do any physical activity at all. As many as 63.3% of subjects in the less physically active category were obese.[4]

Enlargement of adipose tissue in obesity, causes blood supply to adipose tissue to be reduced. Endothelial damage in adipose tissue leads to macrophage infiltration and local inflammation in

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adipose tissue. Adipose tissue machrophage (ATM) secretes proinflammatory cytokines, and an increased levels of IL-6 can lead to dysregulation of fatty acid metabolism in adipose tissue. In addition, obesity-induced IL-6 secretion plays a role in systemic inflammation which contributes to various other disease processes such as insulin resistance, cardiovascular disease, and malignancy.[4–6] Therefore, IL-6 examination is important to see the predisposition to inflammation through increased IL-6 inflammatory mediators.

Intermittent fasting is one method that is considered effective for losing weight and changing the body's metabolism as well as proven can reduce the levels of inflammation indicators such as tumor necrosis factor – α (TNF- α) and IL-6. Intermittent fasting has several regimens, including complete alternate-day fasting, modified fasting regimens, time-restricted feeding and religious fasting. Intermittent fasting 5:2 is a type of modified fasting regiment by fasting for two non-consecutive days a week and five non-fasting days.[7–8] The decreased of IL-6 levels after intermittent fasting has been found in several studies. There is a study by Razavi, et al.[9] which compared IL-6 levels in people who did intermittent fasting and calorie restriction. As a result, intermittent fasting can lower IL-6 levels more than calorie restriction.

Our previous study analyzed the effect of 5:2 intermittent fasting for eight weeks on malondialdehyde (MDA) and catalase levels in obese male employees. MDA levels in the 5:2 intermittent fasting group significantly decreased from 1.3 nmol/mL to 0.4 nmol/mL compared to the non-fasting group.[10] Based on the findings above, we determined to examine whether 5:2 intermittent fasting could also decrease IL-6 level. Research on 5:2 intermittent fasting has not been widely carried out in Indonesia and in particular there has been no study assessing a 5:2 intermittent fasting effects on IL-6 in obese employees. Therefore, the objective of this study was to examine the effect of 5:2 intermittent fasting on IL-6 levels in obese male employees in Jakarta.

Methods

Subject Study

This research has received approval from the Ethics Committee of the Faculty of Medicine, Universitas Indonesia with the certificate number of passing the ethical review KET-126/UN2.F1/ETIK/PPM.00.02/2023. Subjects were taken from secondary research data that had been previously conducted by Yudhistina, et al.[10] The data collection in this study was by taking subjects from medical records kept by the company. Initial screening was carried out in male employees with obesity and subjects who met the study criteria were given an information sheet about the research. After understanding the information provided, subjects who were willing to participate in the study were asked to sign a consent form. Involvement of subjects in research is voluntary and the data obtained is confidential.

This study was taken using the total sampling method from stored samples from previous study. The sample for this study came from 50 male employee aged 19–52 years with a body mass index (BMI) ≥25 kg/m^2. Subjects were divided into two groups, the 5:2 intermittent fasting group and the non-fasting group.

Methodology and Sampling Method

The research design used was cross sectional on stored samples from previous studies. Clinical trials have been carried out in a previous study which assessed the effect of 5:2 intermittent fasting on oxidative stress in obese employees.[10] Laboratory examinations were carried out on plasma samples stored in the laboratory of the Department of Biochemistry & Molecular Biology, Faculty of Medicine, Universitas Indonesia, Jakarta.
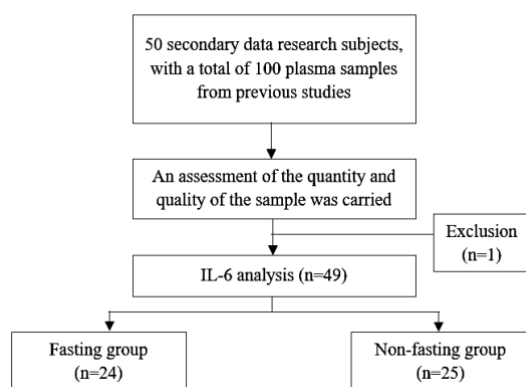
Figure 1. Research subject selection

Sample selection was carried out to determine which samples were in a state of non-lysis and sufficient to be included in this study (**Figure 1**). Secondary sample laboratory tests were conducted to determine IL-6 levels as a molecular marker of inflammation in the body using enzyme linked-immunosorbent assay (ELISA) method. One subject was excluded because the quantity of plasma samples was insufficient for examination.

Analysis of subject characteristics, food intake and nutritional status

Individual characteristics were determined through interviews that have been conducted in previous studies.[10] Age, general identity, education level, nutrition awareness level, type of work, and income level are some of the information collected in primary data. The previous study measured food intake both before and during intervention. The 2x24 hour food recall method was used to assess food intake prior to the study, with the aim of determining the eating pattern of the research subjects prior to intervention. In the 5th week of the intervention, 2x24 hour food recall was carried out to determine the subject's food intake during the intervention phase.[10]

The food record approach was used with the aim of determining how the study subject's food intake pattern was during the intervention. Food intake in the fasting group was obtained by asking participants to record the amount and type of food eaten at dawn and iftar, while food intake in the control group was determined by recording three food records (two weekdays and one weekend).

Enumerators conducted interviews with photo books of food ingredients from the Ministry of Health of the Republic of Indonesia and food models which were carried out on weekdays and holidays. The data was then analyzed using the 2007 nutrisurvey program.

Analysis of IL-6 levels

Blood samples in the previous study were taken from the subject's cubital fossa after the area was sterilized with alcohol cotton. Specimens were taken as much as 3 ml of blood stored in a tube labelled with the identity of the subject. Plasma samples were stored in the -20°C refrigerator. Sample selection was carried out to determine samples that were in a state of non-lysis to be included in this study. The IL-6 levels as a molecular marker of inflammation in the body was examined using the ELISA method (Elabscience, United State) followed manual instruction. The change of IL-6 level was presented as a ratio by dividing IL-6 level post intervention with pre intervention both in fasting and non-fasting group.

Statistical analysis

Data analysis was conducted using SPSS software version 20. The design of data analysis consisted of univariate analysis, the data on numerical scale variables were tested for normality with the Kolmogorov-Smirnov test. Data with a normal distribution are presented in the mean ± standard deviation and data with an abnormal distribution are presented in the median. Categorical scale variable data is presented in frequency. Bivariate analysis was performed to test the means of the two unpaired groups using the independent t-test if normally distributed and Mann Whitney if not normally distributed. Categorical data test using Kruskal Wallis. Correlation test was performed using the Spearman test.

Results

IL-6 Levels Based on the Characteristics of Research Subjects

Table 1. IL-6 Levels Based on the Characteristics of Research Subjects

Variable	IL-6 Levels (pg/mL)	p-value
Nutritional status, median (min-max)		0.154 [mw]
Obese I (n=20)	5.10 (1.06–18.40)	
Obese II (n-29)	3.90 (1.06–38.70)	
Physical activity, median (min-max)		0.460 [kw]
Mild (n=19)	6.00 (1.45–38.70)	
Moderate (n=23)	4.18 (1.06–11.00)	
Severe (n=7)	3.90 (1.06–7.31)	
Smoking history, median (min-max)		0.936 [kw]
Non-smoker (n=19)	5.00 (1.17–8.73)	
Low (n=17)	3.90 (1.06–11.00)	
Intermediate-high (n=13)	4.30 (1.06–38.70)	

[mw]: Mann-Whitney test, [kw]: Kruskal Wallis test

Table 2. IL-6 Levels in Fasting and Non-Fasting Group

IL-6	Group		p-value
	Fasting	Non-fasting	
Before, median (min-max) pg/mL	5.10 (1.06–9.81)	3.65 (1.17–38.70)	0.435 [m]
After, median (min-max) pg/mL	4.64 (1.00–13.39)	6.35 (2.44–19.86)	0.200 [m]
Ratio, median (min-maks)	0.79 (0.19–7.19)	1.82 (0.08–14.81)	0.407 [m]
p-value	0.853 [w]	0.930 [w]	

[m]: Mann-Whitney test, [w]: Wilcoxon

Characteristics of research subjects based on previous research, the age of research subjects has a median value of 32 (19-52) years in the fasting group and 30 (22-54) years in the control group. The mean height of the subjects in the fasting group was 168.3 ± 5 cm and 168.5 ± 6.5 cm in the non-fasting group. Subjects's body weight in the fasting group had an average of 90.5 kg and in the non-fasting group 89.6 kg. The average BMI of fasting subjects was 32.7 ± 4.1 kg/m2 and that of non-fasting subjects was 31.7 ± 4.3 kg/m^2. IL-6 levels based on the characteristics of the research subjects can be seen in **Table 1**.[10]

IL-6 Levels in Fasting and Non-Fasting Group

IL-6 levels in the fasting group decreased from 5.10 pg/mL to 4.64 pg/mL, while in the non-fasting group the IL-6 levels increased from 3.65 pg/mL to 6.35 pg/mL. However, these changes were not statistically significant.

The difference in IL-6 levels in the fasting and non-fasting groups before the intervention was not significant, with a p-value of 0.527. There was also

no significant difference in IL-6 levels in the fasting and non-fasting groups after the intervention, with a p-value of 0.176. Because change in subject's IL-6 level was vary in the form of decrease and increase, therefore changes in IL-6 levels were presented as a ratio to facilitate data analysis. The p-value of the fasting and non-fasting groups in the ratio of changes in IL-6 levels was 0.407, the changes in IL-6 levels in the fasting and non-fasting groups were not significantly different, as shown in **Table 2**.

Changes in IL-6 Levels Based on Subject Characteristics

In our previous study, the weight subjects in the fasting group experienced a significant change (p <0.05), namely 90.8 ± 13.5 kg before the intervention to 90.0 ± 13.4 kg after the intervention, with a change value of 0.8 (-2.2–5.1) kg (p = 0.015).[10] Changes in body weight in the non-fasting group experienced was not significant (p>0.05), namely 89.6 ± 12.8 kg before the intervention and 89.3 ± 12.6 kg after the intervention. However, no

significant difference was found in body weight between the fasting and non-fasting groups (p>0.05).[10] In order to know the effect of body weight change toward IL-6 level change, correlation analysis was performed. The correlation coefficient was 0.120 in fasting group and 0.028 in non-fasting group with a p value >0.05, indicating that there was no correlation between changes in body weight and the ratio of changes in IL-6 (**Table 3**).

Table 3. Correlation Analysis of Changes in Body Weight to the Ratio of Changes in IL-6

Variable	Correlation coefficient (r)	p-value
Fasting (n=24)		
Body weight	0.120	0.576 [s]
Non-fasting (n=25)		
Body weight	0.028	0.892 [s]

[s]: Spearman Correlation test

Changes in IL-6 levels were calculated as ratio values in the fasting and non-fasting groups and were analyzed based on the characteristics of the subjects (**Table 4**). Relationship between respondent characteristics and changes in IL-6 levels indicate a p-value for each respondent characteristic is greater than 0.05. It can be concluded that changes in IL-6 levels were not affected by the characteristics of the research respondents.

This study conducted a correlation analysis between changes in the ratio of IL-6 levels and data on changes in total energy, protein, carbohydrates and fat that obtained from previous studies.[10] In **Table 5**, it can be seen that in the fasting and non-fasting groups there was no correlation changes in total energy, protein, carbohydrates and fat to changes in the IL-6 ratio (p> 0.05)

Table 4. Factors Affecting IL-6 Levels

Variable	Ratio changes in IL-6 levels, median (min-max)		p-value	
	Fasting (n=24)	Non-fasting (n=25)	Fasting	Non-fasting
Nutritional status			0.929[mw]	0.913[mw]
Obese I	0.93 (0.19–5.72)	1.34 (0.27–8.58)		
Obese II	0.80 (0.32–14.81)	1.77 (0.16–5.05)		
Physical activity			0.870 [kw]	0.457 [mw]
Mild	1.73 (0.31–14.81)	1.72 (0.16–8.58)		
Moderate	0.89 (0.19–7.19)	1.26 (0.27–3.04)		
Severe	0.91 (0.32–5.72)	2.52 (1.82–3.24)		
Smoking history			0.079 [kw]	0.951 [kw]
Non-smoker	0.80 (0.19–2.67)	1.58 (0.45–8.58)		
Low	4.82 (0.63–14.81)	1.72 (0.27–5.05)		
Intermediate-high	3.11 (0.32–6.98)	1.40 (0.27–5.05)		

[kw]: Kruskal Wallis test, [mw]: Mann-Whitney test

Table 5. Correlation Analysis of Changes in Nutrient Intake to The Ratio of Changes in IL6

Variable	Correlation coefficient (r)	p-value
Fasting (n=24)		
Total energy change	0.080	0.710 [s]
Total carbohydrate change	0.077	0.722 [s]
Total protein change	0.138	0.519 [s]
Total fat change	0.223	0.296 [s]
Non-fasting (n=25)		
Total energy change	0.125	0.550 [s]
Total carbohydrate change	0.020	0.924 [s]
Total protein change	0.100	0.634 [s]
Total fat change	0.162	0.440 [s]

[s]: Spearman Correlation test

Discussion

Subjects in the obese II category had a lower median IL-6 level (3.90 pg/mL) compared to obese I (5.10 pg/mL) and the highest level of IL-6 was found in subjects in the obese category II with levels of 38.70 pg/mL however it was not significant. Normal IL-6 levels for healthy adults are 0.2– 7.8 pg/mL.[11] Several studies have shown that obese individuals have higher IL-6 levels.[12-14] In this study, the lowest IL-6 level was 1.06 pg/mL and the highest was 38.70 pg/mL detected in obese male subjects. Intermittent fasting 5:2 caused a decrease in IL-6 levels in the fasting group and an increase in IL-6 levels in the non-fasting group, however these changes were not significant both in the fasting group (p=0.602) and in the non-fasting group (p=0.621). This result similar with other study in 2020 which comparing calorie restriction and alternate day fasting. They did not detect any significant changes in TNF-α (p=0.60) and IL-6 (p=0.49) in both groups but found a significant reduction in High sensitivity C-Reactive Protein (hsCRP) levels (p=0.03).[9] Trepanowski JF, et al.[15] conducted a study with similar results by comparing calorie restriction, alternate day fasting and controls. The results found that the comparison of fat-free mass with total mass ratio decreased significantly in both groups, but IL-6 levels did not change significantly in the three groups (p=0.99).[15] Study using the fasting time-restricted feeding method for five weeks compared fasting and control groups showed that time-restricted feeding reduced oxidative stress but did not affect inflammation markers. The results show decreased plasma levels of 8-isoprostane, a marker of oxidative stress (p=0.05), however, it did not affect inflammation markers hsCRP (p=0.77) and IL-6 (p=0.12).[16]

Other study proved the different result by examining the effect of Ramadan intermittent fasting on inflammatory biomarkers in obese male subjects. Biomarker inflammation was measured four times, 24 hours before Ramadan, the 15th day of Ramadan, one day after Ramadan and 21 days after Ramadan. The results showed that there was no significant change in hsCRP (p=0.3), but

significant in the levels of IL-6 (p=0.02) and TNF-α (p=0.01) in the fasting group compared to the control group.[17] Intermittent fasting can reduce fat mass in adipose tissue, therefore adipose tissue hypertrophy will decrease. Moreover, decreased macrophages will inhibit the production of IL-6, TNF-α and IL-1.[18]

The correlation analysis of weight changes to the ratio of IL-6 changes in this study yielded a correlation coefficient in the fasting group of 0.120 and a correlation coefficient in the non-fasting group of 0.028, indicating that there was no correlation between weight changes and the ratio of IL-6 changes. According to research evaluating the impact of Ramadan intermittent fasting on pro-inflammatory cytokine levels, body weight decreased significantly (p<0.001) from 71.82 ± 13.41 kg to 70.58 ± 13.20 kg and IL-6 levels decreased from 155.85 ± 121.18 pg/mL to 67.42 ± 51.25 pg/mL, however body weight did not significantly correlate with IL-6, IL-1ß, and TNF-α.[18] Other study shows a link between BMI and IL-6 levels was discovered in a different study (r=0.84, p<0.05).[12] Interleukin-6 is a pro-inflammatory cytokine secreted by adipose tissue and it expresses mRNA for IL-6, so weight loss can affect IL-6 levels.[14]

The characteristics of respondents with changes in IL-6 levels showed p value is greater than 0.05, so it can be concluded that changes in IL-6 levels are not affected by the characteristics of the research respondents in this study. Research conducted with 62 participants received one of three interventions; aerobic exercise, combined aerobic and resistance exercise, or control. After 12 weeks of intervention, there was a reduction in body fat and IL-6 in the aerobic group (p=0.01) and the combination of aerobics and resistance training (p=0.01) and no changes in the control group.[19] Adipose tissue fat can lessen during vigorous exercise, which in turn lessens the production of cytokines that promote inflammation.[20] In addition, high levels of IL-6 are also thought to be linked to smoking. Al-Tameemi SA, et al.[21] conducted a study with 108 smokers and 51 non-smokers. IL-6 (2.58 ± 0.98 pg/mL) and TNF-α (28.38 ± 7.162 pg/mL) levels in the smoking group were higher

than non-smokers (IL-6: 22.64 ± 7.257 pg /mL and TNF-α: 22.64±7.257 pg/mL).

Changes in total energy, carbohydrates, protein and fat in this study had no correlation with the ratio of IL-6 reduction (p>0.05) in the fasting and non-fasting groups. This result has a similar finding with a study examining the effect of 6-week Dietary Approaches to Stop Hypertension (DASH) on inflammatory biomarkers in children with an average age of 14 years with metabolic syndrome. The type of diet using DASH is designed to be rich in fruits, vegetables, whole grains and low-fat dairy products and low in saturated fat. The study found insignificant result in the levels of TNF-α, IL-6 and IL-2 (p> 0.05), however a significant change was detected in CRP levels (p=0.002) in the DASH group when compared to the group that received general dietary advice only.[22] Another study divided into two groups of very low-carbohydrate high-fat (VLCHF) subjects and their daily habitual diet. After four weeks of intervention, there was no significant difference in adiponectin and IL-6 levels in the two groups (p>0.05).[23] Nevertheless, other studies found that dietary intake influences IL-6. A research assessed the relationship of dietary inflammatory index to inflammatory markers showed a positive relationship between dietary inflammatory index and IL-6 (OR 1.19, 95% CI). The study concluded that increased levels of IL-6 can occur when consuming pro-inflammatory food components such as cholesterol and saturated fat, and relatively low levels of anti-inflammatory food components such as fruits and vegetables.[24] When a person consumes a high intake of fat, free fatty acids will be increased causing increased production of IL-1ß, TNF-α and IL-6. High fat intake also increases NF-κß in the liver which plays a role in increasing proinflammatory cytokines. This sustainable diet will lead to systemic inflammation. Other research also found that the group of people who consumed a healthy diet, namely those with a high intake of low-fat dairy products, fruit, whole grains, poultry, fish and vegetables, had lower IL-6 levels and fasting blood sugar than the group that consumed a high-fat diet (p<0.05).[25]

Our previous study conducted using the same subjects showed that intermittent fasting 5:2

significantly decreased malondialdehyde (MDA) as oxidative stress marker, it turns out that the decrease in MDA was not accompanied by a statistically significant decrease in IL-6 levels.[10] The evaluation of IL-6 levels may be affected by the limitations of this study. Several factors were probably affecting IL-6 level which was not analyzed in this study such as the subject's sleep quality factors. Elevated levels of IL-6 are found in individuals who experience sleep disturbances at night and are sleepy during the day, such as in conditions of excessive daytime sleepiness and obstructive sleep apnoea.[26] In addition, there was no calorie restriction intervention to the subjects during non-fasting period. According to research, fasting throughout Ramadan without restricting calories considerably reduced body weight from 90.8 (72.2-109.4) kg to 89.4 (70.9-107.9) kg (p 0.001).[27] The 5:2 intermittent fasting procedure should be used in conjunction with a 600 kcal/day calorie restriction in order to lose weight.[28] Moreover, the period of intermittent fasting intervention in this study lasted for eight weeks, it is possible causes IL-6 levels have not yet yielded statistically meaningful findings. It has been suggested that major changes in IL-6 levels need at least six months of 5:2 intermittent fasting.[29]

This study was the first study in Indonesia to investigate the effect of 5:2 intermittent fasting on IL-6 levels in obese male employees. Although there was a IL-6 level reduction trend in the intermittent fasting group, but it was not significant compared to the non-fasting group.. Future research is needed to analyze several factors affecting IL-6 levels and to measure other inflammatory cytokines in 5:2 intermittent fasting group with a longer intervention period.

Conclusion

Intermittent fasting 5:2 for eight weeks tend to reduce IL-6 levels however it was not significant.

Conflict of interest

There is no conflict of interest in the whole process of this research.

Acknowledgment

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Eating behavior and health-related quality of life among female students attending higher education during COVID-19 pandemic in Indonesia

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Abstract

Background: Female students attending higher education had lower Health-related Quality of Life (HRQOL) scores and their eating behavior, which is a key element of healthy lifestyle, had changed to become unhealthy as a result of the pandemic's mental effects. There has been no study assessing the asssociation between both during the pandemic in Indonesia, especially after controlling for other factors.

Objective : This study aimed to assess the association between eating behavior and HRQOL among female students attending higher education during Covid-19 Pandemic.

Methods: This was a cross-sectional online survey with 474 subjects aged 18 to 25. The Dutch Eating Behavior Questionnaire (DEBQ) was used to assess emotional, external, and restraint eating. HRQOL was measured using the SF-36 questionnaire, with the subscales Physical Component Summary (PCS) and Mental Component Summary (MCS). Additionally, sociodemographic data, screen time, sleep duration, nutritional status, and physical activity were collected. The data were analyzed using multiple linear regression.

Results: PCS was significantly associated with emotional eating (r = 0.279, p-value <0.001), external eating (r = 0.211, p-value <0.001), and restrain eating (r = 0.116, p-value = 0.012). Besides, emotional eating (r = 0.211, p-value <0.001) and external eating (r = 0.172, p-value <0.001) were also significantly associated with MCS score

Conclusion: During Covid-19 pandemic, the higher the emotional, external, and restraint eating behavior scores of the students, the higher their physical health-related quality of life. The higher the emotional and external eating behavior scores, the higher their mental health-related quality of life.

Keywords: eating behavior, HRQOL, female university students

Introduction

Quality of Life (QOL) is one of the terms commonly used to refer to "health".[1] A 2020 population-based cross-sectional study assessing the quality of life among productive age in Indonesia, showed that the prevalence of good QoL among productive age in the general population was lower than expected (54%) and needs to be improved.[2] However, the health care system and its practitioners do not fully take responsibility for all the QOL problems, and therefore a distinction is made with reference to health-related quality of life (HRQOL).[3] Students who perceive a higher quality of life make use of the numerous facilities and services available and integrate more successfully into social and academic settings.[4]

The 2022 cross-sectional study among degree students in Spain shows that females had lower HRQOL in overall health, vitality, social function, emotional and mental health than males. The

females demonstrated worse levels of general health perception, quality of life, depression symptoms, anxiety, stress, avoidance, and psychological inflexibility compared to males during the pandemic.[5] This could be explained by the fact that women may be subjected to a wider range of stressful life events than men.[6] Furthermore, women are more sensitive to social judgements, making them more vulnerable to worsening their subjective well-being conditions and affecting their HRQOL.[7] There are many factors influencing HRQOL in university students, such as nutrition problem. Inadequate nutrient intake leads to insufficient and unbalanced nutrition, which causes health impairment. Nutrition is as much a psychological need as it is a physical need. Individuals may eat more than usual when they are angry, stressed, or under pressure, as well as experiencing nutritional restriction and unhealthy eating behavior that have a negative impact on their health, and affecting their HRQOL.

Nutrition is as much a psychological need as it is a physical need. Individuals may eat more than usual when they are angry, stressed, or under pressure, as well as experiencing nutritional restriction and unhealthy eating, affecting their HRQOL.[8] A study among Iranian adolescents shows that food responsiveness and emotional eating are significantly associated with HRQOL.[9] University life is often defined as a highly stressful developmental period for young adults.[10] They are a distinct population in that their issues, burdens, and concerns differ from other populations.[11] Especially during the Pandemic, they face uncertain conditions related to academic and social life, financial concern, and emotional health. These circumstances going on for a period of time had some impacts on their psychological state.[12] These can induce risky behavior with unhealthy eating practice.[13] A study among university students in Jakarta reveals that 85% of the students practice emotional eating behavior.[14] Eating behavior, particularly restricted, emotional, and external eating among university students in Turkey increases significantly during Covid-19 pandemic.[8]

HRQOL aims to promote and maintain a healthy lifestyle while eating behavior is a key element of a healthy lifestyle. To date, studies about HRQOL and eating behavior among female university students have been done separately. As eating behavior of university students is noted to alter to become unfavorable during Covid-19 pandemic, their HRQOL may be affected too. Unfortunately, studies assessing the association of both, especially among female students attending higher education, are lacking. For these reasons, this study aimed to assess the association between eating behavior and HRQOL among female students attending higher education during Covid-19 pandemic.

Methods

This study was an online survey using cross-sectional design. This study was conducted in Indonesia through a web-based application, *Limesurvey®*. The sampling method used was convenience sampling with the total subjects obtained was 474 female students attending higher education Indonesia, after being selected based on inclusion criteria, which was aged 18-25 years old female student attending higher education. The students with severe illness and/or disability, on a certain medication or diet, smokers, married, pregnant, and breastfeeding were excluded from this study. The data collection was done from September to October 2022, after receiving ethical clearance from Faculty of Medicine of Universitas Indonesia with approval number: KET 488/UN2.F1/ETIK/PPM.00.02/2022. Subjects were recruited via online advert through different channels (Instagram, WhatsApp, Twitter, and Telegram), which contained the study information sheet and direct link of the questionnaire. Since this was an online self-administered survey, the subjects filled the questionnaire by themselves at any time and place during the data collection period.

The subjects were asked to fill questionnaires about sociodemographic characteristics, screen time, sleep duration, nutritional status, as well as Indonesian version of the International Physical Activity Questionnaire Short Form (IPAQ-SF) to assess the physical activity, with validity level 0.40 and reliability 0.70-0.87. As for screen time, the

students were asked about their screen time increase during the pandemic. There were 6 indicators, namely screen time for streaming/watching entertainment videos, reading/watching news, interactive recreation, education, communication with friends/family, and social media use for non-communication purpose. Then they were categorized into 2, which were non-educational purpose and educational purpose screen time. The students with non-educational purpose screen time increments were summed based on the total of screen time they had an increase on.

Their eating behavior was obtained using validated Dutch Eating Behavior Questionnaire (DEBQ) Indonesia version, which assess 3 subscales of eating behavior, namely emotional, external, and restraint eating. The HRQOL was obtained using validated SF-36 Indonesia version questionnaire, which assess Physical Component Summary (PCS) and Mental Component Summary (MCS). All the tools have been validated to be used among Indonesian student population by previous studies. Pretesting for HRQOL and DEBQ were done before conducting this study using Cronbach Alpha test, with the results >0.6 for all the HRQOL subscales and 0.91 for overall DEBQ. It showed that all the tools used were reliable to be used in this study. DEBQ used a 5-point Likert-type scale, with a scoring system identified as follows: 1 = never, 2 = seldom, 3= sometimes, 4 = often, and 5 = very often. The assessment for each subscale was done by getting an average score. To obtain the average score, the item scores for each subscale were added as the total score. Then, it was divided by the number of subscale items to calculate score per subscale.

The SF-36 was made up of 36 items, divided into 8 subscales. The options of response are on a 2-, 3-, 5-, or 6-point scale. The physical component summary (PCS) score was generated using 21 items, and the Mental Component Summary (MCS) score is generated using 14 items. The PCS included items from four subscales: physical functioning (PF), role limitation due to physical health (RP), bodily pain (BP), and general health perception (GH). Role limitations due to emotional problems (RE), vitality (VT), mental health (MH),

and social functioning (SF) subscales were all included in the MCS. The SF-36 also included a health transition (HT) item, which was not included in the composite score. The subscale score was calculated using the mean score of the items within the subscale. The mean score of the subscale scores within a component scale was computed to generate the PCS and MCS scores. The range of the score was 0 to the highest, 100.

Additionally, the monthly household income was classified into three categories, namely low income (≤Rp.1,990,000), middle income (Rp.1,990,001 - Rp.4,799,000), and high income (≥Rp.4,800,000). The pocket money obtained by asking the students about their monthly pocket money adequacy and classified into poor, moderate, and good. The nutritional status was defined based on BMI classification for Asia-Pacific and categorized into underweight (<18.5 kg/m^2), normal (18.5-22.9 kg/m^2), and overweight/obese (≥23 kg/m^2). Lastly, the physical activity was obtained using Indonesian version of the International Physical Activity Questionnaire Short Form (IPAQ-SF) and categorized into low (MET<600), moderate (600≤MET<3.000), and high (MET≥3,000). Data quality assurance was done during data collection period through some activities, like pretesting, applying screening questions, duplication control, and applying CAPTCHA to avoid robots filling the questionnaire. The data obtained was then analyzed using SPSS 20, univariately to multivariate analysis.

Results

A total of 1280 responses were obtained. Among those responses, 749 responses were excluded with following reasons: 407 responses did not fill the online survey at all, 78 responses did not meet the inclusion criteria, 169 did not pass the screening questions, and 91 responses did not complete the screening questions. Additionally, there were 4 pairs of duplicated responses identified from the identical name, email address, and phone number. Therefore, there were 531 responses who met the inclusion criteria and passed the screening questions. Out of 531, 57 responses did not

complete the online survey and they were excluded as well. Finally, a total response included as subjects in this study was 474 subjects.

More than a half of the female students attending higher education in this study were in their 18-20 years of age (54.9%), mostly living in family with middle-monthly- income which was around Rp.1,990,001 - Rp.4,799,000 (39.2%), had a good adequacy of monthly pocket money (61.4%), and lived with their family. Additionally, almost all of them did not have part-time jobs or volunteering work during the Covid-19 pandemic (92%). Further, **Table 1** also shows that almost all of the subjects (98.5%) had an increased screen time for non-educational purposes during Covid-19 pandemic. These screen time included 5 indicators, which were streaming/ watching entertainment video, reading/ watching news, education purpose, communication with friends/ family, and social media use for non-communication purpose. While for educational purposes, 85.9% of the subjects had screen time increase. Almost half of the subjects had sleep duration below 7 hours per day (48.7%). Most of the subjects had normal nutritional status (47.5%), with moderate physical activity (41.4%) in the last 7 days.

Table 2 shows that the median of emotional eating (3.61) was higher than the medians of external eating and restraint eating, which ranged from 2.92 to 4.15. Furthermore, the average score for each eating behavior is displayed. Emotional eating received the highest score of 3.5. That is, emotional eating was the most prevalent eating behavior among all subjects.

The Physical Component Summary (PCS), which is determined from physical functioning, role limitation due to physical health, bodily pain, and general health perception, had a median score of 67.19, with a range of 56.09 to 79.37 in **Table 3**. The mean score of role limitation due to emotional problems, vitality, mental health, and social functioning were calculated resulting in a Mental Component Summary (MCS) score of 57.02, with a range of 43.25 to 70.53. Furthermore, physical functioning (95) had the highest median score of any subscale. The lowest were role limitation due to physical health and vitality, both with a median score of 50.

Table 4 shows the association between health-related quality of life and eating behavior that was analyzed using Spearman correlation test. Physical Component Summary (PCS) was significantly associated with emotional eating (r = 0.279, p-value <0.001), external eating (r = 0.211, p-value <0.001), and restrain eating (r = 0.116, p-value = 0.012). It showed that they have positive weak correlations. These results demonstrated that the higher emotional, external, and restraint eating behavior score, the higher their physical health related quality of life. Besides, emotional eating (r = 0.211, p-value <0.001) and external eating (r = 0.172, p-value <0.001) were also significantly associated with Mental Component Summary (MCS) score. It means that the higher their emotional and external eating behavior score, the higher their mental health related quality of life.

After adjustment with sociodemographic characteristics and lifestyle behavior (**Table 5**), emotional eating, household income, pocket money, living arrangement, job, and nutritional status were significant to be the predictors of physical health related quality of life among female students attending tertiary education in the Covid-19 pandemic after being adjusted. The model implies that for every one-point increment of emotional eating and external eating score, the MCS score increased by 2.414 and 2.667 point, respectively. Moreover, with every increment of age category level, the MCS score increased by 2.884 which means that the subjects aged 21 -25 years old had better mental health than the subjects aged 18-20 years old. Additionally, with every increment of the pocket money level and living arrangement, the MCS score increased by 6.143 point and 2.678 point, respectively. The same goes for living arrangements, where the subjects who lived with their family had better mental health among the groups. The table also shows that every increase of living arrangement level, the MCS score increased by 3.000 points.

Table 1. Sociodemographic Characteristics and lifestyle behavior of the Subjects
(N = 474)

Characteristics	n	%
Age		
18- 20 years old	260	54.9
21 – 25 years old	214	45.1
Monthly Household Income		
Low income	150	31.6
Middle income	186	39.2
High income	138	29.1
Monthly Pocket Money Adequacy		
Poor	22	4.6
Moderate	161	34
Good	291	61.4
Living Arrangement		
Living alone	102	21.5
Living with friends	28	5.9
Living with family	344	72.6
Having a Job		
Yes	38	8
No	436	92
Screen Time Increase		
Educational Purpose		
Yes	407	85.9
No	67	14.1
Non-Educational		
Yes	467	98.5
No	7	1.5
Sleep Duration		
< 7 h/day	231	48.7
7 – < 8 h/day	193	40.7
8 – < 9h/day	40	8.4
≥ 9h/day	10	2.1
Nutritional Status		
Underweight	110	23.2
Normal	225	47.5
Overweight/ Obese	139	29.3
Physical Activity		
Low	194	40.9
Moderate	196	41.4
High	84	17.7

Monthly household income category: low: ≤ Rp.1,990,000/month, middle: Rp.1,990,001 – Rp.4,799,000/month, and high: ≥ Rp.4,800,000/month; monthly pocket money adequacy Physical activity category: low (MET<600), moderate (600≤MET<3.000), and high (MET≥3,000).

Table 2 Eating behavior of the subjects (N = 474)

Sub-Scales	Median (Q1-Q3)	Mean
Emotional eating	3.61 (2.92 – 4.15)	3.5
External eating	2.7 (2.3 – 3.1)	2.7
Restraint eating	3.3 (2.7 – 4.1)	3.3

Table 3 Health-related quality of life of the subjects (N=474)

Sub-Scales	Median (Q1-Q3)
Physical Component Summary (PCS)	67.19 (56.09 – 79.37)
Physical functioning (PF)	95 (80 - 100)
Role limitation due to physical health (RP)	50 (25 - 75)
Bodily pain (BP)	67.5 (55 – 87.5)
General health perception (GH)	60 (50 - 70)
Mental Component Summary (MCS)	57.02 (43.25 – 70.53)
Role limitations due to emotional problems (RE)	66.67 (33.33 - 100)
Vitality (VT)	50 (40 - 60)
Mental health (MH)	60 (48 - 68)
Social functioning (SF)	62.5 (50 - 75)

Table 4 Correlation between HRQOL and Eating Behavior (N = 474)

Dependent Variable HRQOL	Independent Variable Eating Behavior	r value	p-value
	Emotional eating	0.297	<0.001**
PCS	External eating	0.211	<0.001**
	Restraint eating	0.116	0.012*
MCS	Emotional eating	0.211	<0.001**
	External eating	0.172	<0.001**
	Restraint eating	0.068	0.141

Statistical analysis used Spearman correlation.

HRQOL: Health Related Quality of Life; PCS: Physical Component Summary; MCS: Mental Component Summary

*Significance level at p-value <0.05; **Significance level at p-value <0.01

Table 5. Multiple Linear Regression Analysis of HRQOL (N=474)

Parameter	Unadjusted Model						Adjusted Model					
	ᵃPCS			ᵇMCS			ᵃPCS			ᵇMCS		
	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value	B	95% CI	p-value
Constant							5.692	-12.940 – 24.325		2.191	-17.717 – 22.09	
Eating behavior score												
Emotional eating	5.372	3.828 – 6.917	<0.001**	4.136	2.347 – 5.926	<0.001**	3.750	1.920 – 5.579	<0.001**	2.414	0.289 – 4.538	0.026*
External eating	4.722	2.669 – 6.775	<0.001**	4.649	2.319 – 6.979	<0.001**	1.879	-0.362 – 4.120	0.100	2.677	0.051 – 5.302	0.046*
Restraint eating	1.801	0.230 – 3.371	0.230	1.151	-0.628 – 2.930	0.204	1.575	-0.107 – 3.257	0.066	1.588	-0.380 – 3.557	0.114
Age	-	-	-	3.497	0.105 – 6.889	0.105	-	-	-	2.884	-0.356 – 6.124	0.081*
Monthly household income	4.187	2.406 – 5.967	<0.001**	3.020	0.984 – 5.057	0.004	3.001	1.295 – 4.708	0.001*	1.610	-0.385 – 3.605	0.114
Pocket money	5.622	3.238 – 8.007	<0.001**	6.350	3.658 – 9.042	<0.001**	4.875	2.601 – 7.149	<0.001**	6.143	3.474 – 8.813	<0.001**
Living arrangement	2.502	0.798 – 4.207	0.004*	2.751	0.826 – 4.676	0.005*	2.615	1.042 – 4.187	0.001*	2.678	0.831 – 4.526	0.005*
Job	6.566	1.377 – 11.754	0.013*	-	-	-	4.885	-0.108 – 9.662	0.045*	-	-	-
Non-Educational Screen Time	-8.520	-20.252 – 3.212	0.154	-9.093	-22.340 – 4.154	0.178	-3.418	-14.188 – 7.352	0.533	-4.253	-16.847 – 8.341	0.507

ᵃDependent variable: PCS score

The multiple linear regression equation is given by: PCS (score) = 5.692 + 3.750 (emotional eating) + 3.001 (monthly household income) + 4.875 (pocket money) + 2.615 (living arrangement) + 4.885 (job) + 2.218 (nutritional status), depending on emotional eating in score, Household income level (1 = low income, 2 = middle income, 3 = high income), Pocket money level (1 = poor, 2 = moderate, 3 = good), and living arrangement level (1 = living alone, 2 = living with friends, 3 = living with family), Job (1 = yes, 2 = no), and nutritional status (1 = underweight, 2 = normal, 3 = overweight/obese) of the subjects
*Significance level at P-value <0.05; **Significance level at P-value <0.01
R square = 20.2%, P-value = <0.01 analyzed with multiple linear regression using enter method

ᵇDependent variable: MCS score

The multiple linear regression equation is given by: MCS (score) = 2.191 + 2.414 (emotional eating) + 2.677 (external eating) + 2.884 (age) + 6.143 (pocket money) + 2.678 (living arrangement) + 1.192 (nutritional status) depending on emotional eating in score, external eating in score, age (1 = 18-20 years old, 2 = 21-25 years old), pocket money level (1 = poor, 2 = moderate, 3 = good), living arrangement level (1 = living alone, 2 = living with friends, 3 = living with family), and nutritional status (1 = underweight, 2 = normal, 3 = overweight/obese) of the subjects *Significance level at P-value <0.05; **Significance level at P-value <0.01
R square = 12%, P-value = <0.01 analyzed with multiple linear regression using enter method

Discussion

During the pandemic situation, the students were having online learning which allowed them to have more screen time compared to before the pandemic. There was an increase of screen time for both educational and non-educational purposes. The same finding was stated in a previous study where more than a half of the college students had increment screen time for entertainment and attending online class during Covid-19 pandemic situation.[15] In this study, more than half of the students had less than 7 hours of sleep per day. It could be due to late night tasking, browsing on social media, chatting, and checking online news from mobile devices. Our finding showed that more than half of the subjects had normal nutrition status. This is in agreement to a study in Bangladesh and Canada that also assessed the nutritional status by self-reported measurement in the Covid-19 Pandemic.[16,17] Furthermore, The result showed that most of the students had moderate physical activity for at least 10 minutes each day. This same result was found in a study by Lesmana et al[18], which mentioned that most of their subjects (university students) had moderate physical activity. During the pandemic, there were many ways to increase physical activity during that time, such as yoga, aerobics, treadmills, static bike, and sports that can be done in the house. Besides, activities like doing home chores and walking in the house are also physical activity and can increase physical fitness.[19]

This study shows that the eating behavior of the subjects tended to be emotional eating among those three eating behaviors. Similar result was found in a study from Turkey, which shown that the university female students tend to have emotional eating behavior during the Covid-19 Pandemic. A study assessing the level of depression, anxiety, and stress of college students in Indonesia during the Covid-19 pandemic concluded that the majority of college students suffer from moderate depression, severe anxiety, and severe stress.[20] Especially in the Covid-19 pandemic situation, the female students tent to perceive higher stress due to some pressures because they were more likely to ruminate during stressful situations and had a lower sense of mastery over their lives, which could lead to emotional eating as their coping mechanism.[21]

In this study, it is shown that PCS had a higher score than MCS. This is in line with the result of the previous studies conducted among university students, that physical and psychological health were the highest and lowest scoring domains, respectively.[22,23] In addition, pandemic situation might affect the mental health of female students generally more than to their physical health, which could lower the mental health score. In the Mental Component Summary, Role limitations due to emotional problems (RE) and Vitality (VT) were the highest and the lowest subscales of MCS. The exact same result was found in a study at a university in Croatia.[24] It might because of they were more likely to feel tired easily, passionless, and unenergized. This might be because of the burdens they carried in the pandemic situation. Female students showed more impairment in the areas of daily physical activity restrictions (physical functioning), energy (vitality), and physical pain, which may be related to physical traits specific to the female gender, as well as a burden from an overload of traditionally female activities and greater emotional sensitivity (role limitations caused by emotional problems, mental health, and the mental component).[25]

The multivariate model of this study states that after adjusting other variables, it was reported that the higher the emotional, external, and restraint eating behavior scores of the students, the higher their physical health-related quality of life. The higher the emotional and external eating behavior scores, the higher their mental health-related quality of life. These findings are contradictive from the existing theory which explains the negative influences of the three eating behavior to quality of life of healthy people.[26-29] However, a study by Frayn et al.[30] states that many individuals maintain a normal weight even though they engage in emotional eating. In addition, emotional eating has been linked to a need to reduce the effects of stress. Following consumption, hormones are released to reduce stress, which increases the desire for comfort foods, perpetuating emotional eating habits. Thus, emotional eating can increase their mental health-related quality of life.[31] External

eating refers to the tendency to eat when exposed to food-related cues such as the sight, smell, or taste of food, even in the absence of physiological hunger. The link between external eating and emotional eating may have theoretical justifications. For instance, it has been proposed that environment and emotions may work together to influence overeating because anxiety has been shown to improve how overweight people respond to outside cues.[32] However, in the long-term, emotional eating and restraint eating could bring damage to physical and psychological health. Unlike emotional and external eating, restraint eating only positively correlated with PCS. Another study in China reported that restricted eaters tend to reduce energy intake to maintain or lose weight, which causes them to prefer low-calorie foods like vegetables or fruits and limit high-calorie foods like cereals and tubers or domestic animals and poultry.[33] Thus, it can help them to increase and maintain their physical health.

After being adjusted with other factors, female university students with higher scores of emotional eating, living in households with higher monthly income, having good amount of pocket money, living with their family, not working, and having better nutritional status, had better physical HRQOL. While higher emotional eating score, higher external eating score, being in 21-25 years old group, having enough pocket money, living with family, and having better nutritional status showed better mental HRQOL. A study by Naim *et al.* that higher pocket money and monthly household income affected HRQOL of the students after being adjusted.[4] Socioeconomic factors play big roles in affecting both eating behavior and HRQOL. Family financial support, as a direct measure of Socio-economic status (SES), is essential in a student's life.[34] Moreover, the students who did not have any work or doing volunteering in the Covid-19 pandemic had better a better physical HRQOL.

Furthermore, the age group 21-25 years old had better mental health related quality of life. A study by Syakila, *et al.*[11], showed that the students aged 21-25 years old, specifically, had the better psychological quality of life. It's because they are expected to be more mature in handling their life

better, thus perceiving a better psychological quality.[11] It can also be expressed that age has predictive effects on student's health-related quality of life.[35] In the present study, the students with emotional and external eating, better socio-economy status, and higher nutritional status had better HRQOL. Overweight/obese subjects have better HRQOL, specifically mental health. This can be associated with eating behavior. Emotional and external eating lead to overeating, which has been linked to weight gain and a higher body mass index.[36] emotional and external eaters tent to consume foods high in sugar, fat, and salt excessively as their coping mechanism to hinder stress.[37] Thus, making their mental health HRQOL better. Nonetheless, a high BMI causing better HRQOL suggests that 'healthy people with obesity' may be on the verge of an unhealthy future.[38]

Additionally, a previous study in Indonesia concluded that female university students had psychological health problem due to pandemic situation.[39] Another study among female university students in Turkey shows a similar result suggesting higher emotional and external eating during Covid-19 pandemic situation. It was due to negative emotions such as anxiety, stress, anger, sadness, depressed feelings that cause an increase in BMI in the long term and hence obesity.[40] Furthermore, a previous study concluded that 71% of young Saudi women were reported to have moderate stress, and 12.5% reported severe stress. It resembles information from surveys conducted during the COVID-19 pandemic in Saudi Arabia, Spain, India, and China.[41] Thus, in this study, the students also might have stress due to pandemic situation and lead them to emotional and external eating behavior.

The present study was the large survey observing HRQOL and eating behavior among female students attending higher education during Covid-19 Pandemic that provides new insight about the determinant factors of HRQOL, which is still limited being examined in Indonesia. The result of this study can be used as a guide for government or the universities in Indonesia to develop a program or recommendation related with quality of life and eating behavior especially for female students. Since the sociodemographic of

this study was quite homogenous and reached the female students from several domiciles in Indonesia, the findings of this study can be generalized in healthy female students attending higher education in Indonesia population. This study had some limitations. Firstly, the cross-sectional study design only showed the correlation between variables and could not provide a causal relationship between the factors and HRQOL. The second one is this study did not assess the food intake of the students and only evaluated eating behaviors via a self-report subjective questionnaire which may introduce reporting bias in this study.

Although this study showed that emotional, external, and restraint eating had increase HRQOL during the Covid-19 Pandemic, it's not recommended to keep these eating behaviors for long-term period as it can negatively affect physical and mental health, such as weight gain, eating disorder, and psychological issues. Stress management needs to be learned to hinder these eating behaviors to become coping mechanisms.

This study can be used for ministry of health collaborating with ministry of higher education and academic practitioners in making the strategy to provide better lives through healthcare and public health intervention specifically for female students attending higher education and the general population. Future research is needed to to develop an intervention study focusing on HRQOL and eating behavior is needed especially among the female college students, specifically variables that are related to health and nutrition. Moreover, we suggest conducting interview-based data collection.

Conclusion

During Covid-19 pandemic, the higher the emotional, external, and restraint eating behavior scores of the students, the higher their physical health-related quality of life, means they had better condition of their body which allowed them to function their body well and had better fitness to move or do their activity during the Covid-19 pandemic. The higher the emotional and external eating behavior scores, the higher their mental health-related quality of life, means they have more

stable mental well-being that can help them to cope with psychological stress and handle their life better during the Covid-19 pandemic.

Conflict of Interest

The authors declare that there is no conflict of interest regarding this article.

Acknowledgment

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ORIGINAL PAPER

Formulation and potential of purple cabbage (*Brassica oleracea L.*) as a nutraceutical product in maintaining cardiovascular health

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Abstract

Purple cabbage (*Brassica oleracea L.*) is one of the agricultural products that contain anthocyanins which have the potential as antioxidants. The amount of production in Indonesia is still relatively low due to a lack of consumer demand and a lack of innovation in its utilization. So it is necessary to make new innovations, one of which is by processing it into flour to make Almond Crispy which is then given the name "Ceamond Crispy". The reason Almond Crispy is made, because it is easy to process and can be consumed for a long time. This study aims to determine the anthocyanin compounds contained in processed food "Ceamond Crispy". Almond Crispy is made with a ratio of purple cabbage flour and moderate protein flour in 3 formulations namely formulation 1 (1:2), formulation 2 (1:1), and formulation 3 (2:1). This research was conducted by organoleptic test, anthocyanin, nutritional content. Therefore, it can be concluded that the organoleptic test results obtained brown color, taste like chocolate, vanilla aroma, and crunchy texture. The anthocyanin test results obtained positive results in all three formulations. The results of the nutritional content test showed that the 3 formulations contained the same protein, carbohydrates (starch), and carbohydrates (glucose), but did not contain fat. The results of the preference test showed that formulation 3 was the most preferred formulation. Thus, proving that "Ceamond Crispy" can be received with a positive response by the community and has the potential to be developed into an innovative food that is beneficial for the heart. Thus, proving that "Ceamond Crispy" is safe for consumption by the public and can be developed into innovative foods that are beneficial for heart health.

Keywords: purple cabbage cookies, nutraceutical, cardiovascular health, anthocyanin

Introduction

Purple cabbage (*Brassica oleracea L.*) belongs to the Brassicaceae family which contains lots of vitamin A, B, and C. In the antioxidant potential of cabbage varieties, the highest antioxidant is obtained from purple cabbage (*Brassica oleracea L.*), and according to Wahyuni[26] the ethanol extract of purple cabbage (*Brassica oleracea L.*) has an IC50 value of 44.64 ppm which shows very strong antioxidant activity.

Purple cabbage (*Brassica oleracea L.*) is one of the agricultural products whose existence is quite well known by the public. The amount of purple cabbage production in Indonesia is relatively low, this is due to the lack of consumer demand for this commodity. The use of purple cabbage in Indonesia is only limited to making salted vegetables and as a mixture in salads.[1] The

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nutritional content of purple cabbage can be seen in **Table 1**.

Purple cabbage is a vegetable rich in anthocyanins. Anthocyanins in red cabbage have a good level of stability. purple cabbage has an anthocyanin content of 113mg/100g.[2] Along with the times, many people still do not know the benefits of purple cabbage, one of which is as an antioxidant.

Table 1. Nutritional content in every 100 grams of purple cabbage (*Brassica oleracea L.*).[27]

Nutrient	Amount
Proteins	1.4 g
Carbohydrate	5.3 g
Fat	0.2 g
Calcium	46 mg
Phosphor	31 mg
Iron	1 mg
Vitamin A	80 IU
Vitamin B1	0.06 mg
Vitamin C	50 mg

Antioxidants are compounds that can withstand, eliminate, and clean up the effects of free radicals which can cause various degenerative diseases such as premature aging, heart disease, stroke, cataracts, osteoarthritis, and cancer. One type of antioxidant that can be found in purple cabbage is anthocyanin.[3]

Anthocyanins are pigments composed of flavonoids (anthocyanidins) with an aromatic ring in ring B, a C6-C3-C6 cyclic ring, and sugar groups in different positions. Anthocyanins include water-soluble pigments found in epidermal cells in flowers or mesophyll cells in leaves. The types of anthocyanins contained in Purple cabbage are cyanidins with sugar groups either acylated with cafeic, ferulic, synapic acid, and p-coumarate or not.[4] Many studies have shown that anthocyanins have a positive effect on health. There is also a lot of evidence that anthocyanins are non-toxic but also have positive therapeutic and pharmacological properties.[5]

Anthocyanins have many health benefits, namely as anti-diabetic, anticancer, anti-inflammatory, antimicrobial, anti-obesity and help prevent cardiovascular disease. In the context of cardiovascular pathology, anthocyanins have been reported to have cardioprotective effects against isoproterenol-induced myocardial infarction damage.[3]

Cardiovascular disease is one of the non-communicable diseases that causes the number 1 death in the world, which is around 80%. Cardiovascular disease is widely known as a disease with disorders of the heart and blood vessels.[6] Cardiovascular disease can develop due to hypertension, platelet aggregation, high blood Low-Density Lipoprotein (LDL), and dysfunction of endothelial cells in the blood vessels. Epidemiological studies show that consumption of vegetable and fruit-based foods can increase protection against heart disease due to the presence of bioactive compounds, one of which is anthocyanin. The mechanism of the cardioprotective effect of anthocyanins is by preventing LDL oxidation, protecting the integrity of the endothelial cells lining the blood vessel walls so that damage does not occur, and preventing platelet aggregation. One way that anthocyanins protect endothelial cells is by inhibiting the

induction of tumor necrosis factor alpha (TNFα) which triggers inflammation through monocytes.[7] Functional or nutraceutical foods are natural ingredients that are processed into food products, so they have the potential to have a higher health value than nutritious foods in general.[28] Development of purple cabbage nutraceutical products to become one of the foods suitable for consumption by the public. One of the snacks known by the public is Almond Crispy. Almond Crispy is a variation of cookies or pastries that are flat and have a crunchy texture.[8]

Crispy Almonds were chosen because they are easy to process, namely through the mixing and roasting process, the texture resembles biscuits, can be stored in a closed container, and can be consumed for a long time.[2] This research obtained a cookie product namely Almond Crispy Purple cabbage (*Brassica oleracea L.*) which contains anthocyanin which can maintain heart health. This product was created to innovate purple cabbage (*Brassica oleracea L.*) food products into Crispy Almond products. The utilization of purple cabbage (*Brassica oleracea L.*) here is expected to be a snack that can provide added value and can maintain heart health. Therefore, this study was conducted to determine the presence of anthocyanins contained in purple cabbage Crispy Almonds (*Brassica oleracea L.*) using various comparisons of purple cabbage flour (*Brassica oleracea L.*) and other ingredients by setting the right drying temperature to get the taste and consistency appropriate.

Methods

Research design

The research design used was a qualitative analysis method by observing the presence of anthocyanins and nutritional content (protein, carbohydrates, and fats) in purple cabbage flour (*Brassica oleracea L.*) and "*Ceamond Crispy*" products.

Time and place

This research was conducted in the Phytochemistry Laboratory, Department of Pharmacy, Faculty of Medicine and Health Science, Maulana Malik Ibrahim State Islamic University Malang, on 8th December 2022.

Tools and materials

The tools used in the manufacture of this research are a mixer (Miyako HM-620), digital scales (SF 400), sieve, baking sheet, baking paper, spoon, and oven (Hakashima Electric Oven 23 Lt).

The tools used for testing in this study were analytical balances (Ohaus CP 214), oven (Memmert Universal Oven Original UN 30), test tubes (Herma), test tube racks, watch glass, gauze, bunsen, tripod, beaker glass 100 ml (Iwaki), 250 ml beaker glass (Iwaki), stirring rod, 5 ml measuring pipette (Iwaki), 10 ml measuring pipette (Iwaki), pushball, spatula, 100 ml measuring cup (Iwaki), spoon horn, wooden tongs, and a dropper (Pyrex).

The materials used in the manufacture of this research include purple cabbage, egg whites, powdered sugar, salt, vanilla powder, medium protein flour, butter, almonds, and grated cheese. All ingredients are obtained from the cake ingredients shop.

The materials used for testing in this study were NaOH, HCl, Lugol's reagent, Fehling A, Fehling B, $CuSO_4$, and $KHSO_4$. All ingredients are obtained from pharmacy stores.

Research methods

Large purple cabbage is cut into small pieces and washed thoroughly with water then drained. Slices of Purple cabbage were dried in an oven (MEMMRT Universal Oven Original UN 30) at 50°C for 24 hours. Then grind it into powder.[9]

The mixing of dry ingredients in the production of "*Ceamond Crispy*" includes medium protein flour, purple cabbage flour, vanilla powder, and salt, mixed using a mixer (Miyako HM-620) until well blended. The purpose of mixing the dry ingredients is to do it separately first so that the dry ingredients get even conditions so that when stirring is done, the dough will be more even and there will be no accumulation or clumping of the dough.[10]

The product "Ceamond Crispy" is made by weighing all the ingredients first. Next, mix the egg whites and sugar using a mixer (Miyako HM-620) until stiff peaks (swell). Sift the dry ingredients that have been mixed and put them into the egg-white mixture in three stages, stirring until evenly distributed. Pour in the melted butter and stir again until smooth. Prepare a baking sheet lined with baking paper. Take enough dough, about ¼ tsp, put it on baking paper, and flatten it with the back of a spoon to form a circle. Sprinkle with almond chips and grated cheese on top of the dough. In the oven (Hakashima Electric Oven 23 Lt) at 50°C for 1 hour. In the last step, Ceamond Crispy is weighed as much as 20 grams and put into the package. The product formulation can be seen in **Table 2**.

Table 2. Product formulation of "*Ceamond Crispy*"

Ingredients	F1 (%)	F2 (%)	F3 (%)
Purple Cabbage Flour	20 g	30 g	40 g
Medium protein flour	40 g	30 g	20 g
Egg whites	2	2	2
Fine granulated sugar	50 g	50 g	50 g
Salt	1/8 tsp	1/8 tsp	1/8 tsp
Powdered vanilla	1/4 tsp	1/4 tsp	1/4 tsp
Butter	45 g	45 g	45 g
Almond Chips	qs	qs	qs
Grated cheese	qs	qs	qs

Organoleptic test

Organoleptic is a food ingredient test based on preferences and desires for a product. Organoleptic test, also known as sensory test or sensory test, is a method of testing using the human senses as the main tool for measuring product acceptance.[11] The product "Ceamond Crispy" which was tested organoleptic consisted of 3 formulations added with Purple cabbage flour (Brassica oleracea L.) according to the formulation of the addition of flour respectively (20 grams, 30 grams and 40 grams). Organoleptic testing of "Ceamond Crispy" includes color, taste, aroma, and texture. The senses used in this test are sight, taste, smell, and touch. Organoleptic testing was carried out simultaneously with hedonic testing, involving 35 panelists living in the Malang districts.

Hedonic test

The hedonic test is a test in organoleptic sensory analysis which is used to determine the magnitude of the difference in quality between several similar products by providing an assessment or score of certain properties of a product and to determine the level of preference of a product.[29] The parameters of the "Ceamond Crispy" hedonic test included color, aroma, taste, texture, and overall. The selected panellists were untrained panellists who were randomly selected according to the age group of 35 panellists who live in Malang district.

Anthocyanin test

The anthocyanin test was carried out to determine the anthocyanin content in purple cabbage and "Almond Crispy" products. The first step, the

sample is put into a test tube, then the sample is heated above Bunsen with a drop of 2M HCl solution for 2 minutes using a temperature of 100 °C, the color of the sample is observed. If the red color in the sample does not change (constant), it indicates a positive anthocyanin. In the second stage, the samples were mixed by adding 2M NaOH drop by drop. If the sample from red turns to blue-green and fades slowly, it indicates that the sample is positive for anthocyanin.[12]

Nutritional content test

Carbohydrate test

1. Put the sample solution into 2 test tubes, 2 military each.
2. Test tube 1 added 2-3 drops of Lugol's reagent, and a positive reaction for starch shows a blue or purple-black color.
3. In test tube 2, 2 mL of Fehling A and Fehling B solutions are added each, then add 4 drops of 10% NaOH solution. Positive for glucose if there is a brick-red precipitate.

Protein test

1. Make a 2% sample solution in distilled water, then take 1 mL to put it in a test tube.
2. Add 1 mL of 10% NaOH, and 1 mL of 0.1% CuSO4 solution and shake. The positive reaction of the protein occurs purplish-blue.

Fat test

1. Put 3 drops of the sample solution into the test tube.
2. Add 1 tablespoon of KHSO4 and then heat it. A positive reaction of grease has the smell of burnt fat with white smoke.

Results

Organoleptic test results

An organoleptic test is used to see how the appearance of the product "*Ceamond Crispy*" is

assessed by the five senses. Organoleptic results can be seen in **Table 3**.

Table 3. Organoleptic test results for "*Ceamond Crispy*" products

Parameter	F1	F2	F3
Color	Chocolate	Chocolate	Purplish brown
Flavor	Like chocolate	Like chocolate	Like chocolate and slightly bitter
Aroma	vanilla	vanilla	vanilla
Texture	crispy	crispy	crispy

This "*Ceamond Crispy*" product has the same texture in the three formulations because in the manufacture it is formed flat and thin. In addition, the aroma is the same because when making the dough, vanilla powder is added. This "*Ceaamond Crispy*" product is made with powdered sugar which makes it taste slightly sweeter than the original taste of purple cabbage flour (*Brassica oleracea L.*). The color of the product "*Ceamond Crispy*" is influenced by the presence of anthocyanin which is a color pigment in Purple cabbage (*Brassica oleracea L.*) and can act as a natural dye.

Hedonic test results

The hedonic test is a test used to determine panelist preferences for the "Ceamond Crispy" product. The population in this hedonic test were men and women ranging in age from children around 6 years to parents aged 72 years with a total of 35 untrained panellists. The percentage of male panellists was 49% and 51% female. Data on the number of panellists by age and gender can be seen in **Figure 1** and **Figure 2**.
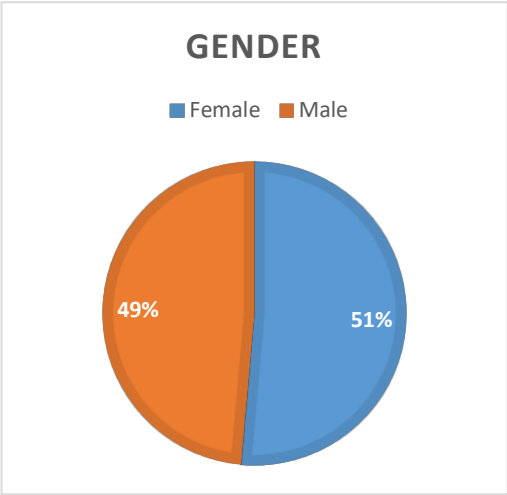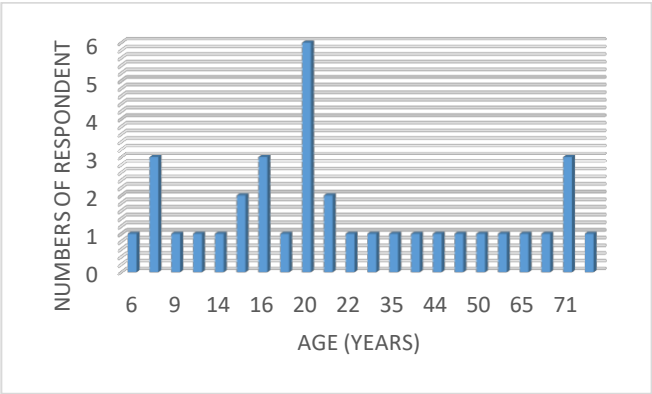
Figure 1. Respondent's gender

Figure 2. Respondents' ages

The hedonic test was conducted to assess the level of preference for the "Ceamond Crispy" product in the people of Greater Malang with a total of 35 panellists of various ages with hedonic test parameters including texture, color, smell, taste, and an overall assessment of the "Ceamond Crispy" product with a score 1-5 through a questionnaire using the google form media. The hedonic test results are shown in **Table 4**.

Table 4. Hedonic test results of "Almond Crispy"

Question	1	2	3	4	5
Do you like the texture of Crispy Almond products?	0 (0%)	0 (0%)	2 (5.7%)	11 (31.4%)	22 (62.9%)
Do you like the smell of Crispy Almond products?	0 (0%)	5 (14.3%)	14 (40%)	11 (31.4%)	5 (14.3%)
Do you like the color of Crispy Almond products?	0 (0%)	2 (5.7%)	12 (34.3%)	12 (34.3%)	9 (25.7%)
Do you like the taste of Almond Crispy products?	0 (0%)	0 (0%)	0 (0%)	13 (37.1%)	22 (62.9%)

Based on the results of testing the filling out of the questionnaire on question number 1, there were 22 panellists who chose option 5 which means they really like the texture of "Ceamond Crispy", 11 panellists who chose option 4 which means they like it, and 2 panellists who chose option 3 which means neutral. The results of test number 2 on the questionnaire, 5 panellists chose option number 2

which means dislike, 14 panellists chose option 3 which means neutral, 11 panellists chose option number 4 which means like, and 5 panellists chose number 5 which means really like the smell of "Ceamond Crispy" product. The results of test number 3 on the questionnaire, 2 panellists chose option 2 which means they don't like it, 12 panellists chose option 3 which is neutral, 12 panellists chose option 4 which means they like it, and 9 panellists chose option 5 which means they really like the smell of the product "Ceamond Crispy". The results of test number 4 on the questionnaire, 13 panellists who chose option 3, namely neutral, and 22 panellists who chose option 5, which means they really like the taste of the "Ceamond Crispy" product.

Processed product of Red Cabbage (Brassica oleracea L.) "Ceamond Crispy" has good properties in terms of texture, smell, color and taste so that the product can be accepted and enjoyed by people of all ages. Based on the questionnaire that has been given, the community tends to prefer formula 3 with a percentage of 54% (**Figure 3**).
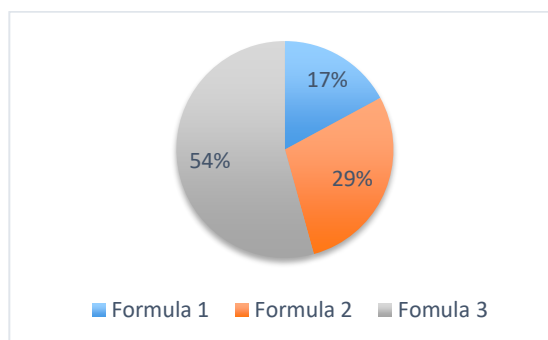

Figure 3. Respondent's formula preference

This proves that the product "Ceamond Crispy" is received with a positive response by the public and can be developed into an innovative food that is beneficial for cardiovascular health.

Anthocyanin test results

This test was carried out to identify anthocyanin compounds in the form of a color test using 2M NaOH and 2M HCl reagents. The results of the anthocyanin test on purple cabbage Flour and "*Ceamond Crispy*" Products can be seen in **Table 7**.

Table 7. Anthocyanin test results

Sample	Results		Color	
	2M HCl	2M NaOH	2M HCl	2M NaOH
Purple Cabbage Flour	Positive (+)	Red Green Blue	Red Green Blue	Blue-green
F1	Positive (+)	Red Green Blue	Red Green Blue	Blue-green
F2	Positive (+)	Red Green Blue	Red Green Blue	Blue-green
F3	Positive (+)	Red Green Blue	Red Green Blue	Blue-green

This test was conducted to determine the presence of anthocyanins in purple cabbage Flour (*Brassica oleracea L.*) and the product "*Ceamond Crispy*". The results of the anthocyanin test on all samples were positive (+) indicated when the sample solution was dropped with 2M HCl it produced a constant red color and when 2M NaOH was dropped the red color changed to blue-green and faded slowly. These results indicate the characteristics of anthocyanins, where the color change is caused by changes in the anthocyanin structure caused by the influence of H^+ and OH^- ions.[13]

Anthocyanins belong to phenolic substances which are widely found in plants and give them blue, red, or purple colors.[3] One of the factors that affect the color of anthocyanin is a change in pH.[4] In acidic media, anthocyanins are red, purple in neutral solutions, and green-blue in alkaline solutions.[3] Apart from changes in pH, pigment concentration, presence of mixtures with other compounds, the number of hydroxy and methoxy groups also affect the color of anthocyanins. The dominant hydroxy group causes the color to tend to be blue and is relatively unstable, while the dominant methoxy group causes a red color and is relatively more stable.[14]

Purple cabbage (*Brassica oleracea L.*) anthocyanins are preferred because of their good solubility and easy extraction.[5] Anthocyanin is a natural pigment in purple cabbage which is water soluble and has antioxidant properties.[15] The antioxidant activity of purple cabbage (*Brassica oleracea L.*) extract powder was 84.69%. These results are to the research of Karoui et al. (30) which stated that the antioxidant activity of purple cabbage extract powder ranged from 80-93.89%. The antioxidant activity of purple cabbage (*Brassica oleracea L.*) extract powder can be derived from phenolic compounds, α-tocopherol, ascorbic acid, and carotenoids present in purple cabbage. In addition, the anthocyanins in purple cabbage are also quite high, ranging from 40.53-76.16 mg/100 g of purple cabbage (*Brassica oleracea L.*).[3]

Anthocyanin is a plant pigment that has a wide range of colors, namely purple, blue, orange, and red to slightly greenish blue.[16] Anthocyanins can be used as alternative dyes in food and medicinal products.[17] Anthocyanin stability is strongly influenced by temperature, both during processing and storage. The higher the temperature, the greater the possibility of anthocyanin color degradation.[18] Much evidence shows that anthocyanins are not only non-toxic but also have positive pharmacological and therapeutic properties. Therefore, this pigment can be consumed without showing negative effects on health.[19]

Nutritional content test results

The nutritional content test was carried out to determine the levels of protein, carbohydrates, and fat in the product "*Ceamond Crispy*" Formula 1, Formula 2, and Formula 3. The results can be seen in **Table 8.**

Carbohydrate test results

Carbohydrates are the main source of calories for almost the entire population in the world. Although the number of calories that can be produced by 1 gram of carbohydrates is only 4 kcal when compared to protein and fat, carbohydrates are a cheap source of calories. In the body, carbohydrates are useful for preventing ketosis, excessive breakdown of body protein, and loss of minerals, and are useful for helping fat and protein metabolism.[20]

The carbohydrate test was carried out using two test tubes for each formulation, where the Lugol test was carried out in the first tube and the Fehling test in the second tube. Lugol's test or iodine test is a qualitative test of carbohydrates to determine the presence of complex carbohydrates. The iodine test is one of the test methods used to differentiate polysaccharides from disaccharides and monosaccharides. The color change of the solution occurs because, in the starch solution, there are glucose units that form. The principle of the iodine test is that starch or starch which reacts with iodine will form a blue color, dextrin will form a purplish-red color, and glycogen will form a brownish-red color.[21] This research was conducted by dripping 2 ml of the sample with 2-3 drops of Lugol's solution, samples containing complex carbohydrates will

cause a discoloration to blue or dark purple. The Lugol carbohydrate test experiment using "*Ceamond Crispy*" showed positive test results for each formulation marked by the formation of a purple color.

Fehling's test is used to test the reduced sugar content in a sample. This test is based on the presence of a free aldehyde or ketone group. Fehling's reagent is divided into two, namely Fehling A (copper (II) sulfate) and Fehling B (KOH and sodium potassium tartrate). Fehling's test is used to show the special properties of carbohydrates in the presence of reducing

carbohydrates. The test results show that glucose and sucrose are sugars that can reduce Fehling's solution and as reducing carbohydrates. Fehling's reagent plus carbohydrates are then heated, then a brick-red precipitate will form in the final result.[22] In this "*Ceamond Crispy*" carbohydrate test experiment, positive test results were indicated for each formulation marked by the formation of a brick red precipitate.

Table 8. The nutritional content of "*Ceamond Crispy*" products test results

Sample	Test	Smell	Color	Result
F1	Proteins	-	Purple	+
	Carbohydrates (starch)	-	Purple	+
	Carbohydrates (glucose)	-	Brick Red Precipitation	+
	Fat	-	-	-
F2	Proteins	-	Purple	+
	Carbohydrates (starch)	-	Purple	+
	Carbohydrates (glucose)	-	Brick Red Precipitation	+
	Fat	-	-	-
F3	Proteins	-	Purple	+
	Carbohydrates (starch)	-	Purple	+
	Carbohydrates (glucose)	-	Brick Red Precipitation	+
	Fat	-	-	-

Protein test results

Proteins are polymers of amino acid monomers connected by peptide bonds. A peptide bond is formed between the carboxyl groups or the amino groups of adjacent amino acids. Protein is needed for growth and an ideal protein must have an amino acid arrangement that suits the needs of humans and animals.[23]

Qualitative protein analysis is an analysis that aims to determine the presence or absence of protein in a food ingredient. In the protein content test study using copper sulfate ($CuSO_4$) reagent which produces Cu^{2+} ions that in alkaline conditions will react with polypeptides or peptide bonds that form proteins to form purple complex compounds and use sodium hydroxide (NaOH) as a base medium.[24] In this "*Ceamond Crispy*" protein content test experiment, positive test results were

indicated by the dormation of purple color in each "*Ceamond Crispy*" product formulation.

Fat test results

Fats and oils are triglycerides or triacylglycerols, both of which mean "triester (of) glycerol". The difference between a fat and an oil is arbitrary: at room temperature fats are solid and oils are liquid. Most of the glyceride in animals is in the form of fat, while the glyceride in plants tends to be oil. Fats are classified based on the saturation of bonds in their fatty acids. The classification is saturated and unsaturated fatty acids. Fats contain saturated fatty acids, namely fatty acids that do not have double bonds.[25] Due to the relationship between intake of saturated fatty acids and HDL cholesterol levels in CHD patients, this study uses very little fat so that it does not affect heart health.

As for this study, 3 drops of the solution were put into a test tube, the sample was added with 1 spoon of KHSO4, and samples containing fat would smell burnt fat and cause white smoke. The fat test experiment using "*Ceamond Crispy,*" showed negative test results for each formulation, which was indicated by the absence of a burnt fat odor and the absence of white smoke appearing in each formulation.

The addition of purple cabbage extract powder to the "*Ceamond Crispy*" product causes the fat content of the product to tend to decrease with increasing concentration of the extract powder. This could be because the purple cabbage extract powder does not contain fat, so the addition of purple cabbage extract powder to the "*Ceamond Crispy*" dough will cause the weight of the dough to increase. However, this does not increase the fat content of the product, so the "*Ceamond Crispy*" fat content will be lower with the addition of purple cabbage extract powder.[3]

Conclusions

Based on the research that has been done, it can be concluded that the results of laboratory tests showed that the Ceamond Crispy product positively contained anthocyanins, protein, carbohydrates, and negative results for fat. The product "Ceamond Cripy" has a taste like chocolate on F1, F2 and a slightly bitter chocolate taste on F3, and smells like vanilla. The product "Ceamond Crispy" is brown on F1, F2 and purplish brown on F3, and has a crunchy texture. Based on the results of the preference test conducted on 35 panellists for each formula. The most preferred "Ceamond Crispy" product is Formula 3 with a percentage of 54%. The results of the panelist questionnaire stated that they liked the product "Ceamond Crispy". This proves that the product "Ceamond Crispy" is safe for consumption by people of all ages and has the potential to be a healthy food for cardiovascular health.

Acknowledgement

Conflict of Interest

All authors declare there was no conflict of interest regarding this research.

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CASE REPORT

Effect of probiotic supplementation on wound healing in postoperative patients: A case report and literature review

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Abstract

Background: Delayed wound healing, particularly in chronic wounds, is a significant global public health issue. The World Health Organization (WHO) reports that over 6 million people in the United States experience delayed wound healing annually, resulting in a healthcare cost of $25 billion USD. Probiotics, known for their anti-inflammatory properties, have potential in influencing skin immunity by facilitating the transfer of cytokines and immune cells from Peyer's patches to the skin. Nevertheless, the precise impact of probiotics on postoperative wound healing remains an area with limited research.

Objective: Determine the effectiveness of probiotic supplements in wound healing in patients with surgical wounds

Method: Literature search is done by advanced searching on Pubmed, Cochrane, Scopus, and EBSCOhost with eligibility criteria determined by the author.

Results: There were three articles relevant to clinical questions and eligibility criteria that had been established, consisting of one systematic review article from the randomized controlled trial (RCT) study and two RCT articles. The SR/MA article includes good-quality RCT studies. The SR/MA article showed insignificant results on the effect of probiotic administration on healing. The RCT article showed significant results on the effect of probiotics on surgical wound healing, but the confidence level was low in one of the articles.

Conclusion: Probiotic supplementation on wound healing in postoperative patients is not conclusive. This can be affected by the type of probiotic strain, dosage, duration of administration, and location of the surgical wound.

Keywords: probiotic, wound healing, surgical wound

Case scenario

A 41-year-old woman came to the emergency room with complaints of an open surgical wound after incisional hernia repair after 2 weeks of SMRS. The patient said that the wound initially opened a little, then got bigger, and finally all opened after 1 week of SMRS. Initially, the wound oozed pus from the stitches and drain marks. Since all the stitches were open, pus could no longer come out

and pooled in the wound. Within 1 week the patient also complained of fever and pain in the surgical wound. From the physical examination found compos mentis awareness, blood pressure 108/67 mmHg, pulse 86 x/minute, respiratory rate 18 x/minute, SpO2 99% and temperature 36.5 ℃, body mass index 57.5 kg/m2, at physical examination distended, visible surgical scars in the median infra umbilical open with a size of 8 x 4 cm, based on organ impressions, pus and odor present, necrotic tissue present, no active bleeding. There was an open drain with a size of 2.5 cm x 1.5 cm, no pus and active bleeding, normal bowel sounds, supple, VAS 1-2 tenderness, and other physical examination within normal limits. Laboratory

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examination results showed Hb 8.8 g/dL, leukocytes 10,060/µL, platelets 375,000/µL, sodium 136 mg/dL, potassium 3.6 mg/dL, chloride 102.1 mg/dL, GDS 155 mg/dL and Albumin 2 mg/dL. The patient has received therapy for wound problems. In addition, the patient has been given nutrition as needed. The clinic's nutrition specialist plans to provide probiotic supplements to help heal wounds on the skin. The effect of probiotic supplementation is still being debated, so the authors want to find further evidence regarding the effectiveness of probiotic supplementation in the skin healing process in postoperative patients.

Introduction

Delayed wound healing has become a global public health problem, especially in chronic wounds. According to the World Health Organization (WHO), more than 6 million people are affected by delayed wound repairs each year in the United States at a cost of $25 billion (USD) to the Health system.[1] Chronic wounds impact the quality of life (QoL) of nearly 2.5% of the total population in the United States and the management of wounds has a significant economic impact on health care.[2] Caring for surgical wounds presents numerous difficulties, including the patient's underlying health conditions, the surrounding environment, and potential complications. Skin wound healing is a dynamic and highly regulated process of cellular, humoral, and molecular mechanisms that begins immediately after injury and can last for years. Any tissue damage to the normal anatomical structures with successive loss of function can be described as a wound.[3] Wound healing can be divided into four phases, namely hemostasis, inflammation, proliferation, and tissue remodeling.[4] Various things can affect disturbed wound healing. Patients with comorbid problems such as diabetes, vascular disorders, smoking, malnutrition, obesity, infection, immobilization, and administration of immunosuppressants.[4,5] Wound management begins with an assessment of the etiology of the wound and a patient-centered approach to managing systemic and lifestyle factors. Local management often begins with debridement, the removal of necrotic, infected, or

hyperkeratotic tissue by surgery or less invasive modalities.[6]

Apart from amino acids, vitamins and minerals that play a role in the wound healing process with anti-inflammatory effects, probiotics have also been studied to have anti-inflammatory effects. Probiotics are living microorganisms which, when consumed in adequate amounts, confer a health effect on the host. Probiotics primarily impact the inflammation phase, which plays a significant role in wound healing impairment. Recent studies in both humans and animals have shown a clear advantage in wound healing when probiotics are applied, influencing the inflammatory response through mechanisms involving oxytocin. Bacteriocins are antimicrobial peptides produced by both gram-positive and gram-negative bacteria. The gut is considered the major immune organ, with gut-associated lymphoid tissue (GALT) being the most complex immune compartment. Cytokines and immune cells from Peyer's patches can be transported via circulation to the skin, where they can modulate immunity and enhance defense mechanisms, providing a possible link in gut-skin communication.[7,8] Studies have shown that immune modulation derived from probiotic bacteria may be due to the release of anti-inflammatory cytokines in the gut. Nonetheless, the specific molecular interactions between probiotics and hosts are not well defined. The most widely used probiotics in humans are Lactobacillus (L.), Bacillus (B.), and Bifidobacterium (BB.), but also the genus Saccharomyces (S.) which is widely adopted in commercial products.[8] However, the specific role of probiotics in postoperative wound healing has not been widely studied.

Given the high state of inflammation in postoperative patients and there is still debate about the effectiveness of probiotic supplementation in wound healing, further evidence is needed regarding the effectiveness of probiotic supplementation in wound healing in postoperative patients. While laboratory and animal experiments suggest that probiotics could enhance skin healing, it is crucial to thoroughly examine the extent of evidence available in human studies.

Clinical questions

The target population in this study was postoperative patients. The factor studied as a therapy is the relationship of probiotic supplementation to wound healing in patients. The clinical question that we compiled was "Can probiotic supplementation accelerate wound healing in postoperative patients?"

P: Postoperative adult patients
I: Probiotic supplementation
C: Placebo
O: Wound healing

Methods

A literature review was conducted by two authors independently for English literature review of four databases Pubmed, Cochrane Library, ProQuest, and EBSCOhost. The search was carried out using advanced searching until March 2023 by combining the MesH Terms and abstracts/titles of each PICO component and using the boolean operator "OR" to increase sensitivity and "AND" to increase specificity as indicate in Table 1. The keywords used are "Probiotic*", "wound healing*", "surgical wound*", "surgical incision", "wound, surgical", "surgical, wound", "Incisions, Surgical". From each selected publication, information about the main author's name, year, study design, population characteristics, intervention, probiotics used, control group, and main results were extracted as indicate in Table 2. To assess the quality of the studies included in the literature review, critical assessment tools and levels of evidence are based on the Oxford Center for Evidence-Based Medicine was used.

Eligibility criteria

Inclusion criteria including patients undergoing surgery, received oral probiotic, study design was systematic review, meta-analysis, randomized controlled trial or clinical trial and has duration of wound healing and wound area outcome, publications in the last 10 years and was written in English. Exclusion criteria including research not conducted on humans, full-text *article* not available, articles in languages other than English.

Results

The results of the papers obtained in this study are shown in **Figure 1**, **Table 1**, **Table 2**, **Table 3**, and **Table 4**.

Discussion

The systematic review conducted by Togo et al.[9] aimed to compare the effects of oral or enteral probiotic supplementation on the wound healing of oral or skin wounds between the intervention group and the placebo-controlled group. Out of the 22 included studies, only 7 studies (n=6268) provided information on the effects of probiotic supplementation on surgical wound healing. The subjects were divided into two groups, totaling 348 subjects. The intervention involved oral probiotics or lozenges with a dosage of 2-15x109 CFU/day, administered before treatment, during treatment, or for up to 12 weeks. The outcomes assessed included the need for debridement, wound healing time, wound area, and clinical wound condition scores. The systematic review revealed a significant reduction in the need for debridement among pediatric patients receiving probiotic therapy. Positive results were also observed in surgical wounds and diabetic ulcers, with a higher incidence of wound complications in the control group.
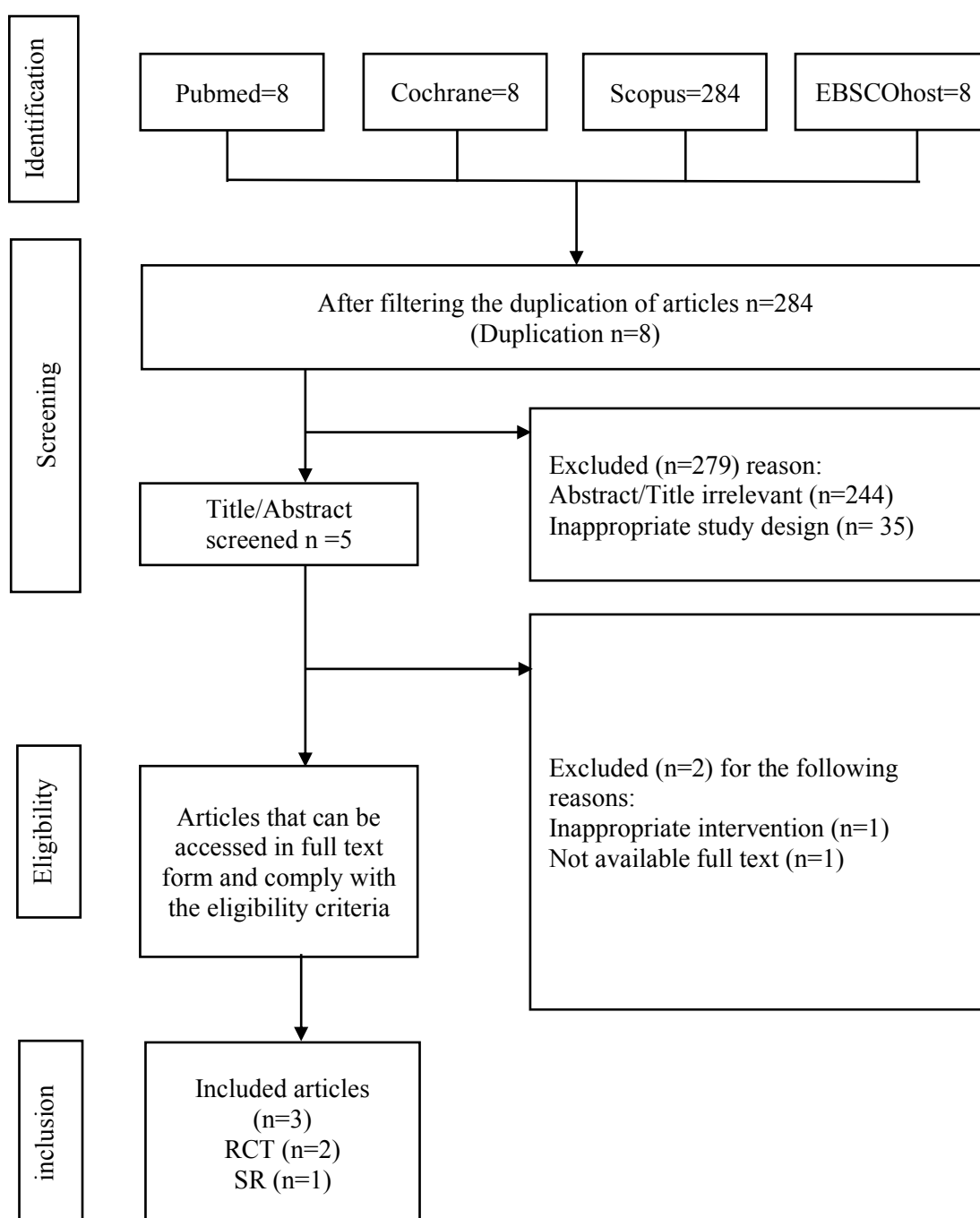
Figure 1. Prisma's flow chart

Table 1. Resources and search strategy

Database	Search Strategy		Hits
Medpub	(((Probiotic[Title/Abstract]) OR (Probiotics[Title/Abstract])) AND ((((Wound Healing[Title/Abstract]) OR (Wound Healings[Title/Abstract])) OR (Healing, Wound[Title/Abstract])) OR (Healings, Wound[Title/Abstract]))) AND (((((((Surgical Wound[Title/Abstract]) OR (Surgical Wounds[Title/Abstract])) OR (Wound, Surgical[Title/Abstract])) OR (Wounds, Surgical[Title/Abstract])) OR (Surgical Incision[Title/Abstract])) OR (Incision, Surgical[Title/Abstract])) OR (Incisions, Surgical[Title/Abstract])) OR (Surgical Incisions[Title/Abstract]))		8
Cochrane Library	ID Search Hits		8
	#1	probiotic OR probiotics	7982
	#2	MeSH descriptor: [Probiotics] explode all trees	3004
	#3	wound healing OR Healing, Wound OR Healings, Wound OR Wound Healings	15326
	#4	MeSH descriptor: [Wound Healing] Explode all trees	7605
	#5	Surgical wound OR Wounds, Surgical OR Surgical Wounds OR Surgical Incision OR Incision, Surgical OR Wound, Surgical OR Incisions, Surgical OR Surgical Incisions	22394
	#6	MeSH descriptor: [Surgical Wound] explode all trees	496
	#7	#1 OR #2	8980
	#8	#3 OR #4	16854
	#9	#5 OR #6	22394
	#10	#7 AND #8 AND #9	8
	#11	#10 in Trials	8
Scopus	(probiotic OR probiotics) AND (wound AND healing OR healing AND wound OR healing AND process) (surgical AND wound OR surgical AND site OR surgical AND incision OR wound AND surgical)		284
EBSCOhost	AB probiotic AND AB (wound healing or healing process) AND AB (surgical wound or surgical site)		8

Table 2. Study characteristic

Article	Study Design	Population	Intervention	Outcome
Wälivaara D.-Å., et al. (2019)[9]	*Randomized controlled trial*	Subject is: 64 patients over 18 years of age with impacted or partially impacted mandibular third molars with a history of pericoronitis	Patients divided into 2 groups received either L. reuteri probiotics or placebo lozenges for 2 weeks	Distribution of clinical cure scores after 1 and 2 weeks after third molar surgery.
Togo C, et al. (2022)[10]	*Systematic Review*	Subject is: 348 patients aged 11 months to 85 years with probiotic therapy on surgical wound healing	One arcticle evaluated probiotic: patients were divided into 2 groups receiving probiotics and a placebo	Laboratory taken at baseline, 60th day, 120th day
Mohseni S, et al. (2017)[11]	*Randomized controlled trial*	Subject is: 60 patients aged 40-85 years with grade 3 diabetic foot ulcers	Patients were divided into 2 groups that received probiotic capsules consisting of *Lactobacillus acidophilus, Lactobacillus casei, Lactobacillus fermentum,* and *Bifidobacterium bifidum* (2×10^9 CFU/g respectively) for 12 weeks	Rate CRP, IL-6, TNF-α

Table 3. Validity criteria

	Number of patients	Randomization	Similarity treatment and control	Blinding comparable treatment	Domain	Determinant	Measurement of outcomes	Quality of evidence*	Level of evidence**
Wälivaara D.-Å., et al. (2019)[9]	+	+	+	+	+	+	+	Moderate	1B
Togo C, et al. (2022)[10]	+	+	+	+	+	+	-	Moderate	1A-
Mohseni S, et al. (2017)[11]	+	+	+	+	+	+	+	Moderate	1B

* Quality of evidence according to GRADE guidelines, https://www.ncbi.nlm.nih.gov/pubmed/21208779
**Level of evidence according to Oxford Center of Evidence-based Medicine (CEBM), http://www.cebm.net.
+ clearly mentioned in the article; - not done; ? Not stated clearly
- Systematic review and meta-analysis with troublesome heterogeneity

Table 4. Relevance criteria

Authors	Population similarity	The similarity of determining factors	Outcome similarity
Wälivaara D.-Å., et al. (2019)[9]	+	+	+
Togo C, et al. (2022)[10]	+	+	+
Mohseni S, et al. (2017)[11]	+	+	+

In the RCT study by Wälivaara et al.[10], patients who underwent third molar tooth extraction surgery were given oral lozenge supplementation with three lozenges per day containing two strains, namely *L. reuteri* (DSM 17938 and ATCC PTA 5289, ProDentis®, BioGaia AB, Stockholm, Sweden), or placebo for 2 weeks. The active lozenges contained at least 2×108 live bacteria of the combined strains per lozenge. At the end of the 2-week follow-up, there was no difference between the groups. However, when analyzing the subset of 25 patients who attended the follow-up at 1 week separately, the distribution of healing scores showed a positive impact for the probiotic intervention group. In another study by Mohseni et al.[11], conducted on diabetic foot ulcer patients, supplementation with probiotic capsules containing *Lactobacillus acidophilus*, *Lactobacillus casei*, *Lactobacillus Fermentum*, and *Bifidobacterium bifidum* (each 2×109 CFU/g) or placebo was given. The results showed a reduction in the length, width, and depth of the ulcers. Additionally, the study had a low loss to follow-up rate of 1.6%. Therefore, the results of this study are statistically significant with a high level of confidence.[12] The study by Mohseni et al.[11] explains that cells from the ulcer layer examined after 10 days of *Lactobacillus plantarum* treatment showed a decrease in the number of wound bacteria, apoptotic and necrotic cells, modified interleukin (IL)-8 production, and induced wound healing. The anti-infective mechanism of probiotics in patients with diabetic ulcers may be attributed to their increased ability to combat pathogenic microorganisms or modulate the host immune response, as well as their production of various antimicrobial substances such as organic acids, hydrogen peroxide, low molecular weight antimicrobial agents, diacetyl, bacteriocins, and their anti-inflammatory properties. Additionally, the study by Wälivaara et al.[10] explains that the administration of probiotics in third molar surgery showed no significant difference in clinical wound healing scores between the groups and that there were no major complications or secondary infections in both groups. This lack of impact is likely due to the use of antibiotics after the procedure.

The study by Togo et al.[9] explains that the health-enhancing properties of probiotics depend on the strains provided. The type and characteristics of the strains are crucial because probiotics can regulate cytokine production and activate antimicrobial immune responses. For example, some probiotics can induce interleukin (IL)-12, which enhances interferon (IFN)-γ secretion and activates natural killer (NK) cells. However, probiotics also stimulate increased production of IL-10, which induces antibody production and reduces inflammatory responses, thus balancing and contributing to healing processes. *Lactobacillus* strains are capable of inducing the production of pro-inflammatory cytokines such as IL-12 and IFN-γ, as well as anti-inflammatory cytokines like IL-10, while Bifidobacterium strains generally exhibit better induction of IL-10 compared to Lactobacillus strains. However, an in vitro study found little evidence for strain-specific effects of six probiotics on NK cell activity and NK or T cell activation. Cytokine production is differently influenced by probiotic strains from different species. Therefore, the biological significance of these strain-specific effects in vivo still needs to be clarified. In this study, wound assessment was conducted using clinical scores, and probiotic treatment did not show significant effects. Skin grafting is the preferred treatment for deep skin burns, where necrotic tissue and inflammation are removed, and physiological wound closure is expedited. The reduced need for grafting in patients treated with probiotics may be attributed to a lower incidence of infection, which is the second most common cause of graft failure. There is a possibility that therapeutic microorganisms can enhance systemic immune function that supports the healing process. Furthermore, oral probiotic administration also enhances the deposition of collagen, which is essential for wound healing.

The differences in the results obtained in the three articles of this study can be attributed to several factors, such as the types of strains used, the dosage of probiotics, the duration of administration, and the types of wounds experienced, as described in the studies included in Togo et al.[10] research. The study by Wälivaara et al.[10] explains that the clinical healing was assessed

2 weeks after the surgery, which was different from the initially planned assessment at one week after the procedure. Additionally, only 25 patients were available for follow-up in the first week, which supports the idea that probiotic administration can enhance healing. Mohseni et al.[11], who administered probiotics for 12 weeks, observed a significant reduction in the size of diabetic foot ulcers.

In the three studies, no serious side effects were reported during the interventions. The strengths of these studies include one study showing good validity and two articles reporting significant results, although the research by Wälivaara et al.[10] had a low level of confidence. The limitations of these studies are the relatively small sample sizes, variations in the types of strains used, and varying dosages of probiotics, which could potentially affect the effects on surgical wound healing.

In the clinical scenario, a 41-year-old female patient presents with an open surgical wound complaint following the repair of an incisional hernia. The age and diagnosis characteristics in the three studies are similar to those of the patient in the clinical scenario. The supplementation of probiotics for patients with surgical wounds cannot be recommended at this time due to the variations in probiotic strains, dosage, and duration of administration, as well as the low level of confidence in the research results.

Conclusion

The effectiveness of probiotic supplementation in accelerating wound healing in patients with surgical wounds has not shown consistent results. Based on the reviewed journal articles, it cannot be concluded that probiotic supplementation may improve surgical wound healing. This could be influenced by different strains, dosages, and locations of the surgical wounds, resulting in the administered probiotics not being strong enough to provide a significant effect in accelerating wound healing. Therefore, further research is needed to investigate the supplementation of probiotics in the wound healing of patients with surgical wounds, considering adequate strain types, dosage, duration

of administration, as well as evaluating any potential side effects and safety.

Conflict of Interest

The authors declare that there is no conflict of interest.

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