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EDITORIAL

Seaweed as novel food for prevention and therapy for life style related disease

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Introduction

Seaweed has long been known and consumed as a functional food and folk medicine, especially in people who live in coastal areas. Research on seaweed has recently increased with the surge need for alternative sources of functional food to deal with health problems related to lifestyle, such as obesity, diabetes, hypertension and cardiovascular disease. Epidemiology studies have found that population consumed seaweed is on a regular basis have significantly less diet-related diseases.[1,2] Even the largest population of old age is in Japan, which consumes the most seaweed in the world.[1,3] In countries such as Japan, China, and Korea, approximately 66% of algae species have been used as a daily ingredient in their dishes for many years.[4]

Seaweed are autotrophic organism with unicellular morphology without roots, stems, leaves and flowers and is called a thallus, smooth, has many branches both long and short, the colors are usually red, brown or green. Seaweeds are commonly classified into three taxonomic groups Rhodophyta (red seaweed), Phaeophyta (brown seaweed) and Chlorophyta (green seaweed). The nutrient content in seaweed is very dependent on the type of marine biota, location and environment where the seaweed grows, so it is more varied than land plants.[5,6] Seaweeds are abundant source of nutrient protein, dietary fiber, vitamin and minerals as a result of stressful situations on seaweed tissues, exposure to ultraviolet radiation, changes in temperature and salinity, or environmental pollutants.[7] Seaweed is rich in: essential amino acids, dietary fiber, ω-3 fatty acids, mineral and vitamins A, B, C, and E compared to the terrestrial plants and animal-based foods.[8,9]

Protein

Seaweeds protein content depends on the type of seaweed and varies widely, protein contents was higher in red and green seaweeds (10–47% of dry weight) than those found in brown seaweeds (5–24% dry weight)[9]. Most seaweeds have a higher protein score than all plant-based proteins, with the exception of soy, which has a score of 1.0.[10,11] However, the high polyphenolic content of seaweeds can reduce the digestibility of seaweed proteins, giving a slightly lower score on the protein digestibility-corrected amino acid scale.[12] Seaweed proteins are rich in glycine, arginine, alanine, and

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glutamic acid. Their limiting amino acids are lysine and cystine[9,13]

Bioactive proteins that can be extracted from seaweed are phycobiliproteins and lectins.

Some studies have shown that phycobiliproteins extracted from red algae (phycoerythrin) could be beneficial in the prevention or treatment of neurodegenerative diseases caused by oxidative stress (Alzheimer and Parkinson's) due to their antioxidant effects.[9,14] Lectins can recognise and bind to specific carbohydrate structures and take part in many biological processes like intercellular communication and those isolated to date have highly novel amino acid sequences.[15]The lectins found in Bryothamnion spp. (Rhodophyta) show an inhibitory effect on the growth of strains of Steptococcus spp.; therefore, they can be used as bactericidal compounds.[9,16] Seaweed also contains peptides which have angiotensin converting enzyme inhibitor (ACE-I) activity.[17,18]

Protein digestibility is limited by the non- protein fraction, which accounts for 10–20% of the nitrogen content.The isolation of protein from algae is difficult due to viscous polysaccharides; the use of buffers and detergents for effective cell lysis and removal of polysaccharide was proposed.[19]

Carbohydrate

Seaweeds contains carbohydrate as polysaccharides that has been studied for their physiological and biological potential. Physiological potential of seaweed polysaccharides as sources of fiber. Insoluble fiber: cellulose is an indigestible, non-nutritive polysaccharide as structure of cell walls of seaweeds and constitutes from 2% to 10% of total polysaccharides.[10] Soluble fiber is characterized by its ability to form viscous gels, in contact with water, in the intestinal tract. Soluble fiber is fermented in high proportion, and its main properties are related to the decrease of cholesterol and glucose in blood and the development of intestinal microbiota.[9] Meanwhile, insoluble fiber or cellulose will decrease gastrointestinal transit time and prevent constipation.[9,20]

Seaweed cell walls are enriched with sulfated polysaccharides, that progressively investigated for their potential value in food and pharmaceutical applications.[21] Sulfated polysaccharides in seaweed: laminarans and fucoidans in the *Phaeophyta*, carrageenans in the *Rhodophyta*, and ulvans in the *Chlorophyta*.[22] One of the most vital properties linked with sulfated polysaccharides is their anticoagulant characteristics. Sulfated polysaccharide of green seaweeds from *Ulva* and *Enteromorpha*, are called ulvans, and their oligosaccharides, have demonstrated strong antitumor and immune-modulating activities, antihyperlipidemic activities and anticoagulant activities.[23]

The main products of fiber fermentation are short chain fatty acids (SCFA), mainly acetic, propionic, and butyric, which lead to a drop in pH and even to the stimulation of the growth of certain micro-organisms, modifying the bacterial metabolism in the colon, known as the prebiotic effect.[6] In addition, SCFA may have a beneficial effect on cholesterol metabolism.[9,24] In animal studies fed with red seaweed extract, the number of prebiotics *bifidobacterium* and *lactobacillus* increased.[25] Al-Sheraji, et al., concluded that prebiotics increase absorption of Ca and Mg, can affect blood sugar levels and improve blood fat levels.[26] In experiments with mice, those who were hypertensive and then given a diet containing 10% fiber powder from brown seaweed showed a significant reduction in blood pressure and a reduced incidence of stroke (0 versus 100% in the control group on day 30 of the experiment). In this study, it is suspected that alginic acid from seaweed fibers inhibits the absorption of Na in the digestive tract and has the effect of preventing an increase in blood pressure.[27]

Fat

The fat content of seaweed is low, about 1-5% of dry weight with a composition of polyunsaturated fatty acids such as omega 3 and omega 6. Omega 3 is mostly contained in green seaweed, while red and brown seaweed contains lots of fatty acids with 20 carbon atoms such as eicosapentanoic acid and arachidonic acid.[5,28] The ratio between *n*-6 and *n*-3 fatty acid is considered an index for evaluating the nutritional value of a dietary lipid source.[29,30] An imbalance between *n*-6 and *n*-3 FAs in biological tissues is known to cause inflammatory processes in the body.[30] since in western diets, the ratio has risen to around 15–20:1,[31] this far beyond the ideal

ratio,(<5:1).[29] Since the *n*-6/*n*-3 ratio of the seaweed was within the recommended range of <5:1, they have the potential to enhance the nutritional quality of food products, e.g. by regulating low-density lipoprotein and cholesterol levels, and help to prevent inflammatory, cardiovascular diseases and nervous system disorders.[10,29]

Fatty acid composition also varies between different geographic regions; for example in warm water *chlorophyta* contain higher saturated fatty acid and oleic acid, but in cold water it will have higher polyunsaturated fatty acids levels.[14,32,33] Polyunsaturated fatty acids (PUFA) are useful in regulating blood clotting, blood pressure, helping the function of the brain and nervous system. PUFA produce mediators called eicosanoids to regulate inflammatory reactions.[5] Long chain PUFAs (LC-PUFAs) play key roles in cellular and tissue metabolism, including the regulation of membrane fluidity, electron and oxygen transport, as well as thermal adaptation.[14]

Vitamin and mineral

Seaweeds contain both water- and fat-soluble vitamins.[6,28] Seaweed foods offer one of the few vegetarian alternatives for cobalamin (vitamin B_{12}) in the diet. Ortiz in 2006 reported that 100 grams of seaweed can meet the daily needs of vitamins A, B_2, B_{12} and two-thirds of vitamin C.[34] The content of red seaweed vitamins includes vitamin B_{12}, vitamins C, vitamin E and carotene. Vitamin C levels can reach 100-800 mg / kg in red seaweed. Vitamin E which acts as an antioxidant is also contained in seaweed. The availability of vitamin E in brown seaweed is higher than green and red seaweed. This is because brown seaweed contains α, β, and γ-tocopherol, while green and red seaweed only contains α-tocopherol.[28,35.] This vitamin is beneficial to health as an antioxidant, strengthens the immune system and is anti-aging.[5,35]

Seaweed also contains minerals more than 36% dry weight with the content: calcium, magnesium and iodine as the main minerals.[28] The natrium content in seaweed is generally low around 2-3%, while the levels of kalium is around 5-6%, so the natrium / kalium ratio of seaweed is around 0.3. Composition of Na and K in seaweed is thought to be useful as an antihypertensive in mild hypertension.[36] Seaweed also contains high levels of magnesium and calcium compared to land plants such as vegetables.[20] Seaweed calcium can reach 7% of dry weight.[28]

Limitation

Seaweed bioactive consistency is a challenge for commercial application, since bioactive substance of seaweed is greatly vary and influenced by many factors, such as natural variability: type of species, time and location of harvest.[32] Other limitation are accumulation of undesirable elements, heavy metals and other pollutants, such as: cadmium, mercury, plumbum and arsenic.[29] Cadmium level was relatively low in green seaweed compared with red and brown seaweed. The concentrations of mercury were relatively low in all species.[29,37] Lead was found to be low in red and brown seaweed compare with in green seaweed.[29,38] Arsenic in biological matrices exists either in organic forms or as inorganic arsenic form, organo arsenic forms are considered to be non-toxic or of low toxicity. Total arsen were found in brown algae higher than other taxonomic groups with gradation as brown seaweed > red seaweed > green seaweed.[37,38,38]

Conclusion

Seaweed has long been consumed as a functional food and folk medicine for people who live in coastal areas. Seaweed contains elements of protein, carbohydrates including fiber, vitamins and minerals with a composition that can play a role in the prevention and therapy of diseases associated with modern life patterns. There are limitations of seaweed that can be applied commercially, namely the consistency of bioactive levels and the presence of unwanted substances such as heavy metals and other pollutants.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ARTICLE REVIEW

Medical nutrition therapy in enterocutaneous fistula: A step-by-step approach

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Abstract

As part of ECF management, nutrition plays a vital role in determining the prognosis as a predicator for both morbidity and mortality. Malnutrition can occur as a preceding situation or complication in ECF cases caused by the underlying disease, decreased food intake, increased protein requirements associated with systemic inflammation, and increased nutrient loss associated with the amount of fistula output. Therefore, nutrition management can act as prevention, therapy, or even both. The purpose of nutritional medical therapy in ECF cases is to adequately estimate nutritional needs, maintain fluid and electrolyte balance, and stimulate spontaneous ECF closure whenever possible. An analysis of nutrition needs has to be carried out individually by considering the etiology, the anatomical fistula location, and the amount of output. In the following article, we will discuss a comprehensive step-by-step nutrition treatment, by taking into account nutritional routes, macronutrient and micronutrient requirements, specific nutrients, pharmacotherapy, and monitoring and evaluation as to produce an optimal clinical outcome.

Keywords enterocutaneous fistula, malnutrition, nutrition

Introduction

Enterocutaneous fistula (ECF) incidence varies from 5 to 10% according to the etiology.[1] About 75% of ECF cases are adhered to iatrogenic causes which generally result from surgical complications, while the rest are linked to spontaneous causes such as inflammatory, radiation, and trauma conditions.[2,3] At the present, there is no incident data concerning ECF cases in Indonesia.

It is estimated that 50-90% of ECF patients experience nutritional problems, including malnutrition, dehydration, or electrolyte disorders.[4] Sepsis, malnutrition, and fluid and electrolyte imbalance, referred to as "fistula triad", significantly increase the risk of mortality and significantly reduce the rate of spontaneous fistula closure.[2] Patients with ECF are at high risk of malnutrition due to decreased food intake, ineffective nutritional therapy resulting from a large number of nutrients that come out along with enteric secretions, and changed metabolism caused by the underlying disease.[5,6]

Optimal ECF management involves a multidisciplinary team, consisting of surgery, nutrition, nursing, and pharmacy departments. Institutions with sufficient experience and appropriate ECF treatment can reduce the mortality rate by up to 50%.[1] In terms of prognosis, it is found that patients experiencing no malnutrition are 15 times greater to have spontaneous closure of fistulas.[7,8] As cited from Davis KG et al, the rate of

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fistula closure is also twice lower in patients who do not receive nutritional interventions than in those who receive nutritional interventions.[4] Thus, it is crucial to comprehend a step-by-step approach of nutrition management in order to reduce the rates of both morbidity and mortality in ECF cases.

Step-by-Step approach in ECF nutrition management

In ECF nutrition management, fluid resuscitation, electrolyte imbalance correction, and sepsis control have to be conducted before nutrition is given to ECF patients.[1] However, it is important that a nutrition plan has previously been well prepared for them. In this regard, nutrition management typically includes assessing patients' nutritional status, selecting the nutrition routes, determining macronutrients, micronutrients, and specific nutrients, providing pharmacotherapy, and carrying out monitoring and evaluation. These proposed steps are presented in **Figure 1**.

1. Assessing patients's nutritional status

Malnutrition screening has to be done at the beginning of the diagnosis. If malnutrition is not detected during the initial diagnosis, periodic screening then becomes necessary. To date, no malnutrition screening methods are validated explicitly for use under ECF conditions.[11] Some of the validated screening tools that can be used easily are Nutritional Risk Screening (NRS) 2002, Malnutrition Universal Screening Tool (MUST), and Subjective Global Assessment (SGA).[16]

Patients with ECF often experience malnutrition caused by the underlying disease, decreased food intake, increased protein requirements associated with systemic inflammation, and increased nutrient loss associated with the amount of fistula output. Nutritional status functions principally as a predictor of spontaneous fistula closure. According to de Aguilar-Nascimento, et al., patients with no malnutrition are 15 times greater to have spontaneous closure of fistulas (OR = 15.4 [95% CI = 1.1-215.5]; p = 0.04).[8]

Despite being frequently measured before and during nutritional therapy of ECF patients, serum protein levels do not function as a marker for sensitive nutritional status. Decreased concentrations of serum plasma albumin, transferrin, retinol-binding proteins, and prealbumin are likely a consequence of systemic inflammation associated with ECF.[11] Besides, albumin levels can be found to be extremely high in ECF patients due to decreased plasma volume, especially in high-output fistulas.[17] Prealbumin, also known as transthyretin, is an acute negative visceral protein and reactant that is normally influenced by the same factors affecting albumin levels. Nonetheless, it is more recommended than albumin due to having a relatively short half-life of 2 days. Subsequently, prealbumin concentrations can become a predictor of recent food intake.[18] This means that serum protein concentrations obtained before and during nutritional therapy can not be used as a marker of the nutritional status, but as an indicator of the prognosis.[11]

2. Stabilizing patients through rehabilitation phase

As regards with rehabilitation phase, oral nutrition is normally stopped (nil per os, NPO), and nutrition is given through total parenteral nutrition (TPN). TPN should be given within a short duration to reduce the risk of complications, especially if given through a central route with a target nutritional requirement of 30-40 ml/kg of fluid, 30-40 kcal/kg of calories, and 1.5-2 g/kg of protein. The strict control of blood glucose levels is needed to avoid the occurrence of hyperglycemia. The ratio of carbohydrates, fats, and proteins in TPN can be modified according to patients' medical histories.[3] When hemodynamics are stable, it is advisable to immediately provide enteral nutrition (EN) to prevent villous atrophy, which is also termed as "gut feeding". Clear liquid diets can be given as an option during gut feeding, with components that provide energy, electrolytes, and no concentrated or carbonated sweeteners and leave minimal residues in the gastrointestinal tract. Examples of clear liquid diets include broth, coffee, tea, sugar-free gelatine, or drinks with alternative sugars.[9]

3. Determining patients' nutrition requirements

Nutrition routes

Nutritional routes should be selected based on various considerations, including the location of fistulas, the length of the healthy intestine for nutrient absorption, the signs of distal obstruction, and the amount of fistula output. An in-depth assessment of fistula characteristics (e.g., anatomical position and length) is required. In ECF cases without distal obstruction, patients with low output (<500 mL/day) can tolerate an oral diet. If oral food intake is associated with a significant increase in ECF output or is not tolerated by patients for other reasons, EN can be tried and tolerated when enteral access can be obtained. Relative contraindications to EN include insufficient intestinal length (75cm), intestinal discontinuity, intolerance of symptoms to enteral nutrition, increased fistula output leading to electrolyte disturbances at the beginning of enteral nutrition, and inability to maintain food access.[6]

Patients' EN tolerance and ability to achieve the target intake must be evaluated on a daily basis. If nutritional goals cannot be achieved only with EN, combined nutrition therapy of EN and PN can be initiated. High-calorie supplementary drinks can also be an alternative to meeting patients' calorie requirements.[1] Besides having advantages in terms of lower cost and reduced risk of infection, administration of at least 20% of nutrients through enteral nutrition can help maintain intestinal flora, reduce bacterial translocation, and maintain mucosal integrity and immune function.[10]

ECF patients with high output (>500 mL/day), experiencing intestinal obstruction, ECF drainage that significantly worsens wound conditions and skincare or interferes with the ability to maintain fluid and electrolyte balance when EN is used, require parenteral nutrition (PN) to meet nutritional needs to support spontaneous or surgical ECF closure.[11] Some contraindications to PN administration are impaired liver function, difficulty in vascular access, or infection in the vicinity of the vascular access location. In general, PN is required in most high-output ECF patients, although it is only in the early phase, and it has been used to reduce ECF output secretion by 30% to 50% and contribute to ECF closure.[12] The flow path of selecting nutritional pathways for ECF patients is provided in **Figure 2**.

An oral route can be chosen for ECF patients with high output, with the following modifications: i) limiting low sodium fluid intake to 500mL/day, ii) providing patients with high sodium oral solution (90-120 mmol/L sodium level), iii) giving nutrition in forms of solid food and fluid in a small amount, and iv) providing combined administration of proton pump inhibitors, antimotility drugs, and octreotide.[13] Home Parenteral Nutrition (HPN) is recommended when patients are medically stable and fistula output can be managed. The example can be taken from patients awaiting surgeries.[11]

Fistuloclysis is defined as "a technique using fistulas as the main enteral pathway for access and entry of food ingredients, formulas, or gastrointestinal secretions". Fistulas are a low-cost method compared to the use of standard polymer nutrients instead of PN, but are rarely performed because of technical, anesthetic, and patient comfort issues. Fistuloclysis technique requires the presence of experienced medical personnel for the installation in order for the food hose to remain stable, unleaked, and unattracted by peristalsis. Leakage of fistuloclysis will cause skin corrosion, thus allowing for infection. Fistuloclysis can stimulate fistula epithelialization, so it can reduce the possibility of spontaneous closure of fistulas.[12] Therefore, fistuloclysis is only recommended in fistulas which are predicted not to close spontaneously. In the administration of initial fistuloclysis, it is recommended to use a polymer formula, which can be converted into an oligomeric diet if intolerance occurs.[11]

The volume of ECF output also needs to be taken into consideration. Generally, fistuloclysis can be used an option in ECF cases when the location is proximal to ensure that nutrition can still be absorbed sufficiently or when TPN administration is not applicable or contraindicated. As stated by Coetzee et al.14, re-administration of chyme through fistuloclysis does not cause side effects and can be considered to increase enteral feeding tolerance and maintain fluid and electrolyte homeostasis. Although fistuloclysis is normally carried out in low-output ECF, Niu et al. 15 stated that in high-output ECF cases (in 1500-2000 mL/day),

nutritional administration through fistuloclysis can be conducted by percutaneous enterostomy over a long period of time and can provide good clinical outcome.

Energy requirements

Energy requirements should be assessed for patients with ECF. In this regard, the most accurate method for calculating energy requirements is by using indirect calorimetry. If indirect calorimetry is not applicable, the Harris-Benedict equation can be used to calculate nutrient requirements. ECF patients typically have catabolic and hyper-metabolic conditions. Basal energy requirements can be estimated using the Harris-Benedict equation with a modification of 1 to 2.5 times from basal energy requirements of healthy adults, depending on the amount of output.[1] According to the ESPEN recommendation, the guidelines outlined in the Rules of Thumb can also be applied to ECF patients who have complications of intestinal failure, i.e., energy requirements of 25-35 kcal/kg/day, depending on patients' clinical conditions.[19]

In obese patients with ECF, nutrition can be given to critical patients according to the guidelines set by ASPEN and Society of Critical Care Medicine (SCCM). For instance, requirements vary from 11 to 14 kcal/kg of body weight per day if BMI is in the range of 30-50kg/ m2; and requirements range from 22 to 25 kcal/kg of body weight per day if BMI is more than 50kg/m^2.[20]

Macronutrient needs

In patients with ECF, the amount of protein loss through enteric secretion can reach 75 grams a day.[1] The provision of protein in ECF patients is based on the amount of output produced by enteric secretion. However, it can be given 1.5-2.0 g/kg/day in general. In patients with entero-atmospheric fistulas and high-output ECF, protein administration can stand at 2.5 g/kg/day.[11] In obese patients with ECF, protein administration of 2g/kg of body weight per day is recommended for patients with BMI at a range of 30-40kg/m^2; and protein administration of 2.5 g/kg of body weight per day for those with BMI of >40 kg/m^2.[20] To date, there are no specific recommendations regarding carbohydrate and fat requirements for ECF patients.

Micronutrient needs

Vitamins and minerals are wasted because of either enteric fluid secreted by ECF patients or impaired absorption associated with gastrointestinal dysfunction. As a result, deficiencies for these types of micronutrients can be predicted by examining the anatomical digestive dysfunction that occurs in patients. Fistulas that take place in the proximal jejunum, for example, are likely to make them suffer from deficiencies of fat-soluble vitamins and water-soluble vitamins. However, if fistulas are situated in the ileum, particularly before 50-60 cm of terminal ileum, they will have deficiencies of vitamin B12 and fat-soluble vitamins. In this case, vitamin B12 needs to be injected. Besides, patients will get exposed to suffering from zinc and vitamin C deficiencies. With high-output ECF, patients will also be prone to have magnesium deficiency. Consequently, administration of intravenous magnesium sulfate or oral magnesium chloride can be given to increase enteral absorption.[2] In relation to this, it is suggested to administer twice the standard requirements for vitamins and minerals and five to ten times the standard requirements for zinc and vitamin C, especially for high-output fistulas.[1]

Specific nutrients

As regards with specific nutrients, there is no certain advice on the use of immunonutrient formulas due to inadequate evidence. However, oral glutamine supplementation has been used to reduce the rate of mortality and increase the closure of fistulas. Glutamine, apart from being the main nutrient of intestinal cells, plays an important role in the immune system by increasing secretory IgA production in the intestinal mucosa.[11] As said by de Aguilar-Nascimento, et al.[8], fistula resolution is 13 times greater in patients receiving oral glutamine of 0.3 g/kg/day in addition to PN (OR = 13.2 (95% CI = 1,1-160.5); p=0.04). Nevertheless, glutamine metabolism will not be optimal in individuals with kidney, liver, or sepsis failure, since they have a higher risk of toxicity.[11] According to a study by Martinez et al.[21], enteral administration of 4.5 g of

arginine and 10 g of glutamine in a preoperative ECF patient for seven days can reduce the recurrence risk and the inflammatory cytokines for one week postoperatively. Other immunonutrient supplements such as arginine, omega-3 fatty acids, and nucleotides have yet to be proven in ECF cases.[16] Omega-3 is regularly indicated in critically ill patients, yet the current evidence gives rise to controversy.[22–24]

4. Providing patients with pharmacotherapy

In adult patients with high-output ECF, administration of somatostatin and somatostatin analogs is recommended as a method to reduce effluent drainage and increase spontaneous closure. In relation to somatostatin, it has a very short half-life of 1-2 minutes and is naturally produced in the pancreas of the digestive tract. Besides, octreotide is an example of somatostatin analogs and has a much longer half-life of 113 minutes. Somatostatin and somatostatin analogs can inhibit the release and secretion effects of varying gastrointestinal hormones and increase the absorption of water and electrolytes, thus extending the intestinal transit time and, eventually, reducing the volume of gastrointestinal secretions.[11]

Despite the support of varied meta-analyses[25–27] to the effectiveness of using somatostatin and somatostatin analogs in increasing the likelihood of spontaneous closure, de Vries, et al.[28] mentioned that somatostatin and its analogs are not conclusive in their benefits for reducing fistula output. In the study, three classes of drugs, namely proton pump inhibitors, antimotility agents (loperamide), and histamine receptor antagonists, can reduce fistula output effectively with a confidence level of 2b.

5. Carrying out monitoring and evaluation

Some of the benchmarks for successful nutritional management in ECF cases include achieving an anabolic state, which is regularly signaled by weight gain and increased levels of albumin, prealbumin, and transferrin, and meeting the needs of micronutrients for optimal healing.[1] Albumin, prealbumin, and transferrin themselves are acute-phase proteins whose levels are not accurate under conditions of acute stress and sepsis. Serum albumin is the most common plasma protein, representing about 50% of the total protein content (3.5-5 g/L). Albumin production in the liver is regulated by osmolarity and oncotic pressures. It is stimulated by hormonal factors (insulin, cortisol, and growth hormone) and is inhibited by acute-phase cytokines, such as interleukin (IL) -6 and tumor necrosis factor (TNF)-α. Futhermore, prealbumin and albumin levels provide an indirect assessment of visceral protein storage, while transferrin is the main iron transport protein in plasma. Albumin and transferrin levels have been used to predict the rates of spontaneous closure and mortality.[1] Spontaneous fistula closure is 18.1-fold greater in ECF cases with improvement in serum albumin compared to those without repair.[8] Prealbumin levels can function as an indicator of nutrition, followng that they can describe the adequacy of protein due to a very short half-life.[18,2] The use of the c-reactive protein (CRP) test is not specific in ECF cases, but can be used in conjunction with prealbumin. The ratio of CRP to prealbumin has been validated to be prognostic to spontaneous closure of fistulas. For patients with a ratio of less than or equal to 0.2, fistula closure occurs in 87.0% (95% CI, 74.0-94.3), whereas for patients with a ratio of greater than 1.0, no fistulas are closed.[17]

Anthropometry evaluation in ECF cases is given to body weight, body mass index (BMI), mid-upper arm circumference (MUAC), and thick skin folds. The measurement of MUAC can provide a more accurate estimate in patients with edema. For patients with unstable fistula output, there is a high risk of dehydration, causing the results of weight measurements to become biased. The same condition arises for bioelectrical impedance analysis (BIA). This examination will only be accurate in individuals with stable fluid balance because it is influenced by body cell mass, integrity, and function of cell membranes.[11] Nonetheless, anthropometric and biochemical tests (electrolytes, hemoglobin, CRP, IL-6, albumin) are still recommended to monitor the risk of dehydration and malnutrition.

Intake tolerance needs to be evaluated to assess the provided nutritional therapy and supplemental nutrition. The clinical symptoms of refeeding syndrome also have to be evaluated in patients, especially those with malnutrition. In this regard, malnutrition screening needs to be done regularly to

identify the presence of malnutrition as early as possible, as given in Chapter 2.2.[11] Patients receiving enteral nutrition through either duodenum or jejunum are at risk for developing dumping syndrome's symptoms.

When patients receive EN, their tolerance to EN and ability to achieve the target intake must be assessed daily.[11] The lipid profile can be examined from ECF patients, especially those receiving PN. Increased triglyceride levels are frequently found in ECF cases, which can lead to dysregulated immune system, heart and lung functions, and increased liver steatosis. As stated by Visschers et al.[29], sepsis, PN, high-output small intestinal fistula, and inflammatory bowel disease are independent risk factors for hypertriglyceridemia. In clinical practices, triacylglycerol containing long-chain fatty acids (LCFA) is a major component of PN in PN lipids. The transport of LCFA depends on the carrier protein in the cell membrane, which is responsible for transporting fatty acids into cells and mitochondria to undergo oxidation. Increased levels of LCFA that are beyond the amount of carrier protein will result in accumulation, manifested by liver steatosis.

Nitrogen balance has a clinical significance, which indicates patients' anabolic status.[1] It can be calculated by assessing the amount of nitrogen intake and nitrogen output. To do this, urine needs to be stored for 24 hours to calculate the urine urea nitrogen level. Nitrogen balance will be meaningful only if patients experience sepsis resolution. If the value is negative, this indicates that the nutritional therapy given needs to be evaluated and modified. In ECF cases, a correction factor in the calculation of nitrogen balance due to protein loss through fistula output must be considered with additional 1g of nitrogen output for every 500 ml of fistula output.[30] The modified nitrogen balance equation in ECF patients applies as follows: Nitrogen balance = [Protein intake (g) ÷ 6,25] - urine urea nitrogen (NUU) + 4 g + (2 g × amount of enteric fluid loss in liters)].[12]

Citrulline, a non-essential amino acid produced by enterocyte cells, has high sensitivity and specificity to predict permanent bowel failure when the serum level is below 20 mol/L. Citrulline is also an alternative biomarker to assess the intestinal length that is functional for absorption.[18]

If fistulas do not close spontaneously within 30 to 40 days or they cannot close due to various comorbidities, surgery should be considered immediately by maintaining the nutritional support. Aside from this, an acronym is commonly used to remember the factors that complicate spontaneous closure, namely "FRIEND". This acronym stands for F - Foreign body; R - Radiation; I - Inflammation or infection; E - Epithelialization of the fistula tract, N - Neoplasm; and D - Distal obstruction.[31]

Based on the location, spontaneous closure is more likely to occur in upper gastrointestinal fistulas (proximal to the duodenojejunal flexure). Fistulas located in the upper gastrointestinal tract are generally side fistulas without any residual disease of the gastrointestinal tract. These fistulas differ from lower gastrointestinal fistulas that are commonly associated with Crohn's disease, radiation enteritis, or ischemia. Although the rates of spontaneous closure vary considerably between upper and lower gastrointestinal fistulas, their rates of mortality are quite similar.[32]

Conclusion

Enterocutaneous fistula (ECF) management requires a multidisciplinary team as an approach to achieve an optimal clinical output. The purpose of nutritional medical therapy in ECF cases is to adequately estimate nutritional needs, maintain fluid and electrolyte balance, and stimulate spontaneous ECF closure whenever possible. To achieve an optimal outcome, an analysis of nutrition needs has to be conducted individually by considering the etiology, the anatomical fistula location, and the amount of output. This appears to be so important that the selection of nutritional pathways, the regulation of macronutrient and micronutrient requirements, the use of specific nutrients, and the provision of pharmacotherapy can be made with the right indications.

It is preferred that EN therapy is provided in ECF cases with low output, proximal location, and no distal obstruction. However, combined nutrition therapy of EN and PN can be initiated if the intake cannot be toleranced. Energy requirements should be measured by using indirect calorimetry. If indirect calorimetry is not applicable, it can be altered to other standard equations such as the

Harris-Benedict or the Rules of Thumb. As regards with the provision of protein, it is given 1.5-2 g/kg/day based on patients' clinical considerations. Micronutrient supplementation may be needed in cases of high-output fistulas. Glutamine and specific nutrients can increase the likelihood of spontaneous closure of fistulas and are associated with a better postoperative output. For instance, pharmacotherapy, somatostatin, and its analogs are recommended in high-output ECF cases.

In addition, evaluation and monitoring have to be carried out regularly in order to identify complications, particularly for sepsis, dehydration, and malnutrition. Anthropometric assessments to daily body weight, fluid balance, nitrogen balance, vital signs, and biochemistry (prealbumin, CRP, lactate, lipid profile, organ function, and electrolytes), also function as essential indicators to determine the success of nutrition therapy.

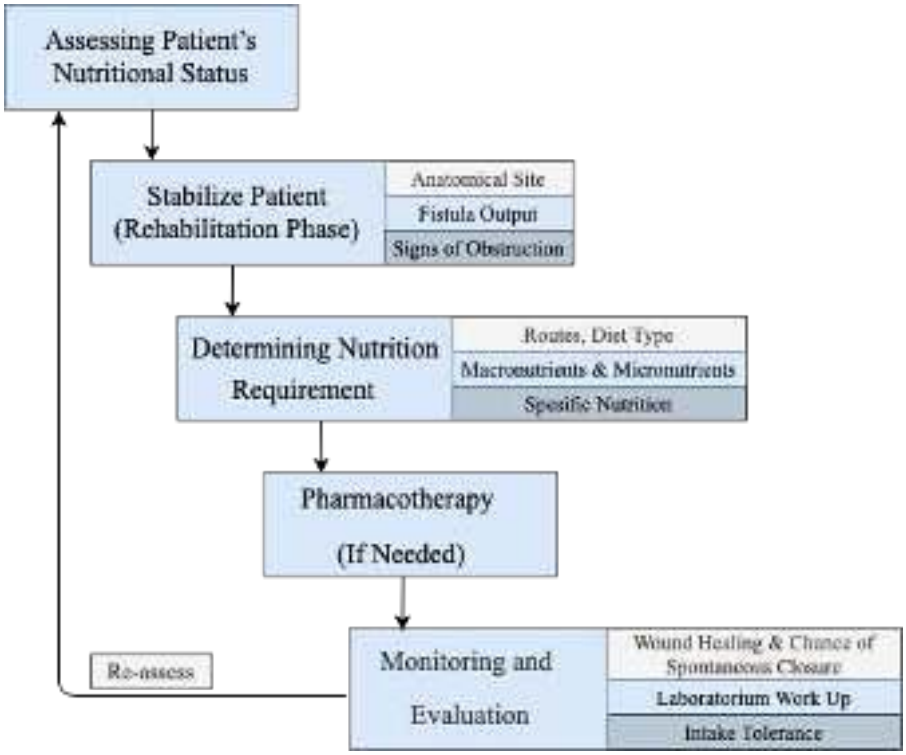

Figure 1. Proposed algorithm of nutrition management in enterocutaneous fistula.

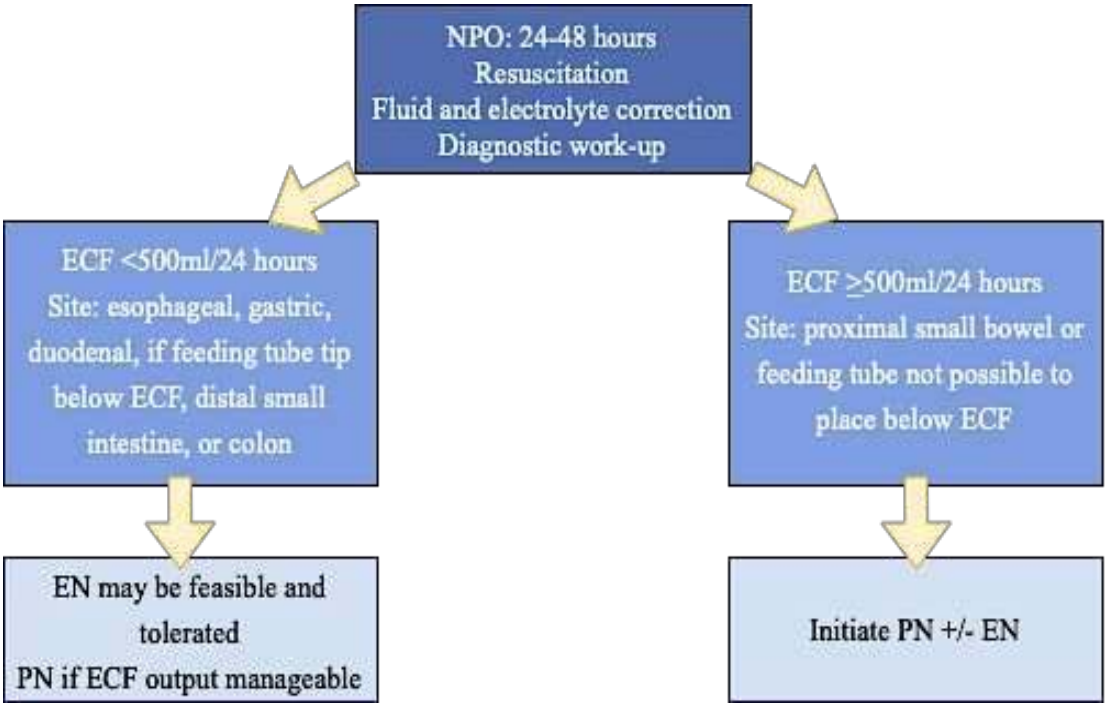

Figure 2. Routes of Nutrition Support Consideration. ECF: enterocutaneous fistula; EN: enteral nutrition; PN: parenteral nutrition. (Adapted from Kumpf VJ, de Aguilar-Nascimento JE, Diaz-Pizarro Graf JI, Hall AM, McKeever L, Steiger E, et al. ASPEN-FELANPE Clinical Guidelines: Nutrition Support of Adult Patients With Enterocutaneous Fistula. J Parenter Enter Nutr. 2017;41:104–12)

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ARTICLE REVIEW

The effect of thiamine supplementation for critically septic patient: An evidence-based case report

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Abstract

Sepsis has been accounted for various burdens worldwide, especially in critically ill patients. This could eventually lead to inflammatory response, provocation ischemia, and lactic acidosis. Several studies showed that thiamine deficiency is found in septic patients, with prevalence 20–70% in septic shock. Of these studies, thiamine deficiency could worsen patient's outcome. On the other hand, thiamine was suggested as a coenzyme which could improve the outcome of those patients. Unfortunately, the role of thiamine supplementation in septic patients is not conclusive. Thus, we conducted an evidence-based case study with research on PubMed, ProQuest, and Scopus using a search strategy focusing on randomized controlled trial (RCT) or cohort study on thiamine supplementation/level towards the outcome of critically ill patients with sepsis. We found three articles eligible for review after full-text assessment. Articles were appraised using the University of Oxford's tools for critical appraisal. It was known that all studies were good in terms of validity and applicability. This study showed that thiamine supplementation could improve lactate clearance and reduce mortality risk, moreover, thiamine deficiency could increase the risk of lactate acidosis. However, a high level of thiamine was associated with a high level of lactate in patients with liver failure. Therefore, thiamine supplementation could be recommended for critically ill patients with sepsis and normal liver function. Further research, such as RCT or systematic review and meta-analysis on thiamine supplementation for age groups to make this study more applicable.

Keywords thiamine, supplementation, sepsis

Introduction

Sepsis has been remaining as a condition which causes a lot of burdens. Unfortunately, its incidence has not declined. Although not yet defined before late of 20th century, sepsis has caused lot of morbidities and mortality, especially in era where antibiotics and supportive medicine not well-developed. American College of Chest Physicians and the Society of Critical Care Medicine (SCCM) introduced sepsis in the early 1990s in terms of systemic inflammatory response syndrome (SIRS), sepsis, severe sepsis, and septic shock based on clinical and laboratory findings. These findings were focused on hemodynamic instability, sign of inflammation, and organ dysfunction. However, SCCM alongside with European Society of Intensive Care Medicine launched new article defining sepsis and related terms in February 2016. Main changes made were elimination of SIRS and severe sepsis, re-definition of sepsis as life-threatening organ dysfunction which stated from change in baseline sequential organ failure assessment (SOFA) score, caused by impairment of

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host's response against infection; septic shock was further defined by sepsis' subset causing cellular or metabolic dysfunction which is enough to increase mortality.[1]

World Health Organization (WHO) stated that there are estimated 48,900,000 cases of sepsis in 2017 which have caused 11,000,000 sepsis-related deaths and later accounted for up to 20% of global deaths. In addition, 85% of them occurred in low- to middle-income countries. Sepsis was contributed largely by diarrheal disease and lower respiratory tract infection. In addition, sepsis has been a classic problem with high burden on developing countries. Non-communicable disease such as maternal disorders also accounted for one-third of sepsis cases. Many cases were resistant to antibiotics, thus caused increased morbidity and mortality.[2]

Sepsis involves an extraordinary inflammatory response when endotoxin or exotoxin is released. Interaction between toxin and toll-like receptors (TLR) of monocytes and macrophages will release pro-inflammatory cytokines which activate complement system, coagulation pathway, and fibrinolysis inhibition. This event will also stimulate margination and rolling of polymorphic cells, release of vasoactive substances which caused pathological shunting of blood. Therefore, there will be ischemia, leading to anaerobic respiration and lactic acid production which in certain point leading to lactic acidosis.[3] This cascade could eventually lead to multiple organ failure (MOF) which linked into critical illness and chronic critical illness (CCI). CCI was later defined by Research Triangle Institute as stay in intensive care unit (ICU) for eight or more days with at least one of following conditions: (1) prolonged mechanical ventilation of >96 continuous hours; (2) tracheostomy; (3) sepsis/severe infections; (4) severe wounds; (5) multiple organ dysfunction. Patient with CCI was known to have minimal survival rate but require high cost. It is known that ICU-admitted patients in 2009 sum up to 20,000,000,000 USD in healthcare costs. More than 60% of them are diagnosed with sepsis.[4]

Thiamine or vitamin B1 is a non-lipid-soluble vitamin which plays important role in human metabolism. It is a cofactor of four enzymes (pyruvate decarboxylase, pyruvate dehydrogenase, transketolase, alpha ketoglutarate dehydrogenase) which play role in production of adenosine triphosphate (ATP) to provide energy.[5,6] Thiamine is transported with transepithelial transport on low concentrations, passed into tissues and blood with both active and passive diffusion. Up to 80% total intracellular thiamine further phosphorylated so that ions could bound to protein. Thiamine transport in some tissues is assisted by natrium ion and transcellular proton gradient. Some amount of thiamine is mainly stored temporarily in brain, heart, skeletal muscles, kidneys, and liver in amount of 25–30 mg.[5] Due to human's incapability of storing thiamine, thiamine deficiency could be easily developed among patients with low intake, alcohol consumption, increased urine output, and acute metabolic stress. This condition could be seen on patient attending surgical procedures or sepsis. There are estimated more than half patients with sepsis that shown with thiamine deficiency among admission. Thiamine deficiency could cause various problems such as cardiovascular failure, neurology disorders, and gastrointestinal mucosal problems.[6] However, thiamine could be easily found in products such as lentils, peas, rice, cereal, and wheat.[5]

Despite critical ill patients are commonly low intake and have thiamine deficiency, thiamine was proven effective in the treatment of patients in ICU. Intravenous administration of thiamine could repair lactic acidosis, cardiac dysfunction, and delirium.[6] It is also proven in animal model that thiamine deficiency on mice with sepsis was associated with greater bacterial in peritoneal fluid, improved oxidative stress and immune response.[7] In addition, several clinical trials have shown beneficial effect of thiamine supplementation on critically ill patients with sepsis.[6] However, drawbacks of thiamine supplementation on ICU patients with sepsis yet to be known. Therefore, we conducted this study with aim to determine relationship between thiamine supplementation and outcome in adult patient with sepsis superimposed on critical illness.

Clinical scenario

A 50-year-old man was transferred to the ICU with unconsciousness. He was diagnosed by sepsis, clinically severe malnutrition according to the American Society for Parenteral and Enteral Nutrition (ASPEN) criteria, and metabolic syndrome with type 2 diabetes mellitus,

uncontrolled hypertension, hypertriglyceridemia, and low level of high-dense lipoprotein (HDL)-cholesterol. He also has a declined renal function with supportive hemodialysis during the ICU stays. Albumin was low and quantitative was high. His blood lactate was 2.7 mmol/L at day 21 and blood gas analysis showed metabolic acidosis. The blood lactate kept on increasing and reached by 4.5 mmol/L at the day 24 despite on an adequate resuscitation. Patient received enteral nutrition and being poor tolerate since hyperlactatemia. Physician clinical nutrition specialist planned to give him thiamine supplementation to delivered metabolic resuscitation and to improve for both the lactate level and blood gas analysis profile. Thus, the support evidence was considered to this patient.

Clinical question

The inclusion criteria in this study was an adult critically ill patient diagnosed by sepsis. Blood lactate level and blood gas analysis improvement is the outcome of the study. The clinical question of this study was "could the thiamine supplementation improve the blood lactate and blood gas analysis in adult critically ill patient with sepsis?

P : adult critically ill patient with sepsis
I : thiamine supplementation and/or thiamine level
C : not-supplemented by thiamine and/or thiamine deficient
O : Lactate clearance/acidosis

Methods

We conducted evidence-based case report with search strategy, critical analysis, and synthesis. Searching was done on PubMed, ProQuest, and Scopus on 26 September 2020, 27 September 2020, and 28 September 2020 respectively. Author used keywords ("thiamine" OR "B1") AND (("critically ill" OR "critical illness") AND "sepsis") on ProQuest and Scopus; and (("Critical Illness"[Mesh]) AND ("Sepsis"[Mesh])) AND ("Thiamine"[Mesh]) on PubMed. Authors selected articles using inclusion and exclusion criteria. Inclusion criteria were: (1) randomized clinical trial or prospective/retrospective study; (2) population of adult critically ill patient with sepsis; (3) thiamine supplementation or level as intervention or indicator; (4) blood lactate and/or blood gas analysis as outcome; (5) written in English. Authors excluded review articles.

Selected articles were appraised using critical appraisal tools from Center for Evidence-Based Medicine (CEBM) University of Oxford, with any discrepancy discussed further for final decision on appraisal result.[8] Appraised studies were extracted on its author(s), study year, design, location, age, sample size, intervention and control treatment, aim of study, primary endpoint, level of evidence according to CEBM Oxford, and outcomes.[9] Studies were synthesized further for results, discussion, and concluded by five authors.

Results

We found total 124 studies after hit on PubMed, Scopus, and ProQuest combined which could be seen on Figure 1. After hand searching and elimination of duplicated study, we found 5 studies eligible for full text assessment and screening of methods and results. Finally, we found 3 studies eligible for this study as one study assessed effect of vitamin B1 together with vitamin C and n-acetylcysteine (Bedreag, *et al*) and one study assessed effect of vitamin B1 together with vitamin C (Yoo, *et al*).[10–15] Therefore, included studies after selection process were studies by Byerly, *et al*; Donnino, *et al*; and Woolum, *et al*.[10–12]

Both studies were appraised, and both studies were eligible and qualified in terms of validity and applicability which could be seen on Table 1. Importance of studies were qualified as the results shown significance and relationship over time. It is known from the study outcome that thiamine supplementation or sufficiency could give protective effect towards lactic acidosis ($p<0.05$). In addition, study by Woolum, *et al* suggested that thiamine could reduce 28-day mortality by 0.67 times (95% CI 0.49–0.91). Byerly, *et al* also suggested that thiamine supplementation alone or with vitamin C were associated with increased in-hospital survival and lactate clearance which could be seen alongside study characteristics in Table 2.

Discussion

Studies qualities were shown in a good condition after critical appraisal. All three studies were sufficient in validity, importance, and applicability.[10–12] Therefore, findings in these studies should be brought into consideration for further practice. However, two studies could not be assessed for follow up as they did retrospective approach, thus follow up is not applicable in this case.[10,12] Study importance was described on study charateristics.

Critically ill patients with shock tend to develop thiamine deficiency as result of low or nil intake, increased oxidative stress in mitochondria, and other existing comorbidities which could provoke rapid deterioration of thiamine supply.[12] Sepsis could increase metabolic requirement due to rapid breakdown of human energy resources and induce inadequate nutrition uptake, thus leading to thiamine deficiency.[13] Acute stress will mobilize building blocks of human in-order to response stressor. In addition, acute stress will suppress feeding pattern and gastric absorption, thus inducing thiamine deficiency.[14] On the other hand, critically ill patients are subject to limited uptake, impaired renal function, and dramatic elevation of oxidative stress, thus lead to thiamine deficiency.[15]

It is known that 10% of critically ill patient with sepsis present with thiamine deficiency on admission, and 10% more will present 72 hours after admission.[11] Thiamine plays a role in Kreb's cycle as it serves as cofactor of pyruvate dehydrogenase and alpha ketoglutarate dehydrogenase. Thus, depleted thiamine level clearly disrupts aerobic metabolism process which inhibit oxidative metabolism and ATP production. These cascades could be manifested as lactic acidosis, hypotension, and death.[12] Sufficient thiamine level by thiamine supplementation could be an answer for this problem as one study by shown that thiamine treatment could improve probability of lactate clearance by 1.307 times (95% CI 1.002–1.704).[12] This coherent with another study that thiamine administration only gave positive impact towards lactate clearance and its impact could be emphasized by vitamin C co-supplementation.[10] This mechanism gave better prognosis for the patient, well-defined by mortality rate. It is known that thiamine supplementation could reduce in-hospital mortality rate by 0.710 times (95% CI 0.550–0.930) 28-day mortality rate by 0.666 times (95% CI 0.490–0.905).[10,12] In addition, co-supplementation with vitamin C could reduce in-hospital mortality 0.223 times (95% CI 0.069–0.735).[12] Moreover, combination of vitamin C and thiamine supplementation yielded positive relation towards lactate clearance and patient's prognosis ($p<0.05$).[16–17] Based on those findings and the fact that vitamin C is a potent antioxidant and anti-inflammatory agent, vitamin C supplementation along with thiamine administration could be considered or studied further for better evidence. However, further studies are recommended to determine vitamin C effect adjunct to thiamine supplementation on critically ill patients with sepsis.

However, there is an anomaly pattern in patient with liver injury (ALT >240 IU/L).[10] Patient with liver injury had generous level of both thiamine and lactate. Dancy, *et al* suggested another finding that alcoholic patients tend to have higher thiamine level.[18] This could be explained by pathophysiologic explanation that patient with liver failure has incapability to store thiamine and to process thiamine as result of mitochondrial damage in liver. Therefore, liver damage will result in breakdown of thiamine-containing complexes which off-loaded in serum circulation. Patient with liver damage also has trouble of lactate metabolism. This explain why patient with liver damage did not benefit much from thiamine supplementation and even worsen his/her lactate status.[10] Another thing to be noted is gender response towards thiamine supplementation. Woolum *et al* suggested that female are favorable responders compared to male, which also means that female is more prone towards thiamine deficiency. Therefore, beside pregnancy and lactation process, there are several things should be taken into notes when female develop thiamine deficiency such as inflammatory response and hypervolemia. This should be considered as hypothesis and taken into future research on thiamine and septic shock on critically ill patients

This is evidence-based study that determine relationship of thiamine deficiency or supplementation with clinical outcome of ICU patients with sepsis such as mortality, lactate clearance, and others that could contribute to

patient's prognosis. However, this study did not determine individual response towards thiamine supplementation. Therefore, it is recommended to do multicenter randomized control trial on thiamine supplementation and factors contributing into therapeutic response.

Conclusion

Thiamine supplementation to maintain thiamine sufficiency was essential in critically ill patients with sepsis as it could improve patient's lactate clearance hence improving survival and prognosis. Therefore, maintenance of thiamine level is recommended to prevent deterioration of clinical performance of critically ill patient; and thiamine administration is recommended for critically ill patient with sepsis. It is also recommended to make further studies on thiamine supplementation on critically ill patients with sepsis with special characteristics such as pregnancy, geriatric, and liver disease to improve applicability of this report. Thiamine supplementation with other substances should be studied further to improve importance of this study.

Table 1. Critical appraisal of selected studies using critical appraisal tools for follow-up study from CEBM Oxford.[8]

Author (Year)	Validity			Applicability		
	Representative sample	Follow-up	Blind	Adjustment	Patient similarity	Clinically important
Byerly, *et al* (2020)	+	N/A	+	+	+	+
Donnino, *et al* (2010)	+	+	+	+	+	+
Woolum, *et al* (2018)	+	N/A	+	+	+	+

Table 2. Characteristic of selected studies[9]

Author (Year)	Study Design	Location	Age	Sample Size	Follow up	Follow up rate	Aim	Primary Endpoint	Level of Evidence[9]	Outcome
Byerly, *et al* (2020)[10]	Retrospective cohort	Miami	58.1±13.6	146,687	N/A	N/A	Evaluate effect of vitamin C and thiamine on mortality and lactate clearance in intensive care unit patients.	In-hospital mortality	2b	(1) Thiamine independently associated with in-hospital survival (AOR=0.71; 95% CI 0.55–0.93); (2) Thiamine was positively related with lactate clearance (AOR=1.50; 95% CI 1.22–1.96); (3) Combination of vitamin C and thiamine supplementation were linked with survival (AOR=0.335; 95% CI 0.130–0.865) and lactate clearance (AOR=1.85; 95% CI 1.05–3.24)
Donnino, *et al* (2010)[11]	Prospective cohort	Boston	34–61	60	0, 24, 48, 72, 162 hours	100%	Determine thiamine deficiency's prevalence in ICU patients with sepsis so that association between thiamine levels and lactic acidosis could be determined.	Lactic acid levels	1b	(1) Positive correlation between thiamine and liver transaminase (p=0.020); (2) Positive correlation between liver transaminase and lactic acidosis (p=0.030); (3) Thiamine was associated negatively with lactic acid level in patients with healthy liver (p=0.014).
Woolum, *et al* (2018)[12]	Retrospective cohort	Kentucky	43–61	369	N/A	N/A	Determine association between thiamine administration in septic shock and clinical manifestations such as lactate clearance.	Lactate clearance	2b	(1) Thiamine supplementation linked positively with improved chance of lactate clearance (HR = 1.307; 95% CI 1.002–1.704); (2) Thiamine supplementation linked positively with reduced 28-day mortality (HR=0.666; 95% CI 0.490–0.905)

Abbreviations: N/A=Not Applicable

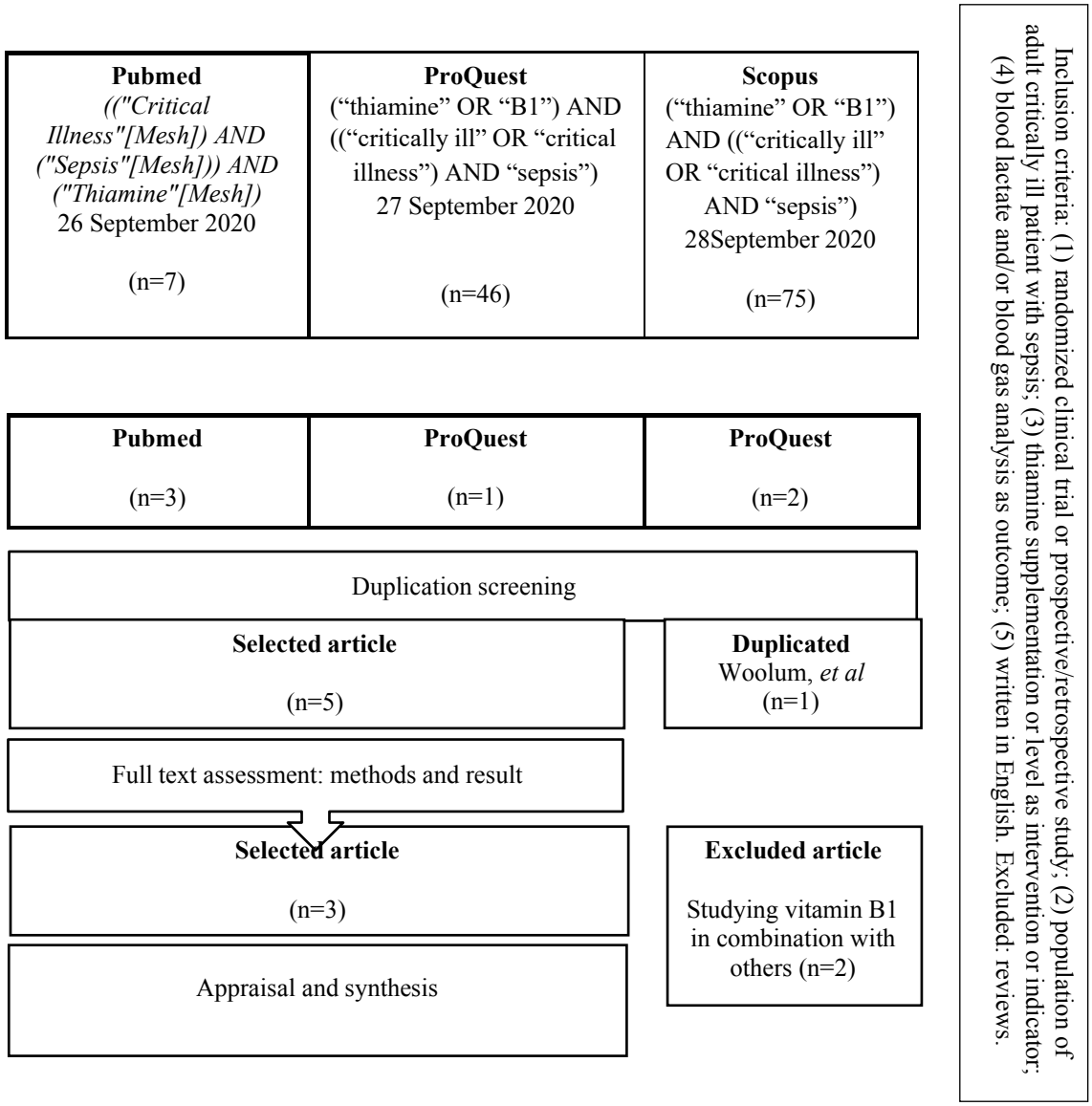

Figure 1. Literature searching process

Conflict of Interest

Authors declare there was no conflict of interest regarding this study.

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CASE REPORT

Resuscitation fluid requirements in burn injury patients using intravenous vitamin C: An evidence-based case report

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Abstract

Background: Based on the Guideline of European Society for Clinical Nutrition and Metabolism (ESPEN) in 2013, vitamin C is an additional therapy for burn patients during the resuscitation process and reduce the amount of fluid resuscitation but still needs further evidence. This study aims to find the effect of intravenous vitamin C administration to reduce the fluid requirements during first 24 hours resuscitation in burn patients.

Methods: Electronic Literature search were performed in PubMed, Cochrane, Scopus and ProQuest databases. Hand searching was also performed. MesH Term was used in PubMed database searching. All literature obtained was screened based on inclusion and exclusion criteria.

Results: Three articles were selected based on the eligibility criteria. Two Randomized Controlled Trial / RCT studies concluded that intravenous vitamin C administration reduced resuscitation fluid requirements in burn patients. But in the case control study there was no significant difference in resuscitation fluid requirements between the two groups. Other study reported that there were significant differences in resuscitation fluid requirements between the two groups. Both RCT studies did not use the blinding method and explained the side effects of therapy. A case control study reported an increase in cases of acute kidney failure in the vitamin C group compared to control (23% vs 7%) although it was not statistically significant.

Conclusions: Intravenous vitamin C can reduce the resuscitation fluid requirements in the first 24 hours in burn patients (grade C recommendation).

Keywords burns, vitamin C, ascorbic acid, resuscitation, fluid requirements

Introduction

Based on data from Dr. Cipto Mangunkusumo Hospital, 72.2% of patients treated at burn center were aged ≥ 15 years. Most of adult patients (73.9%) suffered third degree burns with 11-30% of TBSA. In 2015, the length of stay of patients with burns ≤ 40% of TBSA was 15 days (1–66 days) with the mortality of all patients reaching 27.7%.[1] The study also showed an increase in mortality of burn patients in Dr. Cipto Mangunkusumo General Hospital from 2013 to 2015, meanwhile according to the results of a systematic review there is a tendency of decreasing mortality in burn patients in various countries.[1,2]

According to Australian and New Zealand Burn Association, the first aid in burn treatments include fluids, analgesics, tests and tubes. Fluid resuscitation is the most important in the treatment of burns. Urine production is monitored every hour to find out the adequacy of fluid resuscitation. Adjustment of fluid resuscitation volume can also be done as indicated.[3]

The administration of resuscitation which exceeded expected volume could harm the burn patients. Fluid excess of 25% of predicted volume increased the risk of pneumonia, acute respiratory distress syndrome, multiple organ failure,

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bloodstream infections, and death.[4] This condition was called “fluid creep”.[5]

Vitamin C is an essential micronutrient in our body. One of its benefits is to strengthen blood vessel endothelium. One study found that the mechanism of vitamin C reduces the permeability of blood vessels is through increasing Epac1 protein that binds to cell microtubules and increases its stability.[6] In addition, vitamin C also has a role in reducing histamine which will reduce vascular permeability.[7] Based on ESPEN guidelines, vitamin C requirements is increased during the acute phase of burns (0.5–1 g/day).[8]

According to research conducted by Tanaka H *et al*,[9] vitamin C is needed to reduce capillary leakage and reduce fluid requirements in burn patients where the fluid needs go down by about 45.5% ($p < 0.004$). However, a different result is stated by Nakajima M et al that there is an increase in fluid requirements after administering 10 g/day vitamin C intravenously and do not reduce the fluid requirements with a dose above 24 g/day.[10] Based on this information, it is interesting to know the effect of intravenous vitamin C to decrease the fluid requirements in burn resuscitation.

Clinical scenario and question

A 22 years old male patient came to Emergency Room (ER) with burns on his face, body, both arms and both legs in the last 10 hours before being admitted to the hospital. His motorcycle crashed petrol kiosk and suddenly the fire appeared and burned his body. The patient was taken to the nearest hospital for emergency treatment. A total of 3000 mL fluid resuscitation was administered. Patients were referred to Dr. Cipto Mangunkusumo General Hospital for further treatment.

At the ER, the patient had no complaints due to inhalation trauma. The examination showed compos mentis with normal vital signs and grade II-III burns 31% of Total Body Surface Area (TBSA). The fluid resuscitation was given according to Baxter's formula with a total fluid requirement of 5580 mL so that it still had to be continued with resuscitation of 2580 mL/14 hours. Patients were given pain medication and a urine catheter was placed with the initial urine 1300 mL/10 hours (2.8 mL/kg/hour). During 14 hours of fluid resuscitation, the amount of urine production was 3 mL/kg/hour. Patients was not given other supporting therapies for resuscitation such as vitamin C.

Based on the Guideline European Society for Clinical Nutrition and Metabolism (ESPEN) in 2013, vitamin C is an additional therapy for burn patients during resuscitation which is known to have antioxidant mechanisms and reduce vascular permeability so that the fluid requirements will decrease. However, this therapy still requires further research and validation regarding its effectiveness.

The subjects in this study were patients with burns whose outcome was assessed as the need for fluid resuscitation after giving intravenous vitamin C. Therefore the clinical question is "Does the administration of intravenous vitamin C during fluid resuscitation in the first 24 hours reduce the need for fluid resuscitation in burn patients?"

Methods

Literature search was performed using advanced searching on PubMed, Cochrane, Scopus, and ProQuest on February 24, 2020. MeSH term was used in PubMed database search. The keywords used are "burn", "ascorbic acid", and "resuscitation". The author also performed hand searching method. Duplicated articles were filtered with Endnote program. The title and abstract are screened with eligibility criteria. The critical appraisal was done based on the agreement of three authors.

The inclusion criteria were: 1) The RCT, cohort and case control study, 2) Research carried out on humans, 3) Subjects were burn patients aged >15 years, 4) Subjects had the characteristics of burn area > 20% or burn index ≥15, 5) Used intravenous vitamin C during burn resuscitation. The exclusion criteria were: 1) Research full text was unavailable and 2) Review articles.

Results

Electronic literature searching method was carried out on 4 databases namely PubMed, Cochrane, Scopus and ProQuest using the keywords "burn", "ascorbic acid", "resuscitation". There were 4 literature found in PubMed database, 4 literature from Cochrane Library database, 77 literature from Scopus database, 216 literature from ProQuest

database, and no additional literature was found from handsearching method **(Table 1)**. From all literature obtained, 4 literature met the eligibility criteria, i.e. 3 literature from PubMed database and 1 literature from ProQuest database **(Figure 1)**.

Table 2 shows the study characteristics of the papers. **Table 3** shows the validity criteria. **Table 4** shows similarity with the PICO (problems, interventions, controls, outcomes).

Discussion

Tanaka et al[9] conducted a Randomized Control Trial (RCT) study to determine the effect of intravenous vitamin C administration on the requirement of fluid resuscitation in burn patients. The results of the study are, there is a statistically significant difference between the group with intravenous vitamin C and the group without intravenous vitamin C ($p<0.05$), where the group with intravenous vitamin C requires lower resuscitation fluids than the group without intravenous vitamin C administration. The strength of this study is the RCT design with the evidence level 2B. Unfortunately, there were the relatively small number of patients included in the study and the authors did not mention about concealed randomization of the subjects.

Qin et al[11] conducted an RCT design and stated that there was a statistically significant difference in the effect of intravenous vitamin C on the decrease in fluid resuscitation requirements ($p <0.05$). The weaknesses are the research did not explain in detail the difference in the average resuscitation fluid given and did not provide confidence interval of the result.

Tanaka et al and Qin et al research did not do blinding and explain who and how they gave fluid therapy in detail. In addition, this study also did not mention who assessed the amount of fluid needed. This can lead to research bias.

Lin J et al[12] conducted a case control study. The results of this study is no significant difference in the need for resuscitation fluids after intravenous vitamin C was given ($p=0.6$). The weakness of this study is case control study design with level of evidence 3B, so it cannot be a good reference for application in the therapy.

Kahn SA et al[13] conducted a retrospective review study. This study concludes that the administration of vitamin C can reduce the need for resuscitation fluids by up to 25% and is statistically significant. However, with a retrospective design and level of evidence 3B, this study is not suitable to be applied in the therapy.

All studies did not explain the side effects of intravenous vitamin C during resuscitation, but Lin J et al reported higher cases of acute kidney failure in the group given high vitamin C compared to controls (23% vs 7%, $p=0.06$).[12] Kahn SA et al reported that there were no differences in cases of kidney failure in the intervention and control groups.[13] Further research is needed regarding the side effects of intravenous vitamin C administration.

Research evidence regarding the effectiveness and safety of using vitamin C during resuscitation of burn patients is still very limited (only 2 RCTs in 20 years, 1 case control, 1 retrospective review). Based on our literature search, there were 2 studies (2006 and 2017) that were registered at ClinicalTrial.gov regarding the administration of vitamin C in burn patients (NCT00350077 and NCT01587261). However, the study was withdrawn by reason of lack of evidence and was not approved by the FDA.[14,15]

After evaluating the literature and the evidence obtained, the authors conclude that the overall level of recommendation for intravenous vitamin C in reducing the amount of fluid resuscitation for burn patients is **grade C** because two literature have 2B level of evidence and two literature with 3B level of evidence with different results.

Sensitivity analysis cannot be conducted in this EBCR because all of the studies do not provide confidence interval. The study about vitamin C administration during fluid resuscitation in burn injury was scarce. It contributes to our limitation in concluding the evidence.

Conclusion

The authors conclude that in this case, administration of intravenous vitamin C can reduce the need for fluid resuscitation in the first 24 hours of burn patients with grade C recommendations. There are no clear guidelines regarding the dosage of intravenous vitamin C for burn resuscitation as well as the importance of evaluating the safety of intravenous vitamin C. Studies with a larger number

of patients with better methods are needed to support these conclusions and recommendations.

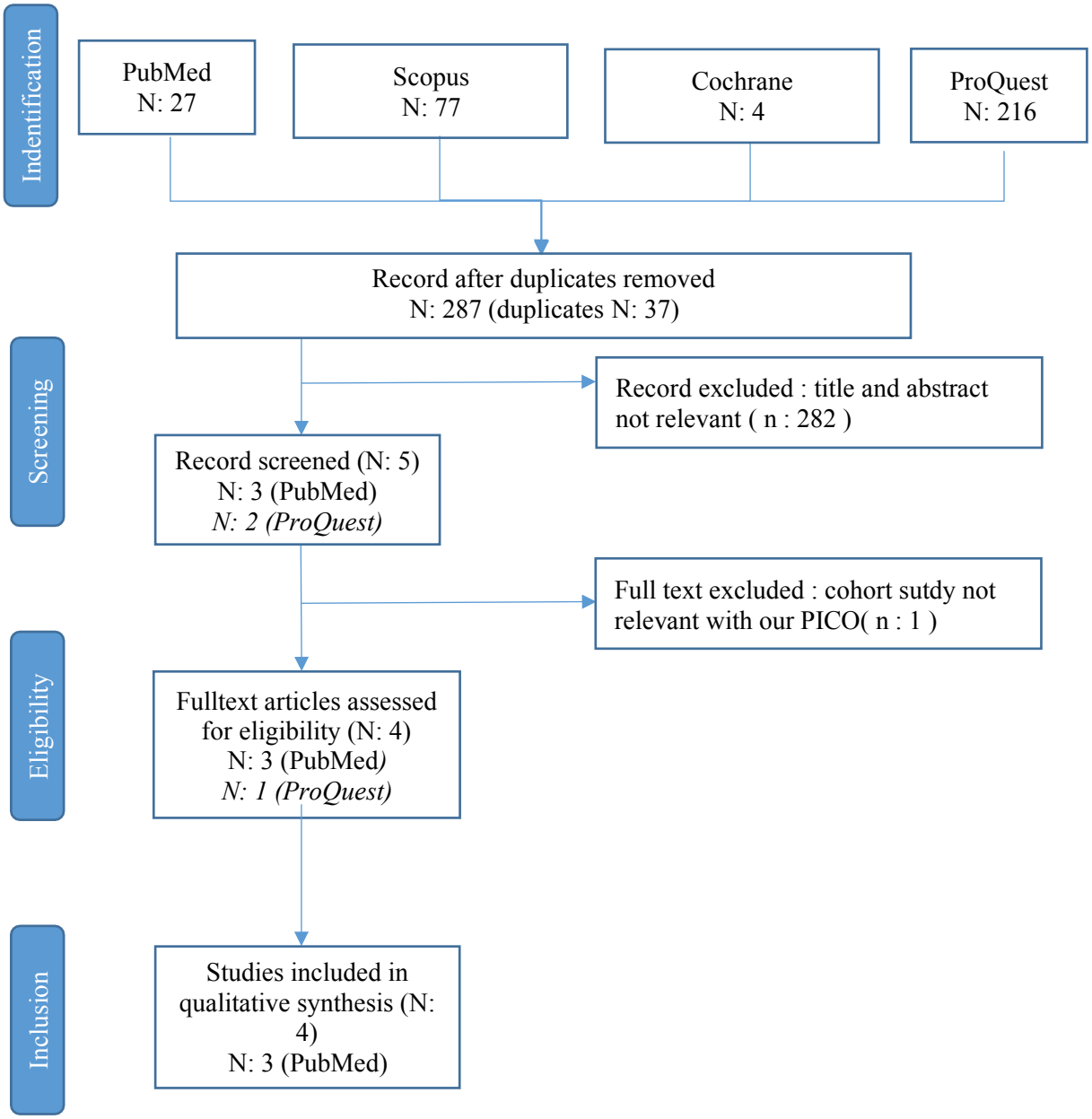

Figure 1. Prisma's flow chart

Table 1. Resources & search strategy

Database	*Search Strategy*	*Hits*	*Selected article*
PubMed	((((ascorbic acid[MeSH Terms]) OR ascorbic acid[Title/Abstract])) AND ((burn[MeSH Terms]) OR burn[Title/Abstract])) AND ((resuscitation[MeSH Terms]) OR resuscitation[Title/Abstract])	27	3
Cochrane Library	#1 "Burn" N: 4103 #2 "Ascorbic acid" N: 3768 #3 "Resuscitation" N: 8280 #1 AND #2 AND #3 N: 4	4	0
Scopus	(TITLE-ABS-KEY (*burn*) AND TITLE-ABS-KEY (*ascorbic* AND *acid*) AND TITLE-ABS-KEY (*resuscitation*))	77	0
ProQuest	Burn AND ascorbic acid AND resuscitation	216	1

Table 2. Study characteristics

Author	Patient group	Outcome	Key Result	Comment
Tanaka H et al, (2000) Arch Surg, Japan[7] RCT (level 2B)	Burn patient more than 30% TBSA from 1 December 1992 – 31 December 1997, randomized to 2 groups Group 1: vitamin C 66 mg/kg/h in the first 24 hours was given Group 2: control group, without vitamin C. Total (n =37)	Fluid requirement in 24 hours adjusted according to urine output	Total fluid in 24 hours in Group 2 was 5,5 ± 3,1 ml/kg/%TBSA, whereas in group 1 was 3.0 ± 1.7 ml/kg/%TBSA ($p<0.05$). The reduction of fluid requirement was 45.5 %	This research concluded that intravenous vitamin C could significantly reduce fluid requirement during resuscitation
Qin FJ, et al, (2019) Drug Des Devel Ther, China[9] RCT (level 2B)	Burn patient with more than 30% TBSA from July 2011 to September 2016 Group A: intravenous Tiopronin (15 mg/kg/day) + standard therapy Group B: intravenous vitamin C (792/kg/day) + standard therapy Group C: Standard therapy with Evans formula, nutritional support, intravenous and topical antibiotics, etc. Total (n = 36)	Fluid requirement in 24 hours adjusted according to urine output	Fluid resuscitation requirement in group A and B reduce than group C ($p <0,05$) Group A: TBSA% × body weight (kg)×1.46 mL (colloid to electrolyte ratio 1:2) + water 2000 mL Group B: TBSA% × body weight (kg)×1.48 mL (colloid to electrolyte ration 1:2) + water 2000 mL Group C : TBSA% × body weight (kg)×1.64 mL (colloid to electrolyte ration 1:2) + water 2000 ml.	This research concluded that intravenous vitamin C could significantly reduce fluid requirement during resuscitation

Table 2. Study characteristics (continued)

Author	Patient group	Outcome	Key Result	Comment
Lin J,et al, (2018) J Burn Care Res, USA[10] Case control (level 3B)	Burn patients from 2013–2015, divided into case group and control group, age and percentage of TBSA were matched (± 5 years and ± 5%, respectively) Group 1: intravenous vitamin C (66mg/kg/h) during resuscitation (n = 38) Group 2: without intravenous vitamin C. (n = 42) Total (n = 80)	Fluid requirement in 24 hours adjusted according to urine output	No difference in total fluid administration (4.6±2.6 ml/kg/%TBSA and 4.3±2.5 ml/kg/%TBSA) (p=0.6)	This research concluded that intravenous vitamin C could not significantly reduce fluid requirement during resuscitation
Kahn SA, et al, (2011) J Burn Care Res, USA[11] Retrospective Review (level 3B)	Burn patients Group 1: intravenous vitamin C (n = 17) Group 2: without vitamin C (cristaloid only) (n = 16) Total (n = 33)	Fluid requirement in 24 hours adjusted according to urine output	Vitamin C : 5.3 ± 1 ml/kg/%TBSA Control : 7.1 ± 1 ml/kg/%TBSA The reduction of fluid requirement was 25 % ($p<0.05$)	This research concluded that intravenous vitamin C could significantly reduce fluid requirement during resuscitation

Table 3. Validity criteria

	Validity											
Articles	Study design	Number of Patients	Randomization	Similarity treatment and control	Blinding	Comparable Treatment	Intention to treat	Domain	Determinant	Measurement of Outcome	Quality of evidence*	Level of Evidence**
Tanaka H, et al[2]	+	37	+	+	-	+	+	+	+	+	B	2B
Qin FJ, et al[3]	+	36	+	+	-	+	+	+	+	+	B	2B
Lin J, et al[4]	+	80	-	+	-	+	+	+	+	+	C	3B
Kahn SA, et al[5]	+	33	-	+	-	+	-	+	+	+	C	3B

* 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; B (*Moderate*) : We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; C (*Low*) : Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.

Table 4. Similarity with PICO

	Similarity Population	Similarity Determinant	Similarity Outcome
Tanaka H et al.[7]	+	+	+
Qin FJ, et al.[9]	+	+	+
Lin J,et al.[10]	+	+	+
Kahn SA, et al.[11]	+	+	+

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ORIGINAL ARTICLE

Low dietary omega-6 to omega-3 fatty acid intake ratio enhances adiponectin level in obesity

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Abstract

Every year around the world, the prevalence of obesity is increasing. Obesity and its associated diseases have become some of the most pressing health problems in developed and developing countries. In its development, adipocytes dysfunction and chronic low-grade inflammation occur in obesity will stimulate diseases at higher risk including type 2 diabetes mellitus (T2DM), atherosclerosis, hypertension, and metabolic syndrome. Western diet and sedentary lifestyle are thought to have significantly contributed to the increase in obesity recently. Diet modification is a sound method to prevent obesity and its complications. Nevertheless, the concern lies in the ratio of omega-6 towards omega-3 fatty acids intake, modern dietary habits induce transition of this ratio from 1-4:1 to 20:1 or higher. Omega-3 and omega-6 are two essential fatty acids that emerge as dominant factors in obesity through adiponectin. Adiponectin refers to a protein hormone conceived by adipocytes to prevent obesity and its subsequent complications by increasing insulin sensitivity, fatty acid oxidation, anti-inflammatory, and antiaterogenic. This study is a literature study with sources from journals and textbooks in the last ten years. This study aims to determine the role of fatty acids in omega-6 towards those within omega-3 by using adiponectin as the indicator of advancement to obesity and its underlying diseases. Several studies that examined the ratio of omega-6 to omega-3 fatty acids intake with adiponectin have shown inconsistent results may be due to dietary diversity and genetic factors in each population. Therefore, further studies in a more various population may be required.

Keywords adiponectin, obesity, omega-3 fatty acid, omega-6 fatty acid

Introduction

Obesity is a global epidemic where more than 650 million people are obese worldwide.[1] In Indonesia, there has been an increase in obesity by 47.2% in the last five years. An estimated 50 trillion rupiah per year is spent on the costs of treating obesity and its subsequent complications such as T2DM, heart disease, stroke, metabolic syndrome, and atherosclerosis.[2,3] Obesity occurs when there is an imbalance between the amount of input energy compared with the amount of energy that excreted in a long time. Western diet and sedentary lifestyle in today's lifestyle is one of the factors that cause an increase in obesity. In addition to physical activity, modification of dietary patterns is also essential for the prevention of obesity.[4–6]

Prolonged overnutrition provokes adipocytes expansion resulting in adipocytes dysfunction, which is characterized by the increase of tumor necrosis factor (TNF) -α and interleukin (IL) -6, monocyte chemoattractant protein (MCP) -1, leptin,

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and resistin. This condition prompts the accumulation of immune cells within fat or adipose tissue and chronic low-level inflammation.[4,7,8] Unlike other adipokines, which increase in obesity, the production of adiponectin is decreasing. Adiponectin is the most adipokines produced by adipocyte cells which have the effect of increasing insulin sensitivity, fatty acid oxidation, anti-inflammatory, and antiaterogenic.[9] Adiponectin is one indicator of the progression of obesity and its related diseases.[10] Decreased production and secretion of adiponectin have even begun occuring in overweight conditions and once uncontrolled will worsen the obesity advancement.[11]

Dietary patterns of fatty acids intake within omega-3 and omega-6 can also affect adiponectin levels.[4,12,13] It is worth-mentioning that fatty acids within omega-3 and omega-6 fatty are essential to hold different roles with each other to adiponectin. In contrast to fatty acid within omega-3 which constitutes anti-inflammatory effects, the one that of omega-6 genuinely form an intertwined effect of proinflammation.[14] Due to these two fatty acids compete with one another in metabolic processes, the intake ratio of fatty acid within omega-6 towards one that of omega-3 shall be maintained optimally. In contrast, in the present age of industrialization, unhealthy dietary patterns cause this ratio to become unbalanced.[15] The role of the ratio between fatty acid in omega-6 towards one that of omega-3 in obesity, particularly in adiponectin, has not been put forward up to this point. Thus, this research aims to investigate the mechanism and the role of the intake ratio in omega-6 fatty acid towards the one that of omega-3 in adiponectin as an indicator of obesity advancement and its related diseases.

Discussion

Omega-3 and omega-6 fatty acids compete each other inside the body

The investigation of fatty acids in the diet was commenced in 1929 by Burr when it was concluded that fatty acids in omega-3 are essential elements to prevent disease. Research on fatty acids continues to grow to date, particularly over its integral role in preventing and curing different types of diseases.[16] Omega-6 and omega-3 possess essential elements called polyunsaturated fatty acids (PUFAs); such acids are obtained from the diet. Furthermore, fatty acids within omega-6 are commonly identified as linoleic acid (LA) (18:2ω-6) and fatty acids in omega-3 fatty are generally termed as alpha-linolenic acid (ALA) (18:3ω-3).[17] Recommended dietary allowance of omega-3 fatty acid from Institute of Medicine (IOM) for male and female adults are 1,6 g/day and 1,1 g/day, respectively. While omega-6 fatty acid daily requirement is 17 g/day for male and 12 g/day for female.[18] Food sources that contain ALA the most obtained from fish, seafood, fish oil, different combinations of nuts and seeds including flaxseed and chia seed. Some fortified foods, such as meat and eggs, are also a source of ALA. While LA is found in many types of vegetable oils and their products (**Table 1**).[19,20]

Both fatty acids will go through the metabolization process into long-chain fatty acids (LCFA) (20 and 22 carbon atoms) through the process of elongation (by adding two carbon atoms) and desaturation (through the addition of a double bond in between two carbon atoms) (**Figure 1**). Later, LA will be converted to arachidonic acid (AA) (20:4ω-6), while ALA will go through conversion into eicosapentaenoic acid (EPA) (20:5ω-3) and docosahexaenoic acid (DHA) (22:6ω-3).[15] Modifications of ALA into EPA and DHA occur are time-consuming processes as the cost of competing acids between LA and ALA in absorbing enzymes throughout the desaturation process; this desaturase enzyme is concealed by the fatty acid desaturase (FADS) gene. This enzyme is more likely to be used by ALA than LA. However, high LA intake, as in the Western diet, can disrupt desaturation and elongation from ALA.[17]

The balance of omega-6 fatty acid intake ratio towards omega-3 fatty acid

Fatty acids within omega-6 and omega-3 cannot be substituted with each other and have metabolic and functional differences. Both ALA and AA will produce eicosanoids as the final product that has the opposite effect. Eicosanoids, which are derived by AA, contribute to inflammatory diseases, including obesity and its complications. High diets in omega-6 fatty acids cause a pro-inflammatory, prothrombotic, and proagregatory state, with

increased blood viscosity, vasospasm, vasoconstriction, and cell proliferation. On the other hand, ALA-derived eicosanoids have less potent inflammatory properties than AA-derived derivatives.[7,17] The presence of competition in the use of enzymes in metabolic processes and end products that have opposite effects prompts a balance between the intake of these two fatty acids to be necessary. The recommended intake for omega-6 to omega-3 fatty acid ratio is 1-4:1. This ratio balance must be maintained optimally for the metabolic processes in the body to run normally.[15]

Before the era of food industrialization in the 20th century, researchers predicted that the ratio of fatty acids in omega-6 fatty towards those that of omega-3 in human food averaged between 1:1 and 4:1. Along with the development of modern agricultural technology, there is a change in eating patterns manifested by the emergence of various processed foods. This shift in dietary patterns causes the ratio of fatty acid intake within omega-6 towards one that of omega-3 to experience a drastic change and reaches the highest ratio of all time, as such estimated to stand between 10:1 and 20:1, possibly even higher.[17] The imbalance in the fatty acid intake ratio of Omega-6 towards one within Omega-3 is predicted to contribute to a surge of overweight and obesity prevalences toward adults in various populations.[7]

The ratio of omega-6 fatty acid intake towards omega-3 and its effect on adiponectin

In the case of obesity, fatty acids within omega-3 and omega-6 play an integral role in impacting adiponectin production and secretion. Adipocyte dysfunction that occurs upon obesity chronically prompts a state of low-grade inflammation indicated by multiple inflammatory markers and adipokines inlcuding leptin and resistin. This inflammatory state also causes dysregulation of adiponectin.[7,8,21] Adiponectin (Acrp30/ADIPOQ) refers to a protein comprised of 244 amino acids with a 30 kDa load concealed by adipocytes. Adiponectin commonly tasked to increase glucose uptake, insulin sensitivity, and oxidation within cells' fatty acids through two primary receptors; adiponectin receptor 1 (AdipoR1) and adiponectin receptor 2 (AdipoR2).[22,23] Low adiponectin levels are associated with a higher risk of obesity and disease related to obesity. Conversely, high adiponectin levels work by elevating insulin sensitivity and oxidation with fat to prevent obesity and its complications. Adiponectin has been widely used as an examination indicator in monitoring the development and treatment of obesity.[21] In adiponectin, fatty acids of omega-3 and omega-6 perform differently through several mechanisms, particularly the process of adipogenesis, fat homeostasis, endocannabinoid, and systemic inflammation (**Table 2**). Therefore, the balance of the ratio between fatty acids in omega-6 and those of omega-3 essential with adiponectin.[3,7]

In the process of adipogenesis and fat metabolism, fatty acids within omega-6 and omega-3 perform as transcriptional factors to control the gene expression involved within the process of diversification of preadipocytes. Differentiation of preadipocytes into mature adipocytes is a vital process in the advancement of obesity. High levels of exogenous fat will fill fat particles in mature adipocytes. Mature adipocytes can no longer divide, resulting in hypertrophy and hyperplasia that induces adipocyte dysfunction in excess energy. Eicosanoid derivatives of omega-6 fatty acids, such as cyclooxygenase (COX), lipoxygenase (LOX), and prostacyclin are bound to prostacyclin receptors (IP-R) on the periphery of preadipocyte cells. Later the protein kinase A (PKA) pathway will be activated, which ultimately rules the expression of various peroxisome proliferators-activated receptors (PPARs) and results to adipogenesis.[7,15,24]

Arachidonic acid metabolites such as prostaglandin (PG) I2 and PGF2 generate an increase in white adipose tissue and a downfall in brown adipose tissue. In contrast, ALA works to repress the adipogenic effects of LA through several mechanisms. The expression of COX2 messenger ribonucleid acid (mRNA) and the production of COX2 have been evidently inhibited by DHA. Later, EPA and DHA also work to obstruct the activity of COX1 and COX2. Prostaglandin effects emanating from AA-derived eicosanoids are also directly inhibited by ALA.[7,15,24] Lastly, EPA and DHA can minimize the production of cyclic adenosine 3′,5′-monophosphate (cAMP) or PKA catalyst subunits in the IP-R pathway. Aside from this inhibitory effect within adipogenesis, fatty acids of omega-3 also

alter lipid homeostasis by having the involved expression of genes suppressed in lipogenesis inclusive of fatty acid synthase, lipoprotein lipase and stearoyl-CoA desaturase-I and also increases the genes expression within β-oxidation including acyl-CoA oxidase. The result is a reduction in body fat mass, especially in the liver, skeletal muscle, and adipose tissue.[24] In adipose tissue, there is an improvement in adipocyte function which will affect increasing the production and secretion of adiponectin.[13]

Other potential impacts of fatty acids in omega-3 and omega-6 fatty toward adiponectin are also related to the fusion of the distinctive eicosanoids it produces. PGE2, PGI2, and tromboxan (TXA) 2 and 4-grouping leukotrienes (LT) B4 generated from omega-6 fatty acids are potent pro-inflammatory agent. In contrast, prostaglandins 3-grouping (PGE3, PGI3, and TXA3) and 5-grouping LTB5 formed from omega-3 fatty acids from the same enzyme are less pro-inflammatory. Also, the formation of E series of 5-LOX (E1 and E2) derived from EPA and resolvin, protectin, and maresin, which originated from DHA, has potent anti-inflammatory characteristics. In animal studies, intake of omega-3 acids convincingly minimizes the expression of inflammatory markers including MCP-1, IL-6, interferon-γ (IFN-γ), and plasminogen activator inhibitor-1 (PAI-1). In human subjects, high diets in omega-3 massively shrinking the omega-6 ratio towards omega-3 in plasma, reduce the circulation of c-reactive protein (CRP), IL-6, TNF-α, MCP-1 levels, and the number of tissue macrophages adipose. Through the effect on decreasing the activation of these inflammatory markers, a balanced ratio of fatty acids in omega-6 towards those of omega-3 can increase adiponectin secretion.[7,15,17,24]

The expression and the concealment of adiponectin are also directly modulated by fatty acids of omega-3. As commonly mentioned in vitro studies, it is known that EPA and DHA act as natural ligands from peroxisome proliferator-activated receptor γ (PPARγ). PPARγ is recognized to be an important regulator of adiponectin gene transcription. However, in contrast to DHA, which stimulates adiponectin secretion via the PPARγ channel exclusively, EPA is understood to have other additional mechanisms that are still unknown. This additional mechanism is thought to involve the activation of the 5' adenosine monophosphate-activated protein kinase (AMPK) enzyme in increasing adiponectin secretion.[7,25]

Appetite regulation and energy balance are also influenced by fatty acids in omega-6 and omega-3. LA-derived endocannabinoid metabolism can stimulate appetite and lipogenesis in the liver through activation of its receptors in various tissues. While fatty acids within omega-3 reduce the production of endogenous endocannabinoids or decrease the sensitivity of their receptors, and also induce the production of other anorexia oxygenic neuropeptide neuropeptides in the hypothalamus, which serves to suppress appetite and lead to decreased energy intake. The decrease in energy intake will result in improved adipocyte function which affects increasing adiponectin production and secretion.[7,17]

Several kinds of research examining the relationship between fatty acids in omega-3 and omega-6 fatty toward adiponectin have been performed (Table 3). A study that involved 44 patients with dialysis, plasma adiponectin levels were found to be in progressive correlation with omega-3 fatty acids ($r=0.58$) and inversely related to fatty acids of omega-6 ($r=-0.64$), both of which statistically significant ($p<0.01$).[27] A meta-analysis investigation inferred that intake of fatty acids in omega-3 particularly those obtained from high dose supplementation (>2 g) can boost the levels of adiponectin in prediabetes and T2DM patients. However, the heterogeneity of results in these studies is still very high.[32] Yang et al. also, in his research on subjects with polycystic ovary syndrome, show increased levels of adiponectin ($p=0.002$) after administration of omega-3 fatty acids with varying doses (900-4000 mg) compared with placebo.[33] Similar results were also obtained by studies in non-alcoholic fatty liver disease (NAFLD) patients who were given capsules of fish oil whose containment embodies the benefit of EPA 182 mg and DHA 129 mg twice daily for three months showed a significant boost in adiponectin levels ($p <0.001$).[28]

In contrast to the results of the studies above, an individual investigation deliberated by Sabour et al. show results that an absence of visible development was indicated in adiponectin levels within the

regulation of fatty acids of omega-3 in 14 months timespan towards patients with spinal cord injury.[29] Torres-Castillo et al., in his research on subjects aged 18-65 years with BMI ≥18.5 kg/m2, show that adiponectin levels showed a decreasing trend when the ratio of fatty acids intake between omega-6 toward those of omega-3 was increased. However, this difference has not statistically significant (p=0.061).[12] The administration of high omega-3 diets for six months in T2DM patients also showed no contrasting difference compared to the control group.[31] Studies on supplementing fatty acids in omega-3 with lifestyle modification for 12 weeks in female subjects with overweight also did not provide a significant increase in adiponectin levels compared to the control group.[30] Identical findings were revealed by Jacobo-Cejudo et al. in his study of T2DM patients, where no significant difference in adiponectin levels was found after six months of supplementation towards fatty acids within omega-3 when compared to placebo.[31]

Studies that examined the ratio of fatty acids intake in omega-6 toward those of omega-3 with adiponectin levels have not been widely examined and show different results. The diversity of the population remains limited, whereas it is understood that one's environment strongly influences a person's dietary patterns. Each population has different characteristics of dietary patterns, including food sources within intake ratio of fatty acids between both omega-6 and omega-3.[3,24] Population differences also affect the metabolic processes of these two types of fatty acids. The metabolism process of these fatty acids in omega-3 and omega-6 is acknowledged to be influenced by genetic variations of the FADS enzyme, which can provoke differences in the rate metabolism towards these fatty acids and the composition of those in plasma.[35] The ADIPOQ gene polymorphism has also probably played a part in the various findings of these studies. Genetic variations of ADIPOQ may be influence different response of adiponectin gene to these two fatty acids.[36] Interactions among genetic factors and dietary patterns in diverse populations will lead to someone's different risks against obesity seen from the level of adiponectin as an indicator.[17]

Conclusion

Fatty acids contained within omega-3 and omega-6 are essential compounds that have different functions from one another to adiponectin. Both types of fatty acids in omega-3 and omega-6 perform an integral role in adiponectin through the process of adipogenesis, fat homeostasis, endocannabinoids, and systemic inflammation. The balanced ratio between these two fatty acids can increase adiponectin levels to hold prominence in the prevention of obesity and its underlying diseases. Previous researches that examined the ratio of fatty acids intake from omega-6 to omega-3 with adiponectin levels is still limited, and the results have not been consistent; this is considered to be prompted by dietary diversity and genetic factors in each population. Modification of omega-6 to omega-3 fatty acid intake ratio on diet potentially against obesity through adiponectin regulation. However, further research on the relationship between the ratio of fatty acids intake from omega-6 to omega-3 with adiponectin in a more diverse population is required.

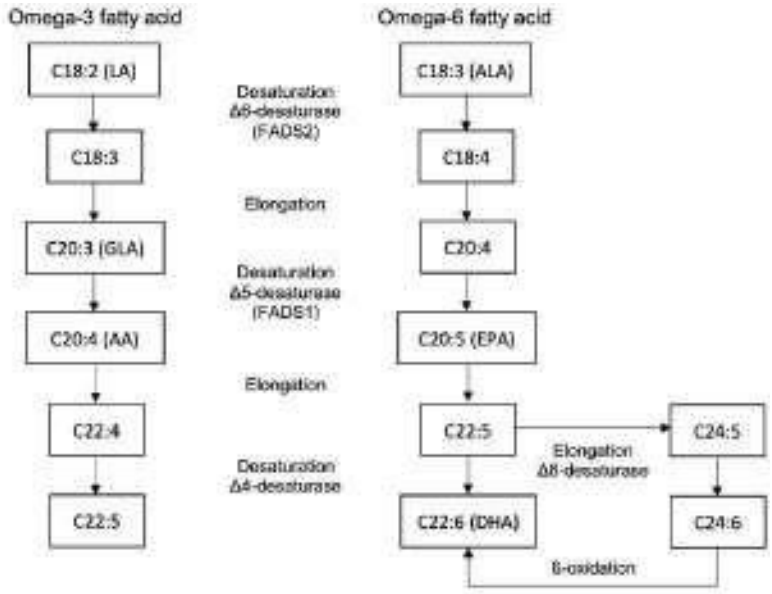

Figure 1. Desaturation and Elongation Process of Omega-3 and Omega-6 Fatty Acid[15]
Additional information: AA: arachidonic acid; ALA: alpha-linolenic acid; DHA: docosahexaenoic acid; EPA: eicosapentaenoic acid; FADS1: fatty acid desaturase 1; FADS2: fatty acid desaturase 2; GLA: gamma-linolenic acid; LA: linoleic acid.

Table 1. Omega-3 and omega-6 fatty acid food sources[19,20]

Omega-3 Food Sources (per 100 grams)	Fatty Acid Content (g)	Omega-6 Food Sources (per 100 grams)	Fatty Acid Content (g)
Flax seed	6.4	Sunflower oil	65.7
Chia seed	4.9	Sesame oil	41.3
Mackerel	2.299	Corn oil	53.52
Salmon	1.966	Canola oil	19.63
Herring	1.571	Peanut	17.192
Sardine	1.43	Pistachios	13.485
Cauliflower	1.07	Safflower oil	12.724
Mussel	0.441	Almond	12.061
Catfish	0.38	Palm oil	9.5
Brocolli	0.258	Margarine	9.1
Cod	0.184	Walnut	7.782
Eel	0.147	Tofu	4.339
Shrimp	0.138	Chicken	2.96
Clam	0.107	Tempeh	2.518
Yellowfin tuna	0.1	Chicken egg	2.25
Tilapia	0.091	Butter	2.17

Table 2. The role of omega-6 and omega-3 fatty acids to adiponectin[7,15]

Mechanism	Omega-6 Fatty Acid	Omega-3 Fatty Acids
Adipogenesis	- COX activates the PKA pathway - COX and LOX Increase PPAR gene expression leading to adipogenesis	- Reducing mRNA expression and COX-2 production - Restrains the effect of omega-6 fatty acid metabolites directly - Reducing the production of cAMP or PKA subunits
Fat metabolism	- Increase triglyceride content	- Decreases gene expression associated with lipogenesis - Increases genes expression of oxidation-β related
Inflammation	- Increase the production of inflammatory markers	- Prevents inflammation
Endocannabinoid	- Increase appetite and energy intake	- Reduces the production of endocannabinoids and their receptor sensitivity - Stimulates proopiomelanocortin - Activating PPARγ and AMPK pathways

Additional information: AMPK: 5' adenosine monophosphate-activated protein kinase; cAMP: cyclic adenosine 3′,5′-monophosphate; COX: cyclooxygenase; LOX: lipoxygenase; mRNA: messenger ribonucleic acid; PKA: protein kinase A; PPAR: peroxisome proliferators-activated receptor; PPARγ: peroxisome proliferator-activated receptor γ.

Table 3. Characteristics of the studies that examined omega-3 and omega-6 fatty acids with adiponectin

Author	Study Design	Subjects	Results/ Conclusion
An et al., 2011[27]	Cross-sectional study	73 dialysis patients and 10 healthy subjects	Plasma adiponectin was associated with erythrocyte omega-3 fatty acid ($r=0.581$, $p=0.023$) and inversely associated with omega-6 fatty acid ($r=–0.640$, $p=0.010$) in the dialysis patients
Qin et al., 2015[28]	Double-blind, randomized clinical trial	80 NAFLD associated with hyperlipidemia patients; trial group=40, control group=40	Administration of fish oil capsules (EPA 182 mg; DHA 129 mg) twice daily in 12 weeks showed increased levels of adiponectin compared with control group ($p<0.001$)
Sabour et al., 2015[29]	Double-blind, randomized clinical trial	104 spinal cord injury patients; trial group=54; control group=50	No significant differences in adiponectin between groups after administration of omega-3 fatty acids capsules (DHA 465 mg; EPA 63 mg) for 14 months
Balfegò et al., 2016[30]	Double-blind, randomized clinical trial	35 T2DM patients; trial group=19, control group=16	No significant difference in adiponectin between groups after administration of high omega-3 diets for 6 months

Table 3. Characteristics of the studies that examined omega-3 and omega-6 fatty acids with adiponectin (continued)

Author	Study Design	Subjects	Results/ Conclusion
Jacobo-Cejudo et al., 2017[31]	Single-blind, randomized clinical trial	54 T2DM patients; trial group=29; control group=25	No significant differences in adiponectin between groups after 6 months of administration of 520 mg fish oil capsules (320 mg EPA; 200 mg DHA)
Torres-Castillo et al., 2018[12]	Cross-sectional study	170 healthy subjects	No significant differences in adiponectin between groups based on tertiles of dietary omega-6/3 ratio
Becic et al., 2018[32]	Systematic review, meta-analysis	10 studies involved 489 prediabetes and T2DM patients; trial group=251, control group=238	Administration of high dose (>2 g) in ≥12 weeks showed increased levels of adiponectin compared with control group ($p<0.00001$)
Yang et al., 2018[33]	Systematic review, meta-analysis	3 studies involved 190 PCOS patients; trial group=103, control group=87	Administration of omega-3 fatty acid (900-4000 mg) in 6-12 weeks showed increased levels of adiponectin compared with control group ($p=0.002$)
Sedláček et al., 2018[34]	Parallel-group randomized clinical trial	34 overweight women; LSM & omega-3 group=11; LSM group=10; control group=8	No significant differences in adiponectin between groups after administration of omega-3 with LSM for 12 weeks

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ARTICLE REVIEW

Dietary fiber's effect on high sensitivity C-reactive protein serum in sedentary workers

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Abstract

Low grade inflammation has been recognized of being involved in the pathogenesis of chronic disease pandemic. Individual lifestyle plays a major role in the development of low grade inflammation. Sedentary workers are at risk of low grade inflammation due to the nature of their work. Dietary habit also contributes to inflammatory status in the body. Dietary fiber intake indirectly affects the immune system. It has been hypothesized that fiber has anti-inflammatory effects, both body weight-related and body weight-unrelated This review will focus more on body weight-unrelated anti-inflammatory effect of fiber, especially through fiber's fermentation metabolites, the short chain fatty acid (SCFA). Its anti-inflammatory effect can be seen by monitoring a biomarker of inflammation in the body, the high sensitivity C-reactive protein (hsCRP). This review's objective is to cover the mechanisms and role of dietary fiber intake on serum hsCRP level as a marker of low grade inflammation on sedentary workers.

Keywords dietary fiber, high sensitivity C-reactive protein, low grade inflammation, health promotion

Introduction

Inflammation is the body's response over harmful stimuli which leads to the activation of various mechanisms on a molecular level. Depending on the severity, inflammatory reaction could be seen locally or generalized throughout the body.[1] There are many causes of inflammation such as bacteria, tissue damage, or metabolic stress.[2] Low grade inflammation is a type of chronic, asymptomatic inflammation.[3] Low grade inflammation has been hypothesized to be a cause of insulin resistance, dyslipidemia, atherogenesis, type 2 diabetes, and hypertension.[4] Risk factors for low grade inflammation are imbalance diet leading to overweight and obesity, smoking, and low level of physical activity.[3] These risks are commonly seen on sedentary workers in large cities. Their lifestyle is closely related to their work demand, which causes them to spend a majority of their time doing sedentary activities, having low physical activity, a smoking habit, and consumes high fat diet.[5,6] All together, these factors contribute to the development of low grade inflammation which may result in declining of working productivity.[7]

A laboratory examination occasionally used to detect low grade inflammation is high sensitivity C-reactive protein (hsCRP), a value of >1 mg/L marks the presence of low grade inflammation.[8] During an acute phase of inflammation, CRP is primarily synthesized by the liver and is actively involved during the course of inflammation.[9,10] Chronic

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elevation of CRP is possibly related to the development of cardiometabolic diseases.[11] On low grade inflammation, CRP is only slightly elevated compared to in acute inflammation. Therefore, a more advanced laboratory examination is needed to detect this lower concentration of CRP. With the innovation of hsCRP, a lower CRP concentration can be detected accurately.[12]

Studies have shown a probable link between dietary pattern and inflammation, especially with the consumption of dietary fiber.[13] Dietary fiber plays a major role on a person's diet, however, often a modern Western diet contains low levels of dietary fiber. Low dietary fiber consumption leads to low fermentation metabolites, which has a crucial role on maintaining a healthy physiological and immune function. Low fiber diet is also one the causes of global obesity and chronic illness.[14] Nevertheless, there are not many studies explaining dietary fiber's effect on biomarker of inflammation such as hsCRP, particularly on the sedentary working population. Hopefully, this study will be able to explain better of the impact of dietary fiber on serum hsCRP in sedentary workers.

Materials and methods

This is a literature study assessing the association between dietary fiber intake and serum level of hsCRP on sedentary workers with source from scientific publications dating back to 10 years ago. The data-bases were PubMed and Google Scholar. Search term used were using the explode function for subgroup terms with operators ("and,"or") for "dietary fiber", "worker", "employee", "C-reactive protein", and "dietary intake". Hand-searching were used to identify further potential eligible studies. There were no language restrictions, however only publications with full texts available were included. More than 200 publication titles and abstract were screened for their relevance to this literature review. Information extracted from each publication includes the study design, location, demographic characteristics of subjects, and dietary assessment method.

Results

After screening process, three publications were finally included. Two publications were cross-sectional studies, and one was a randomized clinical trial. Two publications found association between dietary fiber and serum level of hsCRP, while one publication reported no association was observed among the two variables.

Discussion

Three studies discussing the association between dietary fibers and serum of hsCRP had inconsistent results. A cross-sectional analysis was done by Gibson et al.[15] with 6898 workers of mean age 41,1±9,1 years old, and mostly white men. Majority of subjects had moderate to high physical activity, with BMI above 25 kg/m^2, almost 70% of subjects were in the never smoker group. Total fiber intake was 17,3±6,0 g/day assessed using 7-days estimated weighed food diaries. Result showed that serum level of hsCRP is significantly lower in the highest quintile of fiber intake. A randomized controlled trial by Edrisi et al.[16] was done on 105 overweight and obese workers, age 20-50 years and mean body mass index (BMI) was 29,14±3,37 kg/m^2 with low physical activity. Subjects were divided into three energy-restricted diet groups receiving rice bran, rice husk powder, and a control group for 12 weeks. Subjects were mostly female, with moderate physical activity level. Dietary intake, including dietary fiber and two inflammatory markers IL-6 and hsCRP were measured at baseline and endline. Mean total fiber intake (g/day) were 14,96±6,89 to 19,97±7,99 collected using multiple 3-day dietary record. There were no significant differences found between rice bran and rice husk groups on serum levels of IL-6 and hsCRP. Nevertheless, hsCRP reduction in both intervention group is significantly higher than in the control group.

In contrast, Khorasaniha et al.[17] reported a different finding. Subjects were 257 male shift workers, age 20-60 years, mean BMI of 26,4±2,9 to 27,3±3,2 kg/m2, and had high physical activity. Based on their main dietary pattern assessed using semi quantitative Food Frequency Questionnaire (FFQ), subjects were divided into three groups: green, yellow, and cruciferous vegetable (VEG); liquid oils and mayonnaise, fast food and eggs (LFE); tea and coffee, refined grains and spice

(TRS). The VEG dietary pattern was significantly associated with lower concentration of serum levels of IL-6 and TNF-α. A significant positive association was detected between LFE dietary pattern with levels of serum IL-6 and TNF-α. However, no significant association was found between VGE and LFE dietary pattern with serum hsCRP and between TRS dietary pattern with all of the inflammatory cytokines.

Different findings between the studies might have been attributed to several factors that possibly affect hsCRP concentration. Existing studies have used the term inflammaging for showing that aging may cause chronic low grade inflammation, resulting an increase on hsCRP level.[18] Aging causes an increase of fat mass, reduced sex hormones, and increased tissue damages from oxidative stress.[19] However, in the three studies compared on this review, age group of subjects are comparable. Previous studies found that serum hsCRP were higher in women compared to men.[20–22] Higher value in women might be caused by estrogen fluctuation related to the menstrual cycle.[23] Furthermore, women generally have higher body fat accumulation compared to men, and fat is known to be a source of proinflammatory cytokines.[24] A more prominent gap is seen on menopause, where a decrease of estrogen will stimulate the production of proinflammatory markers.[25,26] In the study by Khorasaniha et al.[17] subjects were exclusively male in comparison to the other two studies that included both genders.

Ethnicity is also a main contributing factor that cannot be overlooked. Asians are known to have lower level of serum hsCRP in comparison to African-American, Hispanic, and European-American.[27] Genetic variation in the form of CRP gene polymorphism is linked to level of serum CRP in the circulation, different frequencies of this gene are seen among ethnics.[28] Besides genetic, the role of ethnicity is also attributed to anthropometric measures and other risk factors, such as dietary habit and socio-economic status.[29] Gibson et al. included mostly white subjects and was based in the U.K, while the study by Khorasaniha et al.[17] was based in Iran. However, Edrisi et al.[16] also conducted their study in Iran, so ethnicity factor could not elaborate the gap found between the two studies. As mentioned, anthropometric measure like BMI is strongly related to level of serum hsCRP. Overweight and obese subjects are at risk of having a higher hsCRP level by 1,83 and 2,63 times compared to those with normal body weight.[30] An increase of white adipose tissue amount in obesity causes a rise of proinflammatory cytokines synthesis such as TNF-α and IL-6,[31] which stimulates the production of hsCRP in liver. Edrisi et al.[16] only worked with overweight and obese subjects, which had a higher mean BMI compared to the study by Khorasaniha et al.[17]

Additionally, medications, physical activity and smoking habit are hypothesized to affect hsCRP concentration as well. Medications like statins and non-steroidal anti-inflammatory drugs (NSAID) may lower hsCRP concentration.[32] Edrisi et al.[16] were the only one who excluded participants consuming lipid-lowering medication. Physical activity has an inverse relationship with hsCRP. Individuals with higher level of physical activity have lower levels of cytokines such as IL-6, IL-1, TNF-α, *toll like receptor* 4 (TLR4), and hsCRP compared to individuals with low levels of physical activity.[33] Subjects included by Edrisi et al.[16] mostly had low physical activity, on the other hand, a majority of subjects from the study by Khorasaniha et al.[17] had high levels of physical activity. Contrary to physical activity, smoking might increase hsCRP concentration. Unfortunately, out of all the studies compared in this review only Gibson et al.[15] assessed smoking status. Edrisi et al.[16] and Khorasaniha et al.[17] excluded participants who smoked. Cigarette smoking triggers an immune response and vascular trauma which causes elevation of inflammation biomarker like hsCRP.[34]

Dietary pattern could also affect hsCRP levels. High intake of simple carbohydrates such as flour and sugar may cause an increase of postprandial hyperglycemia that leads to elevation of free radicals, pro-inflammatory cytokines, and hsCRP.[35] Gibson et al.[15] found an attenuation of the relationship between fiber intake and CRP and BMI in participant with high carbohydrate intake, defined as carbohydrate being ≥50% of total energy intake. High fat diet also affects the concentration of hsCRP. A high fat diet will induce migration of intestinal lipopolysaccharide (LPS) and free fatty acid to the systemic circulation, causing low grade inflammation.[36,37] Despite that, only Edrisi et al.[16]

assessed total daily fat intake of subjects. Not only carbohydrate and fat intake, dietary fiber has also been reckoned to influence hsCRP concentration. Among the three studies reviewed, only two assessed total dietary fiber intake while Khorasaniha et al.[17] did not. However, VEG dietary pattern are abundant in plants,[17] and high fiber intake in plant model diet is related to a lower concentration of inflammatory markers.[38] Although a lack of association was seen between VEG dietary pattern and serum level of hsCRP, a significant negative association was found with IL-6 and TNF-α concentrations. Possibly IL-6 and TNF-α is more sensitive to the effect dietary fiber compared to hsCRP, this finding is also supported by a previous study in post-menopausal women.[27]

A few mechanisms, as seen on figure 1, have been stated to explain the anti-inflammatory effect of dietary fiber, especially on serum level of hsCRP. First, fermentation metabolite of fiber, also known as short chain fatty acid (SCFA), which are butyrate, acetate, and propionate is proposed to have anti-inflammatory effect.[39] This can be seen through its role as an agonist on three receptors inside the body, the free fatty acid 2 (FFA2), free fatty acid 3 (FFA3) dan G protein-coupled receptor 109A (GPR109A). The FFA2 receptor is largely expressed on the immune cells including neutrophil, eosinophil, dendritic cells, and monocytes. The FFA3 receptor is mainly expressed on pancreas, spleen, adipose tissue and its role has been recognized on obesity and metabolic disorders. On the immune cells, FFA3 is also expressed but less when compared to FFA2. The SCFA can activate FFA2 receptor through β-arrestins-2 path, which causes NF-κB inhibition thereby resulting in anti-inflammatory effects.[40] Activation of FFA2 also decreases pro-inflammatory cytokines such as IL-6 an d IL-8.[41] The GPR109A receptor, also known as hydroxycarboxylic acid receptor 2 (HCA2), is found at a largely on adipocytes, and expressed on numerous immune cells.[42] On adipocytes, especially white adipose tissue, GPR109A decrease lipolysis dan macrophage activation.[43] Besides being an agonist to the three receptors mentioned, SCFA also works as an inhibitor to histone deacetylases (HDACs), a histone protein involved in epigenetic DNA modification. These HDACs are mainly expressed on immune cells, endothelial cells, and vascular smooth muscle.[44] When HDACs are inhibited, an increase of anti-inflammatory cells production happens. Exposure of SCFA to mononuclear blood cells and neutrophil causes inactivation of NF-κB and decreases the production of the pro-inflammatory cytokine TNF-α.[45]

The second mechanism is the anti-inflammatory effect of fiber seen from polyphenols. Polyphenols are abundant in high fiber food and are studied for their antioxidant and anti-inflammatory properties. The anti-inflammatory effect of polyphenols is through their capability as a scavenger, regulating immune cells activity and modulating enzymes used in arachidonate metabolism phospholipase A2, cyclooxygenase (COX) and nitric oxide synthetase (NOS) enzyme used in arginine metabolism. On a molecular level, polyphenols inhibit enzymes on inflammation process like COX-2, lipoxygenase (LOX) and iNOS that inhibits NF- κB and AP-1, also activation of mitogen activated protein kinase (MAPK), protein kinase-C, and nuclear factor erythroid 2-related factor.[46]

Obesity is one of the causes of low grade inflammation.[7]. Weight-related anti-inflammatory effect of dietary fiber is through adiponectin. This is the third mechanism proposed. Adiponectin plays a role on regulating insulin sensitivity, also has anti-atherosclerotic and anti-inflammatory properties.[47] On obese subjects, adiponectin level on the blood will decrease, and it is cause by the elevation of inflammatory mediators like TNF-α which inhibits genes that synthesize adiponectin.[48] Adiponectin levels in the body is inversely proportional to the level of serum hsCRP. The adipose tissue contains mRNA CRP. This shows that potentially adiponectin inhibits the expression of CRP in the adipose tissue.[49]

Conclusion

Dietary fiber is an essential component of an individual's diet. Anti-inflammatory effect of dietary fiber can be seen on serum hsCRP. Dietary fiber may lower hsCRP serum through SCFA, polyphenols, and adiponectin. Through these various mechanisms, dietary fiber is possibly linked to the prevention of low grade inflammation and its related diseases. Currently, the number of studies covering the association between dietary fiber and

hsCRP on sedentary workers are very limited, and have inconsistent outcomes. In the future, further studies evaluating the association between dietary fiber and serum hsCRP concentration on sedentary workers may be required.

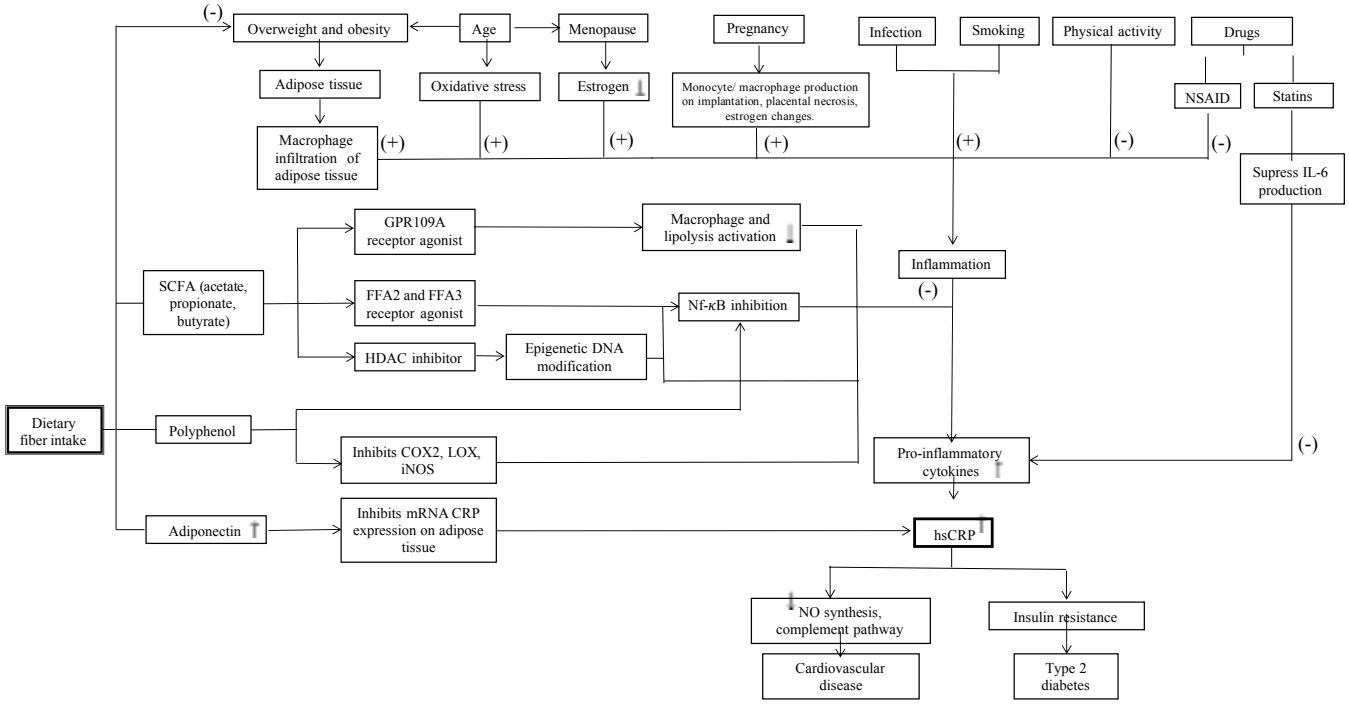

Figure 1. Effect of Dietary Fiber Intake on Serum hsCRP
COX2: cyclooxygenase 2, FFA: free fatty acid, GPR: G protein-coupled receptor, hsCRP: high sensitivity C-reactive protein, HDACs: histone deacetylases, IL-6: interleukin 6, LOX: lipoxygenase, iNOS: nitric oxide synthetase, NO: nitric oxide, NF-κB: nuclear factor kappa B, SCFA: short chain fatty acid.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ORIGINAL ARTICLE

The potential of seaweed salt as an alternative low sodium salt: safety and sensory test

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Abstract

Background: Indonesia is one of the largest producers of red seaweed in the world, but there is very little research done on the role of red seaweed in the health sector. This study is about red seaweed type *Euchema cottoni* and it's potential as seaweed salt that has lower sodium and rich in other minerals.

Methods: This research was divided into two phases and conducted from December 2016 to March 2017. The first phase is a safety analysis in terms of metal, mold and bacteria contamination of seaweed from three different places of Indonesia: Saumlaki, Maluku; Nusa Dua, Bali and Flores, Nusa Tenggara Barat. After the seaweed safety was selected, the seaweed was made into powder at Industrial Research and Development Agency (BPPT), Tangerang. The seaweed powder mixed with ordinary salt with four type of concentrations were subjected to a salty sensory test by nine panellists who have been working at the food production at Hospital for at least one year. The second phase was to do acceptance sensory test of the seaweed salt product taste against a concentration that was selected in first phase to first-degree hypertensive subjects aged 25–59 years by using soup as the meal-media. Chi-square test was used to analyse the difference.

Results: Seaweed from Saumlaki, Maluku was selected as the safest seaweed due to its lowest content of metal, mold and bacterial contaminations. The ratio of seaweed powder to ordinary salt powder 1:1 was selected by nine panellists in salty sensory test. Analysis of minerals from the seaweed salt product found that besides the lower sodium and iodine content, it's potassium and magnesium content were much higher than ordinary salt. Salty taste test by 62 respondents with first degree hypertension with age 25-59 years showed no significant difference in saltiness between seaweed salt and ordinary salt.

Conclusions: In conclusion, the seaweed salt product with a 1:1 ratio to ordinary salt powder is safe and acceptable to be used as an alternative low sodium salt.

Keywords *Euchema cottoni*, seaweed salt, salty sensory test

Introduction

Red seaweed which is widely available in Indonesia is *Eucheuma cottonii*.[1] Seaweed contains minerals of more than 36% dry weight with calcium (Ca) and magnesium (Mg) and iodine (I) as its main

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minerals.[2,3] Na levels in seaweed is generally low around 2-3%, while the K content is around 5-6% .[3] Na content in seaweed is around 1.87 grams per 100 grams and K content is around 5.87 grams per 100 grams. Thus, the Na/K ratio is about 0.32. Some studies suggest that low sodium may reduce blood pressure.[4,5] High K intake is also said to be inversely related to the incidence of hypertension.[5] Recommendations from WHO and European Society of Hypertension/European Society of Cardiology: *Guidelines for the Lifestyle Management t*o Reduce Cardiovascular Risk for Na intake is 2 – 2.4 grams per day (equivalent to 5-6 grams of salt per day).[6,7,8] Recommendations from WHO for K intake of at least 3,51 grams per day.[9] The composition of Na and K in seaweed is thought to be beneficial as an antihypertension in mild hypertension.[10]

Indonesian Basic Health Research 2013 and 2018 showed hypertension prevalence in Indonesian adults increased from 25.8% to 34.1%,[11,12] while data from the Basic Health Research 2007 and 2013 revealed that Indonesian population aged over 10 years consume high daily salt.[11,13]

Seaweeds also contain peptides which have angiotensin converting enzyme inhibiting (ACE-I) activity that may play a role in overcoming hypertension.[10,14] Other nutrients contained in seaweed are fibres with a greater percentage of water-soluble fibres, fatty acids (eicosapentaenoic and arachidonic acids), some vitamins (B_{12}, C, and E), and carotenoids that have antioxidant activity.[2,10,15] Efforts to reduce salt intake are constrained because salt substitute products with low Na content in Indonesia are very limited. Research on the nutrient contents, the role of seaweed and its benefits for health is still limited, especially in Indonesia.[16]

The objective of this study is to analyse the safety of seaweed salt product and to test its saltiness taste as compared to the ordinary salt, to be used as an alternative to reduce blood pressure among mild hypertension subjects.

Methods

The research method was divided into two phases. In the first phase, *Eucheuma cottonii* seaweed from three regions: Saumlaki, Maluku; Nusa Dua Bali and Flores, West Nusa Tenggara were tested for safety from metal contamination at the Analysis and Calibration Laboratory, Center for Agro Industry, Industry Research and Development Agency, Bogor, and safety testing from bacterial contamination at the Industrial Research and Development Agency (BPPT), Tangerang. After obtaining the ethic approval and ethic license from *Harapan Kita* Hospital and Ethics Committee of the Medical Faculty, Universitas Indonesia, *Eucheuma cottonii* seaweed powder from the region with the lowest contamination was made and produced at BPPT, Tangerang. Seaweed that had been cleaned, cut about two or three cm, pasteurized, then grind with 0.5 mm disc mill, filtered, to produce seaweed powder. Furthermore, the seaweed powder is mixed with ordinary salt with a concentration of 1:2, 2:3, 1:1 and 3:2, then salty sensory test was performed to compare those four different concentrations of seaweed salt to the ordinary salt. The test was conducted in the food production department of Hospital, at east Jakarta from December 2016 to March 2017.

The salty sensory test panel consist of healthy nine panelists aged 18 to 59 years, who have worked for at least one year in the food production department at a hospital. The panelists were asked to taste the soup (200 ml) mixed with the 3 gram of seaweed salt and did the salty sensory test that was mostly similar to soup (200 ml) mixed with 3 grams of ordinary salt. The subjects were asked to drink plain water, every time after they tasted the soup. The subjects were asked to taste and compare both soups and did the salty sensory test, from most similar to soup with ordinary salt. Values from not similar (1) to more than ordinary salt (5). Sensory test results were used to determine the concentration that would be used in phase two. Mineral contents of both seaweed salt product and ordinary salt were analysed at Sucofindo Laboratory. The second phase was the savoury test of the chosen seaweed salt product taste against ordinary salt by using soup as the meal-media to 62 first-degree hypertensive or mild hypertension subjects aged 25–59 years. Subjects aged 25-59 years are recruited due to subjects age 25 and above are independent and can plan their own diet while the oldest age of 59 years to reduce the possibility of deterioration of taste and organ function with increasing age.

Results

Eucheuma cottonii seaweed from three regions: Saumlaki, Maluku; Nusa Dua Bali and Flores, West Nusa Tenggara went through safety testing from metal contamination at the Analysis and Calibration Laboratory, Center for Agro Industry, Industry Research and Development Agency, Bogor and safety testing from bacterial contamination at BPPT, Tangerang. The analysis test results of metal and bacterial contamination in **Table 1** showed that seaweed originating from Saumlaki Island, Maluku, is the best one in meeting safety requirements. Seaweed powder was made at BPPT, Tangerang. The process of pasteurization was chosen to reduce the number of bacteria, to maintain the nutritional value of seaweed and decrease water content of seaweed to 10–12 %.

Mixing seaweed powder and ordinary salt ®

First step, the quantity of seaweed powder in gram mixed with quantity of ordinary salt in gram was calculated based on literature study. The conversion values of sodium chloride and salt was as follows: 40% Na and 60% Cl. Whereas 1 gram of Na with 2.6 grams of salt and 1 mmol Na is equal to 23 mg of Na and according to literature studies, Na content in seaweed is around 2–3% dry weight.[3]

Four different ratios of seaweed powder and ordinary salt that have sodium content below 2 gram as WHO recommendation[6], were tested for sensory salty test. The ratio were 1:2 (A), 2:3 (B), 1:1 (C) and 3:2.(D) which contained sodium of: 1.58 grams, 1.44 grams, 1.23 grams and 1.04 grams consecutively.

The results of the salty sensory test from a nine-member panelist, the soup with type C product was the most closely palatable and nice compared to soup with ordinary salt. Therefore, in the second phase of the research formula type C was used: 3 grams of seaweed powder and 3 grams of ordinary salt.

Samples of seaweed salt and ordinary salt used in the study were examined for their Sodium, Potassium, Magnesium and Iodine content at Sucofindo Laboratory (**Table 2**). Sodium and iodine levels in seaweed salt are lower and potassium and magnesium levels are higher than ordinary salt.

The second phase was the sensory salty and acceptance test of the seaweed salt product against ordinary salt by using soup as the meal-media to 62 first-degree hypertensive or mild hypertension subjects aged 25–59 years old.

The same amount of seaweed salt and ordinary salt were sprinkled on two bowls clear chicken soup. The result is shown in **Table 3**, which indicates there is no significant differences found in the salty taste tests of seaweed salted soup and ordinary salted soup (Chi-square test, $p = 0.332$).

Discussion

Seaweed Eucheuma cottonii harvested from Saumlaki, Maluku was selected, due to it's lowest metal, mold and bacterial contamination compared to those from Nusa Dua, Bali and Flores, NTB. The purpose of this research is to study the potential of seaweed powder as an alternative salt function, so the safety criteria refer to guideline of iodized salt for consumption from the National Standardization Agency (BSN) in 2016[17]. The criteria are as follows: metal contamination in miligram/kilogram dry weight: lead (Pb) less than 10, cadmium (Cd) less than 0.5, mercury (Hg) less than 0.1, arsenic (As) less than 0.1, In the safety guidelines for iodized salt products, there is no standardization for contamination of tin (Sn), mold and bacteria. Safety criteria for contamination of tin (Sn), mold and bacteria refer to the guidelines commonly used in France.[2,15] France quality criteria for edible seaweed for tin (Sn) less than 5 mg/kg dry matter, and for mold and bacterial contamination in colony unit/gram: coliform less than 10, anaerobic less than 100. Seaweed from Saumlaki contained cadmium (Cd) less than 0.5 and has smallest mold contamination. This due to Saumlaki's location is in the Maluku islands, where the beach is still very quiet, the population is sparse, and the sea coast is clean and relatively low in pollution compared to the coast of Nusa Dua, Bali and Flores, NTB.

The sensory salty test results selected ratio of 1: 1, that was 3 grams of seaweed powder and 3 grams of ordinary salt, the most closely palatable and nice compared to soup using ordinary salt. Ratio of seaweed powder to ordinary salt 1:2 and 2:3 was less salty and ratio 3:2 was too salty. Six gram of selected seaweed salt ratio contained Na: 1,23 mg compare

to ordinary salt contains Na: 2.28 gr. Na of seaweed salt is lower than ordinary salt and is safer in preventing hypertension.

The salt powder was then analysed for Na, K, Mg and Iodine minerals in the Sucofindo Laboratory. The content of sodium in seaweed salt is around 24.15% and ordinary salt is around 37.6%. Six gram of seaweed salt contained Na:1.45 gr. Sodium levels appear to be higher than the initial count of about 17%, this is because the water content is very different. In the literature study, the data used were dry seaweed materials with water content around 20-30%, while seaweed powder around 10-12%, due to pasteurization process. Potassium and Magnesium levels in seaweed salt are much higher than ordinary salt. Potassium content of seaweed salt was 4 %, while ordinary salt was only 0,03 %. Magnesium content of seaweed salt was 0,16 % and ordinary salt was only 0,002%. Iodine content of seaweed salt in the form of KIO3 is lower than ordinary salt, because ordinary salt products that are used and are on the market was fortified with iodine. Since the standard of Iodine requirement is 30 mg per kg[17], then this salt is not recommended for people with iodine deficiency.

The second phase, sensory salty taste test was done to compare and to evaluate the acceptance of seaweed salt with ordinary salt using clear chicken soup as media to 62 first-degree hypertensive or mild hypertension subjects aged 25–59 years old. There were 8 respondents who said that the saltiness of seaweed salted soup was sufficient and tasty compared to 13 respondents who said that the salty taste of ordinary salted soup was sufficient and tasty. After being tested statistically with the Chi-square test it was found there was no significant differences ($p=0.332$). Eight subjects who chose seaweed salted soup as tasty, comment that soup taste more savory than ordinary salted soup. Taste of seaweed powder was revealed as ocean-like: minerally and salty, fishy taste and has umami flavors.[18,19] Seaweed powder mix with ordinary salt would have salty taste and umami flavor, that was acceptable and nice by the subjects.

In conclusion, the seaweed salt product with a 1:1 ratio to ordinary salt powder is safe and acceptable to be used as an alternative low Na salt

Table 1. Analysis of seaweed metal and bacterial contamination from Saumlaki, Nusa Dua and Flores

Metal * Contamination	Unit	Saumlaki, Maluku	Nusa Dua, Bali	Flores NTB
Lead (Pb)	mg/kg	< 0.040	< 0.040	< 0.040
Cadmium (Cd)	mg/kg	0.02	0.69	0.92
Tin (Sn)	mg/kg	<0.8	<0.8	<0.8
Mercury (Hg)	mg/kg	<0.005	<0.005	<0.005
Arsenic (As)	mg/kg	<0.003	<0.003	<0.003
Bacteria **				
Yeast mold count	cfu/gr	10***	70****	
Coliform	APM/25gr	Negative	Negative	
Escheria Coli (anaerobes)	APM/25gr	Negative	Negative	

*) Analysis and Calibration Laboratory, Center for Agro Industry. Industrial Research and Development Agency, Bogor

**) Institute for Biotechnology Studies Technology Assessment and Application Agency (BPPT), Tangerang

***) Disk without colony at lowest dilution 10

****) Disk outside the number of colonies between 10-300 at the lowest dilution of 10

Table 2. Mineral analysis of seaweed salt and ordinary salt powder SUCOFINDO

Mineral	Unit	Seaweed Salt	Ordinary Salt®	Methods
Sodium (Na)	%	24.15	37.60	SNI 01-3556-2010
Potassium (K)	mg/kg	42,091.56	305.48	AAS-Flame
Magnesium (Mg)	mg/kg	1,622.87	18.02	AAS-Flame
Iodine (KIO3)	mg/kg	5.05	51.09	SNI 01-3556-2000

Table 3. Salty sensory tests of seaweed salt and ordinary salt

Variable	1 Not salty	2 Slightly salty	3 Less salty	4 Same/enough salty	5 Too salty
Seaweed salt		16	31	8	7
Ordinary salt®		8	4	13	37

Chi-square test, p = 0.332

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ARTICLE REVIEW

Partially hydrolized whey protein: A review of current evidence, implementation, and further directions

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Abstract

Background: Human milk is known to be the best nutrition for infants as it provides many health benefits. For non-breastfed infants, cow's milk based infant formula is the most optimal option to provide the needed nutrition. However, approximately 2-5% of all formula-fed infants experience cow's milk allergy during their first year of life. Partially hydrolyzed whey formula (pHF-W) have been widely recommended to prevent the development of allergic disease in infants. However, according to epidemiological data, approximately half of the infants developing allergy are not part of the at-risk group.

Objectives and Methods: This article aims to review the effects of pHF-W in preventing allergy, especially atopic disease, in all non-breastfed infants, as well as the safety aspect of pHF-W if used as routine formula. The role of pHF-W in the management of functional gastro-intestinal (GI) disorders is also reviewed.

Results: Several clinical studies showed that pHF-W decrease the number of infants with eczema. The strongest evidence is provided by the 15-year follow up of the German Infant Nutritional Intervention study which showed reduction in the cumulative incidence of eczema and allergic rhinitis in pHF-W (OR 0.75, 95% CI 0.59-0.96 for eczema; OR 0.67, 95% CI 0.47-0.95 for allergic rhinitis) and casein extensively hydrolysed formula group (OR 0.60, 95% CI 0.46-0.77 for eczema; OR 0.59, 95% CI 0.41-0.84 for allergic rhinitis), compared to CMF as a control, after 15 years of follow-up. pHF-W was also found to be beneficial in the management of functional GI disorders such as regurgitation, constipation and colic.

Conclusions: The use of pHF-W in allergic infants has been recommended in various guidelines across the countries, as a primary prevention of allergic disease. One pHF-W has been approved by the US FDA and the European Commission's European Food Safety Authority (EFSA) for its safety and suitability as a routine infant formula for all healthy infants. According to the data obtained in the management of functional GI disorders, pHF-W is better tolerated than formula with intact protein. Further studies assessing the effect of routine use of pHF-W in a larger population of non-breastfed infants should also be conducted, in order to observe any potential harm and to determine the benefit and cost-effectiveness ratio.

Keywords allergy, breast feeding, formula, functional gastrointestinal disorder, infant, partial hydrolysate, whey

Introduction

Human breast milk is known to be the best nutrition for infants. Breast milk is found to provide protection for the children against infection and malocclusion, as well as improve the intelligence. Growing evidence also suggests that breastfeeding

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might protect against overweight and diabetes later in life.[1]

Nevertheless, due to various circumstances, a large proportion of infants cannot receive human milk.[1,2] Globally, only 38% of the infants are found to be exclusively breastfed.[2] For nonbreastfed infants, infant formula is the most optimal option to provide the needed nutrition. Infant formula is usually prepared from industrially modified cow's milk and processed to adjust the nutritional content according to the needs of infants. However, as cow's milk proteins constitute the most common food allergens in infants, cow's milk formula is one of the most frequent causes of food allergy in infants.[3,4]

Approximately 2-5% of all formula-fed infants experience cow's milk allergy during their first year of life.[5,6] Cow's milk allergy (CMA) is often associated with manifestations in various organ systems, such as gastrointestinal, respiratory tract, and skin. CMA may cause failure to thrive and even sometimes cause life-threatening anaphylactic reactions.[5,7] In order to reduce the allergenic potential, cow's milk protein in the infant formulas can be modified by hydrolyzation processes to reduce the size of the peptides, and therefore could induce tolerance without sensitization.[3,4]

Hydrolyzed formulas (HF), according to clinical studies, may give beneficial effects in reducing the risk of several allergic diseases, especially infants born in families with atopic disease (high-risk infants). Several reports have recommended the use of HF for the at-risk infants.[8-10] Of all HFs available, the partially hydrolyzed whey formula (pHF-W) have been widely recommended to prevent the development of allergies in infants.[13-16] However, according to epidemiological data, approximately half of the infants developing allergy are not part of the at-risk group. This is because the number of infants in the non-at-risk group is significantly larger than that in the at-risk group.[11] The infants in non-at-risk group have approximately 15% risk of developing allergies.[12]

Therefore, this article aims to evaluate and review the effects of pHF-W in preventing allergies, especially atopic diseases, in all non-breastfed infants, both the high-risk and non-at-risk infants, as well as the safety aspect of pHF-W to be used as a routine formula.

Partially hydrolyzed whey formula (pHF-W)

Milk proteins consist of two fractions: casein and whey. Casein is the coagulum portion of milk, which becomes clots or curds inside the stomach. It contains the larger and more complex protein molecules, which are harder to digest. Casein protein also contains more allergenic proteins, which are responsible for the majority of milk allergies. On the other hand, whey is the liquid portion of milk, which makes it easier to digest. It also contains less allergenic proteins. From this standpoint, the casein protein is considered to be more likely to trigger allergies or general indigestion than the whey protein.[2,17]

The composition of casein and whey in cow's milk is different from that in human breast milk. Cow's milk protein is 77% casein and 23% whey, meanwhile breast milk protein is approximately 30% casein and 70% whey, even though the casein/whey ratio in breast milk may fluctuate between 70/30 and 80/20 in early lactation and decrease to 50/50 in late lactation.[2] Other than that, the whey and casein proteins in cow's milk and breast milk might also differ in fraction number, amino acid composition, as well as the peptide mappings. Therefore, raw cow's milk must be processed and modified to resemble the human breast milk composition before it is considered safe for infant consumption.[2]

Hydrolyzed formulas (HFs) are typically derived from cow's milk proteins, either whey or casein, which have undergone several procedures to breakdown these natural proteins into lower molecular-weight peptides. These protein modification procedures may include heating, ultra-filtration, and enzymatic cleavage. Depending on the degree of hydrolysis and modification, the hydrolyzed cow's milk formulas can be differentiated into partially hydrolyzed formula (pHF), of which the molecular weight is 3-10 kDA, and extensively hydrolyzed formulas (eHF), of which the molecular weight is <3 kDa. Compared to the nonhydrolyzed (intact) formula with the molecular weight of 14-68 kDA, hydrolyzed formula have lower molecular weight peptides, which are thought to induce oral tolerance without causing sensitization. Thus, hydrolyzed formula is thought to reduce the risk of allergic disease

compared to the intact formula.[3,4]

The allergy-preventing property of hydrolyzed formula, however, seems to not only depend on the degree of hydrolisation but also on the method of hydrolisation, as well as other factors. The qualitative changes of the peptides due to the hydrolysis process may also affect the potential benefit of the formula. There are at least three factors affecting the allergy-preventing effect of a hydrolyzed formula, which are the protein source (whey and casein), method of hydrolysis (temperature, pH, and the type of enzyme used), and the degree of hydrolysis.

Due to these reasons, it is safe to say that every HF is different and might even have contradictory characteristics from one to another, even with the same degree of hydrolysis. Nutten et al also confirms this statement. They studied the physicochemical profile of 76 commercially available whey- and casein-based eHF (eHF-W and eHF-C) products and found significant variability in the molecular weight profile of the peptides, amino acid components, as well as the allergenicity of the products, which would eventually affect the effectiveness of each product in preventing allergies.[18] Researches studying the effect of HFs should, therefore, evaluate every HFs individually. Pooling together various hydrolysates (HFs) would be inappropriate, as it may cause bias and the results could not represent any of the individual HFs.[3,4]

Partially hydrolyzed whey formula (pHF-W) is one of the partially hydrolyzed formulas composed of 100% whey protein. pHF-W has been demonstrated to result in positive effects on preventing the development of allergies, particularly atopic dermatitis, in infants.[13-16] As yet, only one routine infant pHF-W has been granted a qualified health claim by the U.S. Food and Drug Administration for risk reduction of atopic dermatitis.[4,19] The following sections discuss the current evidences found regarding the effect of pHF-W in preventing atopic disease, as well as the possibility of pHF-W to be used as a routine formula.

pHF-W and prevention of atopic disease

Atopic diseases are a group of diseases caused by an exaggerated IgE immune response to otherwise harmless allergens.[20] Pediatric atopic disease may include atopic dermatitis (eczema), asthma, allergic rhinitis, as well as food allergy. International Study of Asthma and Allergies in Childhood (ISAAC) reported a significant increase in the worldwide prevalence of pediatric atopic diseases in both developed and developing countries. Approximately 8% of children aged less than 3 years are affected by food allergy, meanwhile the prevalence of children with eczema is estimated to be as high as 30%.[21,22] In general, the development of allergy is influenced by several factors, which are the genetic predisposition, allergen exposure (including time, dose, frequency of exposure, processing and consumption of food proteins such as hydrolysate, gastro-intestinal microbiome, LCPUFAs), and other contributing factors (such as cesarean section at birth, early exposure to antibiotics, seasonal variations, pollution, passive smoking, industrialization, pets at home, infections, lifestyle, and vitamin D). In order to prevent the development of allergic disease, current guidelines recommend several preventive measures, which include no maternal food restriction during pregnancy and lactation, exclusive breastfeeding for the first 4-6 months of life of the infants, timing of introduction of the complementary foods, and also the use of HFs with demonstrated efficacy when breastfeeding is not possible.[9]

The partially hydrolyzed whey formula (pHF-W) has been observed clinically to decrease the number of infants with eczema. Several studies have assessed the effectiveness of initial exposure to pHF-W to reduce the risk of eczema. Two different meta-analyzes published in 2010 showed that healthy infants with a family history of allergies who are fed with pHF-W have a lower risk of atopic dermatitis compared to babies who are fed the intact cow's milk protein formula (CMF). Subanalysis conducted in the meta-analyses showed that the risk reduction of eczema was approximately 52 and 55%, respectively, at the age of 12 months, and approximately 38 and 36%, respectively, at that age of >30 months.[3,23,24]

Baumgartner reported that the number of infants who developed atopic symptoms if fed a pHF-W was only 25% of those fed CMF (OR 0.25, 95% CI 0.18-0.36).[24] The analysis also showed that the effect of pHF-W in reducing the allergic

manifestations is equivalent to breast milk, especially for long-term prevention.[25] A literature review of 8 clinical trials also confirmed that pHF-W supports normal growth in infants, and showed that the risk of atopic dermatitis in infants who are not fully breastfed in the general population also decreases after administration of specific pHF-W, compared to CMF, in the first 4-6 months of life.[26]

The strongest evidence is provided by the 15-year follow up of the German Infant Nutritional Intervention (GINI) study, which studied the effect of pHF-W, eHF-W, and eHF-C in 2,252 participants, compared to CMF as the control, in reducing the cumulative incidence and prevalence of pediatric allergic diseases. The result showed that there was reduction in the cumulative incidence of eczema and allergic rhinitis in pHF-W (OR 0.75, 95% CI 0.59-0.96 for eczema; OR 0.67, 95% CI 0.47-0.95 for allergic rhinitis) and eHF-C groups (OR 0.60, 95% CI 0.46-0.77 for eczema; OR 0.59, 95% CI 0.41-0.84 for allergic rhinitis), compared to CMF as a control, after 15 years of follow-up.[27]

While the above studies showed positive effect of pHF-W for preventing allergies, several other studies showed contradictory results with other HFs. Several issues and weaknesses, however, are found in the methodology of each study that needs to be taken into account.[13,28-30] The common issue is that these meta-analysis pool together different types of pHF from multiple manufacturers, which would give rise to different characteristics of the resulting peptides. Hence, the results of these studies might not be useful, as the collective results could not represent any of the protein hydrolysate.[3,4]

Systematic review and meta-analysis by Boyle found no consistent evidence that both pHF, not only limited to pHF-W, and eHF can reduce the risk of allergies or autoimmune outcomes in babies with a high risk of allergies. This might be due to the inclusion criteria of this study, which included multiple interventions and retrospective cohort studies, excluded 7 pHF interventional studies, as well as the unusual segmentation of age (0-4 years, compared to other meta-analyses in which the segmentations were at 0-1 year).[28]

A randomized-controlled trial (RCT) by Boyle analyzed the use of pHF and prebiotic supplementation, compared to standard formulas, in preventing eczema in high-risk infants. The results showed that there was no difference in incident of eczema between the intervention of pHF+prebiotic and standard formula in high-risk infants within 12 months of follow-up. This might be due to the methodology, such as the use of different pHF and the randomization process which was performed at the age of <1 month (not at birth), which could lead to biased results.[29]

A Cochrane meta-analysis by Osborn also stated that there is no evidence that pHF provides positive effect in preventing allergies, compared to exclusive breastfeeding. However, the analysis of the studies performed in preterm and term infants were combined. Other than that, the study also analyzed different types of pHFs, which could cause the findings of this meta-analysis to be considered invalid, as different pHFs might exhibit different effect on preventing allergies.[30]

The RCT by Lowe et al[13] also revealed that pHF-W could not reduce the risk of allergic manifestations, compared to standard formulas. However, some weaknesses were also found in the methodology of the study as; the end point was conducted by telephone interview, only 50% of infants received formula at 4 months of age, 16.5% never received the allocated formula, and that the study was single blind.

pHF-W for all non-breastfed infants: safety aspects

The use of pHF, including pHF-W, in allergic infants has been recommended in various guidelines across the countries, as a primary prevention of allergic disease, mainly atopic dermatitis, in high-risk infants.[8-10] However, the compliance rates for these guidelines are relatively low. The Pouessel et al[31] study in 2006 revealed that there are still around 50% of children born with genetic risk not given hydrolyzed formulas, including pHF-W, as a form of prevention. The 2008 ASCIA annual meeting also concluded that in practice, guidelines were not followed, and in fact only 2.5% of children born with genetic risk were given a hydrolyzed formula.[8]

Although the use of pHF-W has been recommended for at-risk infants,[13-16] The fact is that half of all infants who develop allergies are not part of the at-risk group, as mentioned above. This is because the number of infants in the non-risk group

is significantly larger than the number of infants in the risk group.[11] Therefore, it is under debate on whether pHF-W should be considered as a routine formula for all nonbreastfed infants, regardless of their risk of allergies.[4]

One pHF-W has been approved by the US FDA and the European Commission's European Food Safety Authority (EFSA) for its safety and suitability as a routine infant formula for all healthy infants, regardless of its relationship to its use in preventing allergies.[20,33] In terms of nutritional content, pHF-W is very similar to CMF, except that the protein content in several pHF-Ws is slightly higher than in CMF. This makes pHF-W also meets all nutrient requirements as required for standard CMF.[6] pHF-W typically contains 67 kcal/100 mL of energy, 11.2 g/100 kcal of carbohydrate, 5.1 g/100 kcal of fat, with the protein content varied in the range of 1.8-2.2 g/100 kcal. Meanwhile, CMF contains 67 kcal/100 mL of energy, 11 g/100 kcal of carbohydrate, 5.3 g/100 kcal of fat, and 1.8 g/100 kcal of protein.[33,34]

Based on limited data of the long-term effect of pHF-W in healthy infants, it was found that there was no significant difference between the growth of pHF-W infants and CMF infants.[27] For the long-term use, Rzehak et al found no significant differences between the BMI trajectory in the pHF-W group, extensively hydrolyzed whey formula (eHF-W), CMF, and breast milk groups after 6 years of follow-up. In fact, it was found that pHF-W shows the closest growth rate to breast milk, among the other infant formula.[35] In another study, the Z-score trajectories showed that the weight gain in pHF infants is normative, despite the accelerated weight gain in CMF infants.[36] A systematic review and expert consensus also concluded that pHF-W was as safe as CMF in terms of supporting normal development. There was no difference found in the nutritional value and safety of pHF-W compared to CMF.[37]

Data regarding the effects of pHF-W in hormonal response and metabolism of healthy infants were also limited. Hoppe et al reported that whey protein increased fasting insulin by 21% (p=0.006) in young boys aged 8 years in 7 days, with no change in IGF-1 (p=0.27), suggesting an increase in insulin resistance. This would naturally arise concern that pHF-W may induce the development of diabetes mellitus.[38] However, as to anticipate this concern, the FDA-approved pHF-W has undergone the process of removing the caseino-Glyco-MacroPeptide (cGMP), resulting in the formation of modified sweet whey (MSW) formula.[34] This formula is found to have lower plasma level of a number of amino acids, such as leucine, isoleucine, threonine, and valine, which are considered to be insulin secretagogues (insulinogenic amino acids). This formula would, therefore, lead to a reduced risk of developing diabetes, compared to the classical pHF-W.[34,39] It was also found that the administration of pHF, including pHF-W, in infants with a genetic risk of developing type 1 diabetes mellitus did not increase incidence of type 1 diabetes.[40]

pHF and functional gastro-intestinal disorders

Functional gastro-intestinal disorders (FGIDs) FGIDs are a frequent cause of parental concern and consequent impaired infants and relatives' quality of life, and impose a financial burden to health care, insurance and families.[41] Management of these FGIDs should focus on improving both infants symptoms and family quality of life. If more than parental reassurance is needed, available evidence suggests that nutritional advice is recommended as it is effective and most of the time devoid of adverse effects.

Troublesome regurgitation occurs in about 25 % of all infants and usually improves spontaneously within the first year after birth.[42] A thickened pHF-W was reported to be more effective than a thickened formula with intact protein.[43]

Infant colic is reported to occur in about 20 % of all infants.[42] Frequent and extensive auto-medication by parents of infants with colic has been reported.[44,45] Therefore, management should focus on sustaining parents to cope with their child's excessive crying and distressed behavior by informing the parents that in general crying peaks at about four to six weeks after birth, may last up to three hours per day in otherwise normal infants and steadily diminishes from 12 weeks onwards.[46] In formula fed infants, when CMPA is an unlikely diagnosis, a partial hydrolysate with prebiotics and beta-palmitate; or a synbiotic formula with reduced lactose and partially hydrolyzed protein may be beneficial.[47]

Functional constipation occurs in about 10% of all infants.[42] A pHF-W, (a mixture of) prebiotics, probiotics, synbiotcs, and beta-palmitate and/or a formula with high magnesium content (but within normal ranges) may offer some benefit.[41]
pHF-W has also been shown to have some beneficial effect on functional GI manifestations, such as regurgitation and constipation.[9] A review by Vandenplas et al. showed that there was a significant decrease in the number of regurgitation events per day with the use of pHF-W. In addition, stool in the infants group with pHF-W was also found to be softer compared to stool in the standard formula[33,43] and soy-based formulas.[43] Other data also showed that the use of pHF-W in non-breastfed infants can accelerate gastric emptying, reduce the incidence of infantile colic, and other functional gastrointestinal symptoms, when compared to CMF.[37]

Conclusion

Breast milk is still the best nutrition for babies. In nonbreastfed infants, CMF can provide adequate nutrition to support normal growth and development. However, CMF is known to often induce cow's milk allergic reaction. In a large-scale GINI study and several other studies, pHF-W has been proven as a formula which is superior in reducing atopic disease and has been recommended in several guidelines to prevent atopic disease in high-risk group infants. Even so, more large-scale clinical studies replicating these studies, particularly GINI study, might be needed to confirm the effectiveness of pHF-W.

As the number of infants developing allergy is greater in the non-at-risk group compared to the at-risk group, the use of pHF-W should not be limited to the at-risk group only. Despite some reported differences in studies, pHF-W has always shown superior benefits among all the available infant formulas, with minimal potential harm for healthy term infants. According to a comparative pharmacoeconomic analysis, pHF-W is also superior over the standard formula in the aspect of family and societal perspectives, as well as the attractive cost-effectiveness.[47] Further studies assessing the effect of routine use of pHF-W in a larger population of nonbreastfed infants should also be conducted, in order to observe any potential harm and to determine the benefit and cost-effectiveness ratio.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ARTICLE REVIEW

The effect of vitamin D supplementation during pregnancy on the risk of having preterm birth: An evidence-based case report

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Abstract

Introduction: Preterm birth (PTB) is a major cause of neonatal morbidity and mortality. Pregnant woman is one of the most vulnerable groups for vitamin D deficiency, that increase the risk of PTB. Vitamin D has the role of immunomodulator, anti-inflammatory, and transcription of genes involved in placental function. Research results on the correlation between vitamin D supplementation and PTB risk are still inconsistent.

Objectives: To observe the effect of oral vitamin D supplementation during pregnancy on the risk of PTB

Methods: Advanced search for relevant literatures in PubMed, Cochrane, and Willey was conducted. After assessing the relevancy and eligibility, articles were selected and critically appraised.

Results: There were three articles that relevant with the eligibility criteria and clinical questions, they were randomized controlled trial, meta-analysis and systematic review. Three studies found that oral vitamin D supplementation in the form of cholecalciferol during pregnancy had a significant reduction on the risk of PTB. A systematic review found that supplementation with combination of cholecalciferol and calcium carbonate may increase the risk of PTB. The different dosages, frequencies, and time of initiation limit the generalizations for efficacy and safety doses.

Conclusions: Oral cholecalciferol supplementation during pregnancy reduces the risk of PTB. While supplementation with combination of cholecalciferol and calcium carbonate requires consideration. Research on the effect of oral vitamin D supplementation during pregnancy on the risk of PTB is still limited and need for more studies. Recommendation for vitamin D consumption based on the RDA needs to be fulfilled in pregnant women.

Keywords pregnancy, vitamin D, vitamin D3, cholecalciferol, preterm birth, preterm labor

Introduction

Preterm birth (PTB) is defined as birth that occurs between 20 to 37 weeks of pregnancy. The rate ranges from 5% to 18% of babies born. Every year an estimated 15 million babies are born prematurely, increasing in most countries and becoming a global issues.[1–3] In 2017, 5.4 million children under 5 years old died and PTB complications are the leading cause of their deaths.[1,4] According to WHO, Indonesia is the ninth country with the highest PTB rate, which is 15.5 per 100 live births. Also the fifth country with the greatest number of PTB, which is 675,700 births.[1]

Preterm babies may be born with serious health problems, include motor and cognitive neurodevelopmental disabilities (cerebral palsy,

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blindness, deafness, mental retardation, and learning disabilities), chronic lung disease and gastrointestinal problems.[2,5,6] PTB is associated with a 3 to 4-fold higher incidence of adverse maternal outcomes including the need for blood transfusion and prolonged hospitalization, and increased frequency of cesarean births more than doubled.[7]

There are several common cause of PTB, inflammation and infection are highly significant risk factors.[1,2,5] Vitamin D is suggested to influence physiological pathways involved in PTB, including inflammation, immunomodulation, and transcription of genes involved in placental function.[8–10] Vitamin D has the effect of suppressing some inflammatory cytokines. Vitamin D receptors are present in immune cells, which produce antimicrobial peptides and prevent perinatal infections.[10] Poor maternal nutrition at preconception and during early pregnancy also affect the risk of PTB.[8] Pregnant women is one of the most vulnerable groups for vitamin D deficiency.[11] Research has suggested that maternal vitamin D deficiency, or insufficiency, has related to several adverse maternal and fetal outcomes, including preterm labor (PTL) or PTB.[6,11]

There have been several studies that describe the relationship between vitamin D supplementation and PTB, however, the results were inconsistent. Mojibian M., et al.,[12] showed that consumption of 50,000 IU vitamin D every 2 weeks from 12 weeks of pregnancy until delivery the incidence of PTL were not significantly different. Meanwhile, Persad MD., et al.,[13] showed that vitamin D supplementation was associated with the prevention of PTB (RR 0.54; 95% CI 0.42-0.68). Therefore, the aim of this study to analyze the effect of oral vitamin D supplementation during pregnancy on the risk of PTB.

Clinical question

Can vitamin D supplementation during pregnancy reduce the risk of having preterm birth?
P: Pregnant women
I: Oral vitamin D supplementation
C: Placebo or without vitamin D supplementation
O: Risk of preterm birth

Methods

Strategy of article searching

Advanced searching was used for this literature searching from three main databases: PubMed, Cochrane, and Willey on May 15th, 2020 (**Table 1**)

Strategy of article selection

Eligibility Criteria

The article was selection based on the inclusion and exclusion criteria. Inclusion criteria were: (1) Pregnant women, (2) Oral vitamin D supplementation, (3) Comparison with placebo or without vitamin D supplementation, (4) Preterm birth or preterm labor as the study outcome, (5) Systematic review of randomized controlled trial (RCT), meta-analysis or RCT (6) Publication within the last 5 years. Exclusion criteria were: (1) Not in accordance with the clinical question, (2) There is no full text available, (3) Article is not written in English.

Method of Critical Appraisal

Articles were reviewed by all authors using the critical appraisal method according to the Center of Evidence-Based Medicine for therapy studies. Critical appraisal was done on the articles, so that the validity, importance and applicability could be assessed. The level of evidence in this study was determined based on the Oxford Center for Evidence-based Medicine – Levels of Evidence.

Results

Following of the search strategy, three original articles were eligible for this evidence-based case report (**Figure 1**). The first study was a RCT with level of evidence of 2, the second study was a systematic review with level of evidence of 1, the third study was a meta-analysis with level of evidence of 1. Characteristics of the studies are shown in **Table 2**. Critical appraisal was carried out in all articles, the results can be seen in **Table 3** and **Table 4**.

Discussion

The first study by Sablok A., et al.,[11] that conducted a randomized controlled trial (RCT) to 180 primigravidae with singleton pregnancy at 14-20

weeks. Participants were divided into two groups, group A formed the non-intervention group whereas group B formed the cholecalciferol supplementation group, with a dose dependent on the estimated 25-OHD serum level at baseline. One of the risk of maternal complications as outcome of this study was PTL or PTB. The result of this study was 21.1% of the patients in group A had PTB compared to 8.3% in group B, a significant decrease in incidence of PTB in the supplementation group (p=0.02).[11]

The second study is a systematic review by Luz Maria D., et al.,[14] that included 15 RCTs involving 2833 pregnant women. One of the primary outcome of this study was to determine whether oral vitamin D supplementation alone or in combination with calcium or other vitamins and minerals can reduce the risk of PTB. This study method was based on a standard template used by Cochrane Pregnancy and Childbirth. GRADE was used to assess the quality of evidence and the strength of recommendations. As only one study was considered of high quality, sensitivity analyzes in this study was not conducted.[14]

Oral vitamin D supplementation in the form of cholecalciferol during pregnancy reduces the risk of PTB compared to no intervention or placebo (RR 0.36, 95% CI 0.14 to 0.93; 3 trials, 477 women, moderate quality). Only one reported case of nephritic syndrome in the control group in one study (RR 0.17, 95% CI 0.01 to 4.06; 1 trial, 135 women, low quality). Due to limitations of data for maternal adverse events, no conclusions could be drawn.[14]

Oral supplementation with combination of vitamin D (cholecalciferol) and calcium (calcium carbonate) increased the risk of PTB compared to no treatment or placebo (RR 1.57, 95% CI 1.02 to 2.43; 3 trials, 798 women, moderate quality). No trial reported on maternal adverse events in supplementation with combination of vitamin D and calcium. There were no studies included in supplementation with combination of vitamin D and calcium compared to supplementation with calcium (without vitamin D), and supplementation with combination of vitamin D, calcium and other vitamins and minerals.[14]

The third study is a meta-analysis by Zhou S., et al,[15] that included six RCTs and 18 observational studies. The six RCTs in this study investigated whether vitamin D supplementation during pregnancy can reduce the risk of PTB. The risk for PTB among women receiving supplement ranged from 0.06 to 1.20, and positive and significant results were reported in one out of the six RCTs. Three RCTs had a low risk of bias, one had a moderate risk of bias, and two had a high risk of bias.[15]

Vitamin D3 dosage used for the intervention groups ranged from a daily dosage of 400 IU to multiple bolus dosage of 120,000 IU. The result of meta-analysis in six RCTs involved 1687 pregnant women was RR=0.57 (95%CI: 0.36–0.91) and test of heterogeneity, I^2=26.2% (p=0.238), suggested that women who received vitamin D3 supplementation during pregnancy had a lower risk of PTB compared to women who received placebo or routine antenatal care. In the subgroup analysis of RCT, the studies with sample size >100, low risk of bias and single-dose supplementation of vitamin D3, could reduce the risk of PTB, but no conclusions could be drawn because the subgroups had only one or two RCTs, and the results may be misleading. RCT sensitivity analysis showed that there were two studies that significantly influence the results. The small sample size produced unstable results, therefore it was difficult to exclude the possibility that the positive association was due to chance.[15]

This meta-analysis tried to explain the effect of vitamin D on PTB risk. The possible protective effect of vitamin D against PTB by reducing infection and inflammation, as the major cause of PTB. Maternal serum 25-OHD and 1,25-diOHD also can inhibit inflammatory factors, such as tumor necrosis factor-α and interleukin 6, while at the same time promoting anti inflammatory cytokine and cathelicidin, responding to microbial invasion through activation of toll-like receptors on monocytes and macrophages. Vitamin D may also affect placental function, given that 1,25-dihydroxyvitamin D3 can reduce oxidative stress, which is associated with iatrogenic PTB.[15] Limitations of intervention studies in this meta-analysis were inconsistent dosage regimen, timing of initiation and quality of design were limited the efficacy of generalization.[15]

Conclusion

All three studies, RCT, meta-analysis and systematic review, found that oral vitamin D supplementation in the form of cholecalciferol during pregnancy had a significant reduction on the risk of PTB. A systematic review found that oral supplementation with combination of cholecalciferol and calcium carbonate may increase the risk of PTB. The different dosages, frequencies, and time of initiation limit the generalizations for efficacy and safety doses. Due to limited data for maternal adverse events, no conclusions can be drawn. Research on the effect of oral vitamin D supplementation during pregnancy on the risk of PTB is still limited and need for more studies. Recommendation for vitamin D consumption based on the RDA needs to be fulfilled in pregnant women for the continuity of fetal growth and development.

Table 1. Resources and search strategy

Database	Search strategy	Hits	Selected Article
PubMed	(((((("pregnancy"[Title/Abstract] AND ("vitamin D"[Title/Abstract] OR "vitamin D supplementation"[Title/Abstract])) AND (("preterm birth"[Title/Abstract] OR "preterm labor"[Title/Abstract]) OR "premature birth"[Title/Abstract])) AND 2015/5/15:3000/1/1[Date - Publication]) AND ("systematic"[Filter] AND 2015/5/15:3000/1/1[Date - Publication])) AND (("meta-analysis"[Publication Type] OR "systematic"[Filter]) AND 2015/5/15:3000/1/1[Date - Publication])) AND (("clinical trial"[Publication Type] OR "meta-analysis"[Publication Type]) OR "systematic"[Filter]) AND 2015/5/15:3000/1/1[Date - Publication])	16	1
Cohrane	ID Search #1 "pregnancy" #2 "vitamin D" OR "vitamin D supplementation" OR "cholecalciferol' OR "ergocalciferol' #3 "preterm birth" OR "preterm labor" OR "premature birth" #4 #1 AND #2 AND #3 with Cochrane Library publication date Between May 2015 and May 2020, in Cochrane Reviews, Trials	65	1
Wiley	search result for [[All: "vitamin d"] OR [All: "vitamin d supplementation"] OR [All: "cholecalciferol' or "]] AND [All: ergocalciferol'] AND [[All: "preterm birth"] OR [All: "preterm labor"] OR [All: "premature birth"]] AND [Earliest: (05/01/2015 TO 05/31/2020)]	23	1

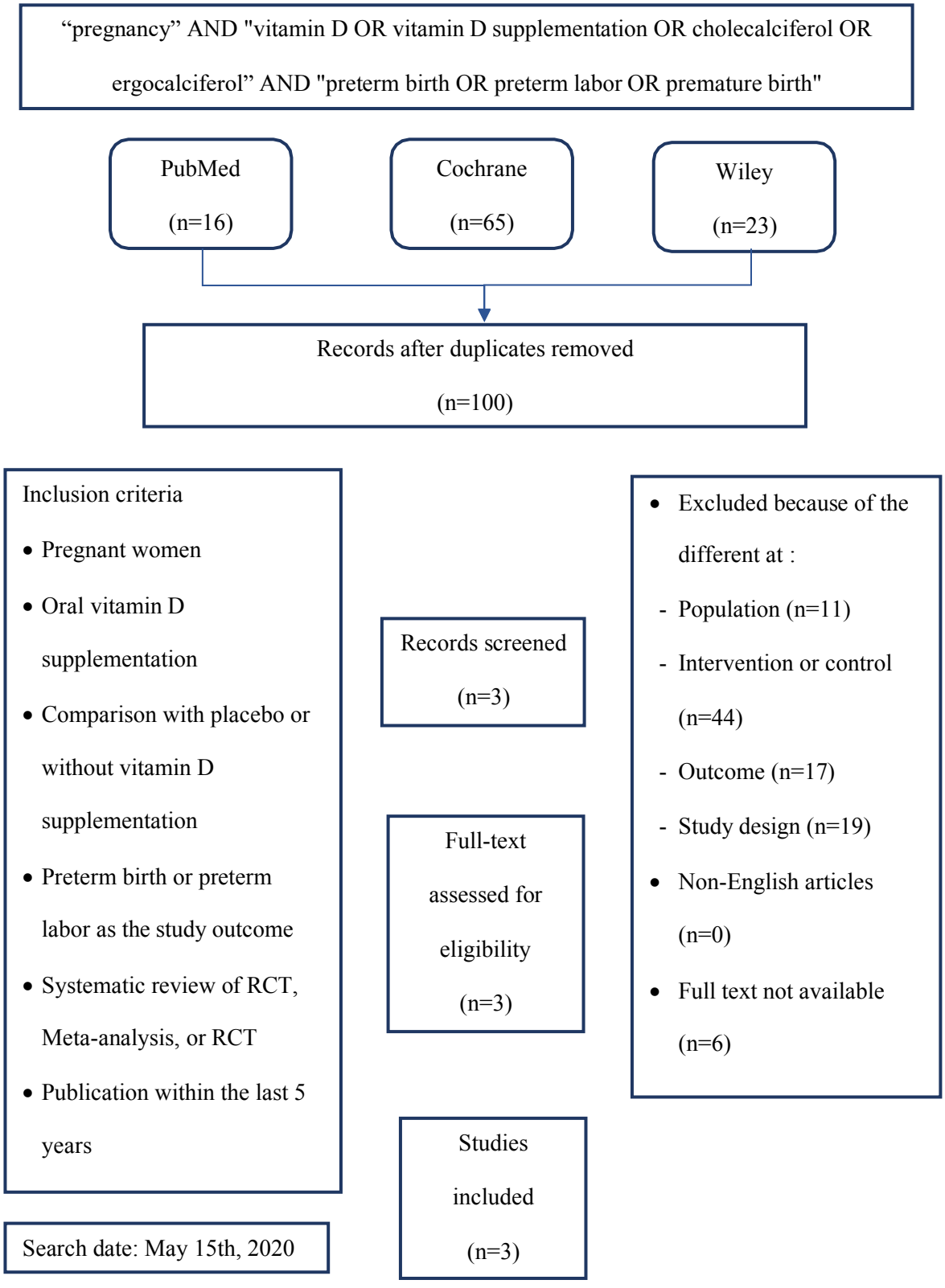

Figure 1. PRISMA *flow chart*

Table 2. Characteristics of study

Article by	Study design	Characteristic of Population	Number of subjects	Therapy	Control	Outcome
Sablok A., et al[11] (2015)	Randomized controlled trials	Primigravidae with singleton pregnancy at 14-20 week	180 participants	Group B (n=120), classified as: - Sufficient levels of VD (> 50nmol/L) received one dose of 60 000 IU cholecalciferol at 20 weeks - Insufficient levels (25-50nmol/L) received two doses of 120 000 IU at 20 and 24 weeks - Deficient levels (<25nmol/L) received four doses of 120 000 IU at 20, 24, 28 and 32 weeks.	Group A (n=60) : NI	- Risk of maternal complications: PTL, pre-eclampsia and GDM associated with VD deficiency - Infants of mothers with VD deficiency: LBW and Apgar score
Luz Maria D., et al.[14] (2016)	Systematic review	Pregnant women without pre-existing condition, at any gestational or chronological age, parity and number of fetuses	15 RCT (2833 participants)	- VD - VD + Ca - VD + Ca + VM VD varied in dosage, regimen and time to start. VD form: cholecalciferol-D3 (10 trials), ergocalciferol-D2 (3 trials), and no report (2 trials). VD daily dose: 200 IU – 2000 IU (*to be continued in the next page)*	- Placebo or NI - Ca - Ca + VM - VM	- Primary outcomes: Pre-eclampsia, GDM, VD concentration at term, adverse effects (hypercalcaemia, kidney stones), PTB (<37 weeks' gestation), LBW (< 2500 g). - Secondary outcomes: Impaired glucose tolerance, caesarean section, GH, maternal death, birth length, head circumference, birth weight, admission to special care during the neonatal period, stillbirth, neonatal death, Apgar score, neonatal infection, very PTB (< 32 weeks' gestation)
				-	-	-

Table 2. Characteristics of study (continued)

Article by	Study design	Characteristic of Population	Number of subjects	Therapy	Control	Outcome
Luz Maria D., et al.[14] (2016) *(continued from previous page)*				(*continued)* VD single-dose: 200,000 IU, 600,000 IU, 35,000 IU per week and dose depended upon the level of serum 25-OHD levels at baseline VD time to start: ≥ 20 weeks of pregnancy Ca supplementation: Ca carbonate, doses ranged from 375 mg - 1250 mg VM supplementation: Iron (60 mg ferrous sulphate) and folic acid (400 mcg)		
Zhou S., et al[15] (2017)	Meta-analysis	Pregnant women without HIV infection	6 RCT (1687 participants) and 18 observational studies	VD3 dosage ranged from 400 IU daily to multiple bolus dosage of 120,000 IU	Placebo or routine care (ferrous sulfate 200 mg and Ca 600 mg daily, but no VD)	- Association between maternal circulating 25-OHD and the risk of PTB or sPTB - Effect of VD supplementation during pregnancy on reduce the risk of PTB

RCT = Randomized Controlled Trial; IU = International Unit; 25-OHD = 25 hydroxyvitamin D; GDM = Gestational Diabetes; LBW = Low Birth Weight; PTB = Preterm Birth; sPTB = Spontaneous Preterm Birth; PTL = Preterm Labor; GH = Gestational Hypertension; VD = Vitamin D; VD3 = Vitamin D3; Ca = Calcium; VM = Vitamin and Mineral; NI = No Intervention.

Table 3. Critical appraisal of the RCT study

Parameters	Question	Sablok A., et al.[11] (2015)
VALIDITY	Was the assignment of patient to treatments randomized?	Yes
	Were the groups similar at the start of the trial?	Not Clear
	Aside from the allocated treatment, were groups treated equally?	No
	Were all patients who entered the trial accounted for?	No
	And were they analyzed in the group to which they were randomized?	Yes
	Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?	Not clear
IMPORTANCE	How large was the treatment effect?	p= 0.02
	How precise was the estimate of the treatment effect?	Precise, the 95% CI of the results are narrow
APPLICABILITY	Is my patient so different to those in the study that the results cannot apply?	No
	Is the treatment feasible in my setting?	Yes
	Will the potential benefit of treatment outweigh the potential harms of treatment for my patient?	Yes

Table 4. Critical appraisal of systematic review and meta-analysis

Parameters	Question	Luz Maria D., et al.[14] (2016)	Zhou S., et al.[15] (2017)
VALIDITY	Did the meta-analysis address a focused question (PICO)?	Yes	Yes
	Does the meta-analysis use it to direct the search and select articles for inclusion?	Yes	Yes
	Did the search find all the relevant evidence?	Yes	Yes
	Have the studies been critically appraised?	Yes	Yes
	Did they only include high quality studies?	No	No
	Have the results been totalled up with appropriate summary tables and plots?	Yes	Yes
	And heterogeneity between studies assessed and explained?	Yes	Yes
IMPORTANCE	Was measure clearly explained?	Yes	Yes
	How are the results presented?	Presented in Figure Analysis 1-2	Presented in Figure 1-4, Supplementary Figure 1-7 and Summary of findings
APPLICABILITY	Can we apply this valid, important evidence about to our patients?	Yes	Yes

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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ORIGINAL ARTICLE

Take-out food frequency was associated with energy intake among mothers of young children in urban slum area in North Jakarta

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Abstract

Background: Inadequate energy intake was prevalent among women of reproductive age, which may contribute to poor diet. Having great concern towards health and nutrition may play a role in shaping eating habit and food-related behavior to achieve a healthy diet. This study aims to examine the association between health concern and energy intake, while considering other factors such as cooking frequency and having food away from home.

Methods: This cross-sectional study was carried out in an urban slum area in Jakarta, involving 233 mothers of young children through consecutive sampling. Data was collected through interview. Health concern was assessed using General Health Interest Scale (GHIS) questionnaire. Energy intake was obtained by 24-hour dietary recall in two non-consecutive days. Consumer Behavior Questionnaire (CBQ) was used to assess frequency of cooking and having food away from home. All statistical analysis was performed using SPSS Version 20.

Results: Energy intake of most subjects did not meet the recommendation, with median of 1,396 kcal/day. Health concern among the subjects had median of 32 out of 48. There was no significant correlation between health concern and energy intake (r = -0.067, P-value = 0.309). The frequency of having take-out food was a significant predictor of the energy intake (β = 7.497, P-value = 0.028). Additionally, a significant negative correlation between health concern and having take-out food was found (r = -0.141, P-value = 0.032).

Conclusions: Having take-out food was associated with energy intake. Provision of health and nutrition information in the food stores might help to increase health concern to shape a healthier diet. Thus, a collaborative effort targeting both food sellers and customers is essential.

Keywords energy intake, diet, women, health concern, health interest, take-out food

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Introduction

Suboptimal diet was observed in global population, characterized by high consumption of sugar-sweetened beverage, processed meats, and sodium, contrasting with the consumption of fruits, vegetables, whole grains and legumes failed to meet the recommendation.[1] Given that the obesity rates were higher among women than men,[2] a healthy diet is an essential aspect for women in reproductive age to prepare for pregnancy and child bearing. However, inadequate energy intake was apparently common in women of reproductive age, including adolescent girls and pregnant women.[3,4] According to Indonesian Total Diet Study 2014 (TDS 2014), more than half adults in Indonesia failed to meet the recommended energy intake. Jakarta as the capital city had the highest mean energy intake for both men and women. However, the energy intake recommendation was still not met.[5] Adequacy is one of the elements comprising diet quality. Thus, inadequate energy intake may contribute to poor diet. Particularly for the child-bearing women, mother's diet was known to be a predictor for the child's diet.[6]

Diet is a multidimensional topic, which involves individual and environmental factors. Previous studies had highlighted the evidence of the environment, where food stores availability in urban slum neighborhood significantly contributes to energy-dense food consumption. In urban slum areas, purchasing ready-to-eat food rather than cooking was also a common practice done by mothers, who usually were the primary food provider at home.[7,8] Being the main food provider means that mothers have control over choosing food and the preparation process, which is a part of food environment at household level. Having a particular concern towards health and nutrition might be a driver to practice healthier behavior related to food and diet. Previous studies have shown that women generally displayed greater interest towards health,[9,10] thus they were more likely to comply to dietary recommendation.[11] Additionally, having health concern was associated with food choice and meal planning.[12,13]

To author knowledge, health concern was rarely assessed in relation with dietary behavior and dietary outcomes especially in Indonesian setting. Knowledge about health and nutrition was more common, yet usually the results show a moderate and good degree of knowledge.[7,14] Given the growing evidence of obesity prevalence and dietary patterns in urban slum areas,[7,15] exploring the perceived concern towards health might contribute to design intervention program to improve not only knowledge, but to shape a healthier food environment. Therefore, this study aimed to assess the relationship between health concern and energy intake among women of reproductive age, particularly mothers of young children, while considering other factors such as cooking frequency and having food away from home.

Methods

The study design used in this research was cross-sectional, carried out from November 2019 up to March 2020 among mothers of young children aged under-five and pre-school children. This study took place in Jakarta province, represented by Pejagalan urban village, located in Penjaringan Subdistrict, North Jakarta City. Jakarta Province was selected purposively as a representative of urban area in Indonesia which has a great proportion of slum areas. The subdistrict and the urban village were selected using a multistage random sampling. Meanwhile the subdistrict and the urban village was selected using a multistage random sampling. This area was considered to be an urban slum area which was flood-prone.

Consecutive sampling was applied in this study, in which all eligible subjects were enrolled until the minimum sample size was fulfilled. The subjects were chosen based on the children list obtained from randomly selected *Posyandu* (community health post). The data collection involved mothers who met the criteria as follows; aged 19-49 years, had a child aged 6 years old or younger, apparently healthy, fluent in Bahasa Indonesia, had the role as the primary food provider at home, and agreed to participate by signing the informed consent. Those who were pregnant, lactating, and under restrictive or specialized diet were excluded. Ethical approval was attained from the Ethical Committee of Faculty of Medicine, Universitas Indonesia No. ND-

6/UN2.F1/ETIK/PPM.00.02/2020, dated 6 January 2020.

The sampling size was calculated using correlation formula with the *r* coefficient referred to previous studies on health concern and dietary behavior.[9,11] Considering the non-probability sampling used in this study, design effect of two was applied in order to increase the variation. The final sample size calculation also considered 80% of response rate, therefore it was added by 20% of the sample size as the non-response rate. The minimum sample size was determined to be 152 subjects with confidence level of 95% and power of 80%.

Eligible subjects who gave their consent were visited for a face-to-face interview using a structured questionnaire. The data included sociodemographic, health concern, family food characteristics, and dietary assessment. Sociodemographic data comprised of subject's age, education level (elementary school, junior high school, senior high school, or university), employment status (unemployed, partially employed defined as working half-day or working at home (e.g. owning a small store at home), full-time employed defined as working full-day or at least eight hours a day), and average monthly household income.

Health concern questionnaire in this study referred to the General Health Interest Scale (GHIS),[16] which was initially a self-administered questionnaire consisting of eight statements related to dietary behavior. The assessment is aimed to measure the degree of how health and nutrition is perceived as importance. This study had translated GHIS statements from English to Bahasa Indonesia and back-translated into English, followed with a preliminary interview with mothers with similar characteristics of the population and resulting in Cronbach's Alpha of 0.711 indicating good reliability. In this study, the self-administration approach was modified into interview, in which the interviewer read the statements and asked the subjects to rate each statement with 7-point Likert, from 0 to declare "strongly disagree" up to 6 to declare "strongly agree". Thus, the possible range for GHIS is 0-48. A higher score of GHIS indicated the higher degree of the subjects perceive health as importance.

Family food characteristics were explored by interviewing the subjects about cooking frequency, eating out frequency, and having take-out food or using food delivery services. This was a part of home food environment questionnaire, derived from a modified version of National Health and Nutrition Examination Survey Consumer Behavior Questionnaire (NHANES CBQ)[17]. This questionnaire was also translated into English and pre-tested among mothers with young children. It aimed to assess whether the subjects usually cook by themselves or purchase ready-to-eat food. For cooking frequency, it was determined by the number of days whether the subject or other household members cook (excluding cooking instant noodles or reheating commercially prepared food) in the previous week. While the frequency of eating out and having take-out food variable referred to the number of days the subjects purchased ready-to-eat food and/or eating out in the past one month.

Dietary assessment was conducted using 24-hour dietary recall in two non-consecutive days. The interviewer provided a food photobook to estimate the amount of food consumed. This study considered underreporting and overreporting energy intake with cut-off 500-3,500 kcal/day.[18] Therefore those whose energy intake was under 500 kcal and exceeding 3,500 kcal were excluded from the analysis. Those who were not able to complete the second day of 24-hour dietary recall were also excluded. Dietary data was analyzed using NutriSurvey for Windows Version 2007.

All statistical analysis in this study was performed using SPSS Version 20. For numerical data, normality test was conducted to determine the data distribution using Kolmogorov-Smirnov, which will be considered as normal distribution if P-value >0.05. Normally distributed data was displayed with mean and standard deviation (SD), whereas asymmetrically distributed data was displayed with median and interquartile range (IQR). Descriptive statistics were applied for sociodemographic characteristics (age, education level, employment status, and household income). Health concern, family food characteristics, and energy intake were compared by the sociodemographic characteristics using correlation Pearson or Spearman for continuous data, and Student t-test or Mann-Whitney for categorical data. Analysis to establish relationship between health concern, family food characteristics, and energy intake used Pearson or

Spearman correlation. Statistical significance level was determined at P-value <0.05.

Results

Total number of subjects participated in this study were 255 mothers. After calculating for underreporting energy intake and checking the completeness of the overall questionnaire, 22 subjects were excluded from the analysis. The subjects enrolled in this study exceeded the minimum sample size as it aimed to prevent removing too many subjects due to incompleteness and the possibility of underreporting energy intake. The socio-demographic characteristics of the subjects are displayed on **Table 1**. The median age of the subjects was 33 years old. Most of the subjects completed senior high school (35.6%) and junior high school (28.8%). Majority of the subjects were unemployed (housewives) (68.2%). The median household monthly income was IDR 3 million (around USD 213.4 as of January 2021). Additionally, the majority of the subjects' households were categorized as low-middle income (76.4%), which the third quartile was approximately the same amount of the regional minimum wage in Jakarta province as of 2020.

The GHIS total score resulted in median of 32. Significant relationship was found between GHIS and subject's age (r = 0.251, P-value <0.001). GHIS total score was slightly but significantly higher among the older age group compared to the younger one, which was 33 and 30 respectively. There was no significant difference in GHIS total score according to education level and household income.

Table 2 displayed the family food characteristics of the subjects. The cooking frequency showed the median of 6 days/week. Almost half of the subjects (48.9%) always cooked meals at home, whereas only 15.9% never cooked. Significant difference of cooking frequency was only observed by the subject's age (r = 0.224, P-value = 0.001), in which the older subjects cooked more frequently. There were no significant differences of cooking frequency by education level, employment status, and household income. Spearman correlation coefficient showed a significant relationship between GHIS total score and cooking frequency (r = 0.235, P-value <0.01), which means those who had greater health concern cooked more frequently. The median of the frequency of having food away from home was 0 for eating out and 8 for having take-out food. More than half of the subjects (61.4%) never ate out in places like restaurants or food stalls in the past one month. Meanwhile, 33% of the subjects had take-out food at least once a week and 36.9% of them had it more than once a week in the past one month. There was significant relationship between eating out (r = -0.277, P-value <0.001) and having take-out food (r = -0.174, P-value = 0.008) by age. We observed that eating out and having take-out food were more frequent among the younger subjects. By income, significant relationship was only observed on eating out frequency (r = 0.265, P-value <0.001). This shows that the higher household income was associated with more frequent eating out. Furthermore, we found that the greater health concern was associated with lower frequency of eating out (r = -0.171, P-value <0.01) and having take-out food (r = -0.141, P-value = 0.032) (**Table 3**).

The median of energy intake of the subjects was 1396 kcal/day. The relationship between energy intake observed by age group, education level, employment status and household income were not found to be significant. Spearman correlation coefficient also did not show a significant relationship between health concern and energy intake, and between family food characteristics and energy intake (**Table 3**).

Multivariate analysis was performed with multiple linear regression using enter method and including all variables. **Table 4** displayed the model with predictor of energy intake of the subjects. The overall model did not show statistical significance (P-value = 0.154). However, the frequency of having take-out food was a significant predictor of energy intake (β = 7.497, P-value = 0.028). We found that every one day increase of having take-out food, energy intake of the subjects would increase by 7.5 kcal.

Discussion

The present study exhibits a similar result with the Indonesian TDS 2014, in which the energy intake of mothers was below the recommendation. The result

of energy intake in this study was also consistent with previous studies among women in urban area.[4,15] The subjects in this study were mothers of under-five and preschool-aged children. Previous findings in a study among parents stated that mothers with children displayed poorer dietary behavior and higher energy intake contributed from fat intake and consumption of sugar-sweetened beverages.[19] Meanwhile, a Japanese study did not found significant difference of total energy intake between mothers with and without children.[20] The dietary difference between parent and non-parent was apparently varied and tended to show no major changes. Nevertheless, it is worthy to note that becoming a mother was known to be associated with weight gain and increase in body mass index (BMI), making them more prone to obesity risk.[21]

The low energy intake among the subjects might be resulted from their eating habit. The subjects in our study generally had two or three meals per day, which one meal consisted of one serving of rice and less than half serving of vegetables as the side dishes, with one serving of protein source food or less, or even no protein at all. Consumption of instant noodles was also common. As we observed from the 24-hour dietary recall, snacking habit among the subjects was varied. The prevalent snacking habit among female adolescents contributed to meal-skipping.[22] Nonetheless, the characteristics differences between adolescents and mothers may play a big role in determining the snacking habit. Similar with other Indonesian studies,[7,15,22] fried food and *cilok* (ball-shaped boiled tapioca flour) were the common snacks consumed by the subjects of this study. Among our subjects, consuming sugar-sweetened beverages seemed to be a part of their daily lifestyle. It was recommended to limit intake from empty calorie food which only provide calories but few or no nutrients, including from sugar-sweetened beverages. According to U.S. Department of Agriculture (USDA), intake limits differed by age and sex.[23] Several diet quality measures determined the limit for these food groups to achieve a good diet. Healthy Eating Index 2010[24] set the intake limit not more than 20% of energy intake, while Diet Quality Index-International[25] set it not more than 10%. At least half of the subjects had more than 10% of energy intake contributed from empty calorie food. Despite the considerable contribution from fried snacks and sugar-sweetened beverages, the food choice and the amount of foods consumed from the main meals were not sufficient to achieve the recommended energy intake.

In this study, significant relationship between health concern and energy intake was not established. However, the negative correlation implied that the higher health concern was related to lower energy intake. A study in Luxemburg found a significant difference in energy intake based on the importance level of nutrition and balanced meals. Similarly, those who perceived nutrition as highly important displayed lower energy intake. The different measure to assess health concern might explain how the results on significance were not in line. Alkerwi et al.[26] used a single question focusing on balanced meals with 3-level of classification from low, moderate, and high. A single question might help the respondents to categorize themselves into respective categories since it was more straightforward. In contrast, we used an instrument comprised of eight statements which had larger scope, including eating behavior, food choice, and balanced diet. Unfortunately, studies about health concern and energy intake was rare. Nevertheless, the existing literatures supported that greater health concern was related to healthier eating behavior[9] and dietary pattern[27].

Based on the multiple linear regression model, having take-out food was found to be a significant predictor of energy intake. Interestingly, health concern was significantly correlated with frequency of having take-out food. Our result suggested that the greater concern towards health, the less frequent the subjects to purchase take-out food. According to a qualitative study among mothers, in the context of household with children, the mothers usually prioritized health and nutrition concern when providing food for the family.[28] For some mothers, given the limited facilities to store fresh foods at home and time constraint for preparation and cooking, they might think differently when it comes to provide food for themselves. It was more likely that they allocated more time to perform house chores, drop off and pick up older children from school, and take care of the young children, resulting to have take-out food as a practical way to fulfil their dietary needs.[8] Among our subjects, we observed that take-out food in the form of side dishes like

cooked vegetables or fried foods were meant to be consumed for the whole family members, since the mothers usually only cooked rice. Meanwhile, take-out food that was consumed by the mothers only was typically one-dish meal (e.g. meatball soup, noodles, *nasi uduk*).

Our result also showed a significant positive correlation between health concern and frequency of cooking at home, which the greater health concern was associated with more frequent cooking. In contrast, the greater health concern was related to the less frequent of eating out. This result was consistent with a study in Brazil. Those who perceived high concern towards health would be more engaged in their meal planning, food choice, and the cooking methods.[13] Various food stores were abundant in urban slum neighborhood, which mostly provided cooked meals (e.g. rice, vegetable side dishes, fried chicken or fish, *soto*, etc) or snack (e.g. fried vegetable fritters), manufactured snack and beverages.[7,8] When food stores were available and easily accessed, this may contribute to more eating out or having take-out, rather than cooking.[29] Although purchasing cooked meals was common in urban slum area, our result found that more than half of the subjects frequently cooked and prepared their meals at home. Cooking at home can be seen as a challenge due to time and cost. Nonetheless, cooking by themselves was preferred by particular women who wanted to ensure the hygiene of the food preparation process.[8]

Apparently, eating out was not common, except for the working mothers. We assumed that eating out was considered as a family leisure activity. In spite of the abundant food stores available, the space provided in the food stalls in a densely populated neighborhood was not suitable for family with young children. In addition, for the low socioeconomic status (SES) community, the term eating out was seen as a luxurious activity (i.e. eating in a restaurant), thus it can be economically challenging. Price is commonly discussed and often perceived as barrier to healthy diet. This study found a significant positive correlation between household income and eating out frequency. This may suggest that the expenditure might be higher as the frequency increases. Previous studies highlighted how socioeconomic status may influence diet through food choices. It was generally believed that higher SES had greater food expenditure, resulting in a healthier food choice.[30]

Consuming meals that are prepared away from home, including eating out and having take-out, was considered to be less healthy. A Korean study demonstrated a significant different diet between those who eat homemade meals and non-homemade meals. Homemade meals were associated with lower energy intake, with more dishes consisted of grains. The cooking methods used was mainly stewing or steaming.[31] This result displayed similarity to ours although it was not statistically significant, the inverse correlation showed the tendency of the more frequent cooking, the lower energy intake. The subjects in our study who frequently cooked mostly had vegetables soup in their menu. On the contrary, those who eat non-homemade meals demonstrated more diverse food and meat-based dish, contributing to higher protein intake.[31] Our results demonstrated a positive correlation between eating out and take-out food towards energy intake. As stated by Lee et al.[31] food away from home was related to more various cooking methods. We observed the food stores in the neighborhood provided numerous choices of food, such as fried food, stir-fry food, coconut-based soup, which might explain how these foods can contribute to higher energy intake. Our multivariate analysis also exhibited that for every one-day increase of having take-out food, energy intake of the mothers would increase by 7.5 kcal as well. Although it is statistically significant, this number is not clinically significant since 7.5 kcal is less than 1% of Indonesian RDI for energy intake for women of reproductive age.

This study had some limitations that should be noted. Underreporting energy intake was not using actual calculation with consideration of individual nutritional status. Several attempts to calculate under-reporting energy intake using the established body weight and height in Indonesian dietary recommendation was done, yet the result would exclude more than half of the subjects. Thus, cut-off 500-3500 kcal was used.[18] Secondly, we applied the general rules of thumb to determine minimum sample size for multiple linear regression analysis, yet our sample of 233 participants (which is more than the minimum number of samples based on the calculation, i.e. 152) was still underpowered to detect significance in predicting the energy intake.

Our findings suggested that frequent take-out food was associated with higher energy intake. The median energy intake who never had take-out food was 1355 kcal/day, meanwhile those who had take-out food at least once a week had slightly higher median energy intake of 1407.5 kcal/day. Previous studies show that take-out food and other forms of food away from home were also associated with higher intake of sodium and fat,[32] higher BMI,[33] and increasing odds of overweight/obesity[34]. Therefore, the findings in this study should be cautiously interpreted, given that most of our subjects' energy intake was below recommendation. As there are various food options provided in the neighborhood food stores, behavior of having take-out food can be modified through an intervention program focusing on giving understanding about healthy food choice along with improving food preparation skill. Furthermore, education on food choice and home-prepared food with relation to expenditure might be more insightful for the mothers, particularly in low SES community.

The negative correlation between health concern and frequency of take-out food suggested that our subjects had fair understanding about the healthiness of food. However, the abundant food stores can be a driver to frequent consumption of food away from home.[35] The external environment factors such as food stores availability and accessibility are less modifiable. Instead, providing sufficient information about the healthiness of food and motivating messages in the food store might help the consumer to consider their food choice. A review of small store-based intervention suggested that combined strategies in physical environment in food stores (e.g. food placement) and behavioral involving both sellers and consumers (e.g. poster) might improve the access and the consumption of nutritious food.[36] This would require a collaboration involving local government, health officials, cadres, and the food sellers in order to establish behavior changes to achieve a better diet. Empowering both consumers and food sellers is a crucial step to enable them to make a better and healthier choice to provide food for themselves and for the family.

Table 1. Demographic characteristics of mothers of young children in Pejagalan, North Jakarta (n=233)

Variables	Median (IQR)	n	%
Age (years old)	33.0 (9.0)		
19-29 years old		75	32.2
30-49 years old		158	67.8
Education level			
Less than elementary school		12	5.2
Elementary school graduate		64	27.5
Junior high school graduate		67	28.8
Senior high school graduate		83	35.6
Diploma / university graduate		7	3.0
Employment status			
Unemployed (housewife)		159	68.2
Partially employed		46	19.7
Fully employed		28	12.0
Average monthly household income (IDR)	3 million (1.950 million)[1]		
Low-middle (≤ 3rd quartile)		178	76.4
High (> 3rd quartile)		55	23.6

IQR : Interquartile range, IDR: Indonesian Rupiah
[1]1 USD=IDR 14,058.6 as of January 15, 2021

Table 2. Family food characteristics of mothers with young children in Pejagalan, North Jakarta (n=233)

Variables	Median (IQR)	n	%
Cooking frequency (days)[a]	6 (5)		
Never		37	15.9
1 – 3 days/week		53	22.7
4 – 6 days/week		29	12.4
Always (7 days/week)		114	48.9
Eating out frequency (days)[b]	0 (3)		
Never		143	61.4
1 – 3 days/month		34	14.6
1 – 3 days/week		35	15.0
More than 4 days/week		21	9.0
Having take-out food frequency (days)[b]	8 (18)		
Never		23	9.9
1 – 3 days/month		47	20.2
1 – 3 days/week		77	33.0
More than 4 days/week		86	36.9

IQR : Interquartile range; [a]Number of days in the past one week; [b]Number of days in the past one month

Table 3. Correlation between health concern, family food characteristics, and energy intake

Variables	Health concern		Cooking frequency		Eating out frequency		Take-out food frequency		Energy intake	
	r	*P*-value[a]	*r*	*P*-value[a]	*r*	*P*-value[a]	*r*	*P*-value[a]	*r*	*P*-value[a]
Health concern	1	.	0.235	<0.001*	-0.171	0.009*	-0.141	0.032*	-0.067	0.309
Cooking frequency (days)[b]			1	.	-0.186	0.004*	-0.602	<0.001*	-0.019	0.773
Eating out frequency (days)[c]					1	.	0.249	<0.001*	0.097	0.141
Having take-out food frequency (days)[c]							1	.	0.093	0.157
Energy intake (kcal)									1	.

[a]Statistical analysis used Spearman correlation, [b]Number of days in the past one week, [c]Number of days in the past one month
*Significance level of *P*-value <0.05

Table 4. Multiple linear regression model for predictor of energy intake (n=233)

Variables	Beta coefficient	SE	*P*-value
Age (years old)	1.804	5.188	0.728
Education level[a]	38.058	32.128	0.237
Employment status[b]	135.963	69.895	0.053
Household income (IDR)	<0.001	0.00	0.222
Health concern	-2.366	4.045	0.559
Cooking frequency (days)[c]	11.649	13.784	0.845
Eating out frequency (days)[d]	4.927	4.640	0.289
Take-out food frequency (days)[d]	7.497	3.380	0.028*

IDR: Indonesian Rupiah, SE: Standard Error
[a]Education level referred to five-level education attainment from diploma/university, senior high school, junior high school, elementary school, and less than elementary school; [b]Employment status referred to employed and unemployed; [c]Number of days in the past one week; [d]Number of days in the past one month; *Significance level at *P*-value <0.05
Multiple linear regression was performed using enter method including all variables altogether
R square = 0.051, *P*-value = 0.154

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ARTICLE REVIEW

The role of nutrition in children with celiac disease

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Abstract

Celiac disease, a permanent, irreversible but treatable disease is an autoimmune disease triggered by gluten ingestion in genetically predisposed individuals, also known as celiac sprue and gluten sensitive enteropathy. The gluten fractions that are toxic are called gliadins triggers an immune reaction that leads to bowel inflammation mediated by T lymphocytes, cause damage to the small intestine and villous atrophy.

Recent findings

Intestinal inflammation and villous atrophy in small intestines by permanent intolerance to gluten in celiac disesea leads to seveare malabsorption. Around 20%-38% patients were basically nutritionally imbalance secondary malabsorption due to mucosal damage. Nutrition plays a very important role in the management of celiac disease. Gluten free diet must be balanced to cover nutrient requirements to prevent deficiencies and ensure children's health, growth and development.

Conclusion

Gluten-free diet is the only accepted and available treatment in CD. It was a life-long treatment, if not carried out with attention, it may lead to nutritional imbalance which can affect children's growth and development

Keywords celiac disease, children, gluten-free diet, growth and development

Introduction

Celiac disease (CD) is a systemic autoimmune disorder caused by permanent intolerance to gluten, such reaction leads to intestinal inflammation, villous atrophy in small intestines which leads to malabsorption.[1,2] CD is a global disease with seroprevalence of 1.4% and biopsy prevalence 0.7% worldwide, with the exception of areas showing low frequency of CD-predisposing genes and low gluten consumption (e.g., sub-Saharan Africa and Japan).[3] It is well known that CD is strongly associated with human leukocyte antigen (HLA) class II, HLA-DQ2 and HLA-DQ8 which are located on chromosome 6p21. The presence of the HLA-DQ2 allele is common in the general population, and it is present in approximately 30% of Caucasian individuals. [3,4] CD is recognized not only throughout historical CD areas such as Northern Europe and United States, but also significantly increase in new regions (Asian countries). Studies have shown that most CD cases remain undetected in the absence of serological screening due to heterogeneous symptoms and/or poor disease awareness.[3,4]

Multiple pathways are involved in the pathogenesis of CD which finally lead to the destruction of the enterocyte and subsequent atrophy of small intestinal villi. The histology of CD studies the mucosa of the small intestine, especially the submucosa, muscularis and serosa. A flat mucosa with villus shortening can be observed which is compensated for by hyperplasia and elongation of

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intestinal crypts. These changes reduce the amount of epithelial surface available for absorption.[1,2]

Gluten free diet (GFD) is the only cornerstone treatment of celiac disease. GFD involves strict lifelong avoidance of all products containing gluten, a protein known as prolamins which are protein storage in starchy endosperm of many cereal grains such as wheat, barley, rye. GFD will result in alleviation of symptoms, normalize autoantibodies and repair intestinal mucosa overtime in CD. [5,6,7] Previous study stated that as about 20%-38% CD patients were basically nutritionally imbalance secondary malabsorption due to mucosal damage of GI tract.[8] The greater small intestines mucosal atrophy also causes greater iron, copper, folate, calcium, vitamin B-12 and zinc deficiencies. [6,8] Hence, suitable GFD must be nutritionally balanced. It must cover nutrient requirements to prevent deficiencies and ensure a healthy life, especially in children where growth and development are highly depending on nutrition supply. Therefore, nutrition plays vital role in treating CD.[9] However, strict and lifelong diet is also challenging to children as major role of non-compliance due to disliking the taste of GFD and temptation. GFD compliance itself varies from 45% to 81% in children in reports by Hill et al.[10] Whereas up until now, GFD is the only treatment accepted and effective for CD, therefore this may affect long-term morbidity and mortality of children with CD.[11,12] Complete termination of gluten is nearly impossible, the gluten free indicates diet containing gluten at minimal level to be considered harmless. Recent reviews conclude less than 10 mg a day is most likely not causing any further damage to mucosal.[5] Gluten-containing foods which need to be avoided in CD patients are bread, cereals, flour and pasta in their daily diet. Two types of GFD available is naturally gluten-free or processed gluten-free that were made through purification. Several naturally GFD are rice, corn, potatoes, seeds, and legumes. Elimination of gluten through purification in processed GFD will inevitably alters macro and micronutrients composition and nutritional value in them.[6]

Methods

In this article, we aimed to provide a thorough review on the role of nutrtion in children with celiac disease. The databases EBSCOHOST, CINAHL, MEDLINE, and Web of Science were searched (2000 to present) using the following key words: pediatric, children, celiac disease, coeliac disease, gluten free diet, nutrition. An ancestry search was also used to find relevant articles.

Result and Discussions

Risk of GFD

A collaborative study investigated different composition of gluten free products (GFP) and gluten-containing products. GFP were mainly high in fat, mainly saturated fat, and low in protein and carbohydrate which leads to lower energy content. Additionally, GF products also had more sodium and less fiber.[13] Some commercially available GFP are also have lower content of micronutrients and minerals. Specifically, vitamin A, thiamine, riboflavin, niacin, vitamin B6, vitamin B12, folate, biotin, vitamin D, pantothenate, magnesium, sodium, iron, cupper, iodine, chlorine, manganese and selenium intakes were lower in GFP.[9,14]As a consequence, life-long therapy of GFD rise concerns about its impact on a patient's anthropometric parameters and its nutritional adequacy.

Nutritional inadequacy consequences in GFD

GFD, the only treatment for CD, is indeed reduces risk of increase mortality and adverse events in CD.[13,14] However, GFD itself is not risk-free, as it may cause further nutritional complication as a result of poor nutrients quality of GFD products described above.[6,9]

Numerous studies revealed imbalance diet contributed by GFD in children with CD. Macro and micronutrient imbalance were found in children consuming GFP. A study conducted by Elliot, examined nutritional quality of package GFP in children and showed packaged GF food have poor nutritional quality compared to regular products containing gluten (88% vs 97%: $p<0.01$). Products with a GF claim had lower levels of protein, sodium, total fat, and saturated fat compared with products without a GF claim. A higher proportion of the GF products had high levels of fat and trans-fat. Calories

from sugar in GFD compared with child-targeted products without a GF claim were similar. [15]

Öhlund et al. conducted a study by using 5-day food record of 25 CD children age 4-17 years on CFD. Thirteen over 25 children did not meet recommended energy intake (below new nordic nutrition recommendation). The dietary intake for CD children on GFD were inadequate regarding quality of macronutrients, mineral and vitamins. Sucrose and saturated fat were higher than recommendation, paradoxically with low fiber, polyunsaturated fatty acids, vitamin D and magnesium contain in GFP.[14] Study conducted by Zucotti et al in assessing dietary intake of 18 CD children age 4-10 years old on GFP with 18 healthy children in Italy. Energy intake in CD children on GFD was significantly higher than that of non-celiac children. The percentage lipid-derived energy was lower while carbohydrate derived energy was higher in CD compared to healthy children.[16] Kulai T et al also assessed nutritional adequacy in packaged GFP in Canada, the study showed comparable calories between GF and regular foods. Although the total calories were comparable, the GF breads were significantly higher in total fat and lower in protein and iron content compared with regular breads. While GF pasta was higher in carbohydrates, but lower in protein, fiber, sugars, iron, and folate content.[17] Gluten-free cereal foods are made using refined gluten-free flour or starch not enriched or fortified, so they are found to be rich in carbohydrates and fats only and low in fiber.[18]

Overall, GFD effects on intake of macronutrient and energy was more fat-derived energy than carbohydrate with higher saturated fatty acid than PUFA. While inadequate fiber was also observed in GFD. However, recent GFP made from pseudo-grains and alternative gluten-free grains like quinoa and buckwheat have equivalent fiber content with glutted contained product. Vitamin and minerals intake in GFD including B vitamin (thiamine, riboflavin, niacin) and folic acid were also did not meet the recommendation intake. While micronutrients intake such as iron were usually added to enrich GFP knowing iron deficiency is a common manifestation of untreated CD.[19] **Table 1** summarizes common nutrient deficiency concerns in CD and the diet.[20]

GFD effects on body antrophometry

Complete elimination of gluten in GFD enables small intestine mucosa to heal and resolving symptoms also nutritional deficiencies. But contrasting results were observed in CD subjects undergone CFD. Normalizaton of body antropometric were found in CD patients compliant with GFD.[9,21,22] A study in Brasil assessed nutritional profile of 31 CD patients followed GFD for at least one year showed no significant differences in weight, height, total body fat percentage, total muscle mass, and body mass index observed compared to healthy groups ($p > 0.05$).[23] CD children on GFP were less frequently obese than healthy control subjects and most of them (77%) reached a normal weight during GFD and none of the underweight subjects became overweight or obese.[24]

While study of 679 patients with GFD showed 15.8% patients moved from normal or low BMI class into overweight class and 22% of overweight patients at diagnosis gained weight after GFD. Risk of obesity of GFD is around the corner by combination of healing of intestinal mucosal which leads to better nutrition absorption and high-calorie intake of GFD mentioned above.[25]

Paradoxically, study by Ciacci et al had shown that patient following a strict gluten-free diet often suffer from various nutrient deficiencies described above. The study showed that long term strict GFD have significantly lower weight, body mass index, fat and lean body mass than control subjects.[26]

Dietary advice for children with CD

Parents' education and compliance

Life-long and strict GFD is important in pursuing mucosal healing and symptoms alleviation in CD. Strict adherence to gluten-free diet may be more challenging in children and adolescents than in adults. Non-compliance to GFD may be one of the major problem which depends not only on children but parents, notably parents knowledge. Garg et al research about predictors of compliance to GFD in CD children noted that only 65.67% children were dietary compliant to GFD. Parental influence was the main role of GFD compliance in children while environmental in adolescents age group. Parents

difficulties were low level of knowledge, budget burden, and also psychological burden. While in adolescents, environmental issues were increased social interaction, increasing peer group pressure, increased outdoor activities, and need for experimentation.[11] Mother's education is a significant factor related with the compliance.[27]

Therefore, several ways to overcome these issue might be counselling aiming to increase disease knowledge (by physician) and awareness of parents regarding cheap and acceptable alternatives to wheat and easy to cook gluten-free food recipes will help ensure compliance to GFD in children (by dietician).[6] Baseline education to adolescent children undergoing peer-pressure affecting compliance is by support to children and parents.[27] Child positive behavior has significant higher degree compliance. [11,27]

Dietary composition of GFD

Ideal GFD should meet individual's nutritional needs and contain balance of macro and micronutrient. Daily recommendation for calorie intake in GFD does not differ with general population.[19] It contains 55% from complex and simple carbohydrates, 15% from dietary protein and 25%–30% or less from lipids.[6] Consumption of natural gluten free food is preferable due to balance nutrients composition, with higher nutrition value of energy, balance lipid composition and vitamin content compared to processed GFP. In GDF, main natural dietary source of protein are animal foods such as meat, milk and dairy products, eggs and fish. Plant foods sources of protein include legumes, nuts, seeds and gluten free cereals. Vegetable oils, nuts, seeds and higher fat fish including salmon, trout and herring are good source of mono saturated fats and omega-3 fatty acid.[28] Consuming iron and folic acid rich natural gluten-free food such as green vegetable, legume fish and meat are more preferable to meet micronutrient need individually.[6] To avoid micronutrient deficiencies in CD, natural source of vitamin and minerals such as fruits and vegetables should be increased. Natural gluten-free food is also cost affective which may increase GFD compliance.[29]

Pseudo-cereals and minor cereals are also frequently consumed in GFD. They are rich of minerals, such as calcium, phosphorus, sodium, potassium, chloride, and magnesium, and also iron, zinc and selenium.[30] They also are good source of carbohydrate, protein, fiber and PUFA. Superior quantity and quality of pseudo-cereals are listed in **Table 2**.

Consumption of pure oats without contamination to gluten may increase fiber, vitamin B, zinc, magnesium and iron supply in GFD.[5] Study by Størsund et al. in CD children suggested that oats may improve GFD nutritional value and compliance.[34] However, small number of people with CD may be intolerant to pure oats and develop immunological response to oat avenin (protein found in oats). Therefore, oat consumption in CD should be followed by monitor for signs and serological change.

Education should not only focus on gluten free natural food available as described above, but of special attention to commercially available GFP regarding labelling and chemical composition should also be done to parents. Since gluten-free cereal foods available are made using refined gluten-free flour or starch not enriched or fortified, so they are found to be rich in carbohydrates and fats only.[18] Thus, gluten free products should not just be gluten-free but comparable to gluten containing food in terms of nutritional profile and meet the recommended dietary allowance requirement.[29] Furthermore, some fortified GFP with vitamins and minerals are preferable than regular GFP.

Clear labelling of GFPs and education of CD patients on how to interpret them is important to help CD subjects make safer and more informed food choices. Food labelling of processed GFP should also be noticed due to several ways of labelling; "Gluten-free", "Free of gluten", "No gluten", "Without gluten". While they all describe food: made only from ingredients which do not contain prolamins from wheat with their crossbred varieties with gluten level not exceeding 20 ppm; or consisting of ingredients from wheat, rye, barley, oats, spelt or their crossbred varieties, which have been have been processed to remove gluten; with a gluten level not exceeding 20 ppm.[6,28,30]

Nutrition requirement for CD

At the time of diagnosis, parents and children should meet with a registered dietitian who is knowledgeable about CD and the GFD. The family and child (if at an appropriate age) should be educated regarding the negative consequences of untreated CD including nutrition related complications such as osteopenia and osteoporosis, iron deficiency anemia. Little is known about the nutritional quality of the GFD in children hence, their intake should also be reviewed for nutritional adequacy. Multivitamin with minerals should be recommended due to the malabsorption that occurred prior to the diagnosis. Nutrients of particular concern include calcium, iron, folate, thiamine and riboflavin as shown in **Table 3**.[35]

Conclusion

Gluten-free diet is the only accepted and available treatment in CD. It was a life-long treatment, if not carried out with attention, it may lead to nutritional imbalance which can affect children's growth and development. Parental education and physician advisory is crucial to achieve nutritionally adequate and balanced gluten-free diet accompanied by a positive support of children environment to improve GFD compliance. Food labelling of available GFP should also be paid special attention to monitor macro and micronutrient intake of CD patients. Therefore, there is an important need to develop gluten-free products that are highly nutritious and at the same time economical. Meanwhile, performing routine follow-up is also as important as commencing GFD to observe nutritional adequacy in CD patients. Frequent follow-up by medical professionals and participation in educational activities and support groups will not only encourage compliance and prevent future complications of untreated CD, but will also improve quality of life.

Table 1. Common nutrient deficiencies in CD.[20]

At Diagnosis	GFD	GFD Products	Long-term GFD
Calorie/protein			
Fiber	Fiber	Fiber	
Iron	Iron	Iron	
Calcium	Calcium		
Vitamin D	Vitamin D		
Magnesium	Magnesium		
Zinc			
Folate, niacin, vitamin	Folate, niacin, vitamin	Folate, niacin, vitamin	Folate, niacin, vitamin
B12	B12	B12	B12
Riboflavin	Riboflavin	Riboflavin	Riboflavin

Table 2. Advantageous nutritional composition of pseudo-cereals

Nutritional Characteristics of Amaranth, Buckwheat and Quinoa[31,32,33,34]
High fiber content, 7–10 g/100 g, approximately the same as wheat fiber 9.5 g/100 g
High content of essential amino acids: lysine, arginine, histidine, methionine and cysteine.
High degree of unsaturated fatty acids, α-linolenic acid (35-50% of total fatty acid, oleic acid (25-35% of total fatty acid), and palmitic acid.
High content of folic acid: quinoa and amaranth, 78.1 µg/100 g and 102 µg/100 g, respectively, vs. 40 µg/100 g in wheat.
Source of vitamins: B, B2, B6, vitamin C and E.
Source of minerals: Calcium, magnesium and iron, twice as high as in other cereals.

Table 3. Nutrition requirement of particular concern [35]

Nutrient	Age (years)	Recommended	Sources
Calcium	1-3	500 mg	1 c. milk = 300 mg
	4-8	800 mg	2 0z cheese = 400 mg
	9-18	1300 mg	6 oz yogurt = 300 mg
			3 oz almonds = 210 mg
Iron	1-10	10 mg	3 oz beef = 1.8 mg
	11-18 (M)	12 mg	3 oz chicken = 1 mg
	11-18 (F)	15 mg	½ c. spinach = 3.2 mg
			½ c. red kidney beans = 2.6 mg
			½ c. enriched rise = 1.2 mg
			½ c. Raisins = 1. 1 mg
Folate	1-3	150 mcg	½ c. Spinach = 130 mcg
	4-8	200 mcg	½ c. Navy bean = 125 mcg
	9-18	300 mcg	½ avocado = 55 mcg
			1 orange = 45 mcg
			1 oz peanuts = 30 mcg
Thiamin	1-3	0.5 mg	3 oz beef liver = 9.2 mg
	4-8	0.6 mg	Corn tortilla = 0.2 mg
	9-13	0.9 mg	½ c. Enriched rice = 0.2 mg
	14-18 (F)	1 mg	
	14-18 (M)	1.2 mg	
Riboflavin	1-3	0.5 mg	1 c. Milk = 0,45 mg
	4-8	0.6 mg	1 c. Yogurt = 0.45 mg
	9-13	0.9 mg	1 egg = 0.27 mg
	14-18 (F)	1 mg	Corn tortilla = 0.27 mg
	14-18 (M)	1.3 mg	3 oz ground beef = 0.16 mg

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ORIGINAL ARTICLE

Fluid consumption, hydration status, and its associated factors: A cross sectional study among medical students in Palembang, Indonesia

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Abstract

Background: Adequate fluid consumption and hydration status of students have become a special concern because being dehydrated by just 1-2% may impair cognitive performance. The objectives of this study were to assess the daily fluid consumption and to analyze the correlation of fluid consumption and other associated factors with hydration status of medical students in Universitas Sriwijaya.

Methods: A total of 93 medical students in Universitas Sriwijaya were recruited to complete a 7-day cross-sectional study. Subjects were asked to complete a self-administered 7-day-24-hours fluid record and provide first morning urine sample on the last day. Gender information was collected. Physical activity was evaluated by self-administered long version of IPAQ. Body mass index was calculated using body weight and body height measurement. Urine specific gravity was determined by urinometer. The 7-day-24-hours fluid record and 1-day-24-hours urine specific gravity were calculated and analyzed.

Results: Majority of the subjects were well hydrated, while 10.8% were slightly dehydrated, 6.5% were moderately dehydrated and 9.7% were severely dehydrated. The average of daily fluid consumption was 1789.28 (989.3-2930) mL. Coefficient correlation of fluid consumption from beverages with urine specific gravity was -0.651 (p=0.00) by Pearson correlation test. The hydration status showed no association with gender, physical activity and body mass index.

Conclusions: Most subjects in this study were well hydrated. A strong association was found between fluid consumption and hydration status. It was feasible to use daily fluid consumption from beverages to predict hydration status.

Keywords fluid consumption, urine specific gravity, hydration status

Introduction

Dehydration is a condition when the body loses fluids due to inadequate consumption or as a result of excessive loss.[1,2] Dehydration can cause a variety of signs and symptoms differentiated based on the percentage of water loss. Mild dehydration (1-5%) can cause excessive thirst, loss of taste, uncomfortable feeling, dry mouth, decreased urine output, work and concentration difficulty, warm skin on palpation, drowsiness, vomitus and unstable emotions. Moderate dehydration (5-10%) can cause an increase in body temperature, increased heart rate and breathing, dizziness, shortness of breath,

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sluggish speech, and blue lips. Severe dehydration (≥10%) can cause seizures, hallucinations, swollen tongue, poor circulation, kidney failure, and decreased blood volume and pressure.[3,4]

Several factors are related to hydration status, such as fluid consumption, gender, physical activity, and body mass index. Adequate fluid consumption is necessary to maintain body fluids in a balanced condition. Study by Zhang, 2017 found that there was a significant difference between the consumption of fluids that came from drinks and hydration status.[5] Men has higher fluid turnover rate than women, hence more dehydration can be observed in men than women.[6] Dieny and Putriana, 2015 conducted a study which showed that there was a significant relationship between hydration status before training and hydration status after training in teenage soccer athletes.[7] Body mass index is related to hydration status in which the water content in the fat cells of obese people is lower than the water content in muscle cells, therefore obese students are more dehydrated than non-obese students in the study by Buanasita, 2015.[8]

The hydration status of students needs serious attention and concern because dehydration, even at mild levels, is associated with impairments in cognitive performance.[9] The objectives of this study were to identify gender, age, physical activity, body mass index, fluid consumption, fluid consumption patterns, and hydration status, to analyze factors associated with hydration status, and to analyze the correlation of fluid consumption with urine specific gravity in students of Medical Education Program, Faculty of Medicine, Universitas Sriwijaya, Palembang.

Methods

This was an observational analytic study with a cross-sectional approach conducted on students of class 2014 until class 2017 of Medical Education who met the inclusion and exclusion criteria. Medical students investigated in this study were all registered as active students in Medical Education Program, Faculty of Medicine, Sriwijaya University. Exclusion was carried out on medical students who were in any of the following circumstances: (1) having fever that was examined directly by the researcher with a thermometer, (2) taking anti-cholinergic drugs (lomotil, phenothiazine, and others), diuretics (furosemide, amiloride, and others), tricyclic antidepressant drugs (amitriptyline, prozac, and others), analgesics (ibuprofen, acetaminophen, and others) confirmed by subject characteristic form, (3) defecating soft or liquid stool at least three times in 24 hours confirmed by selection form, (4) having forceful oral eviction of gastrointestinal contents confirmed by selection form, (5) suffering from kidney problems and diabetes confirmed by a doctor's examination that the subject had previously known, (6) having menstruation that affected urine samples, (7) providing insufficient amount of urine (less than 50 mL), (8) were under 18 years old and did not get parental consent or guardian, and (9) during the study period were not around the Faculty of Medicine, Sriwijaya University.

Selection of subjects is carried out by distributing selection forms and measuring body temperature. Body temperature measurements are carried out by direct examination using a digital thermometer. Physical activity data were collected using the IPAQ physical activity questionnaire form. This physical activity questionnaire was conducted to assess the physical activity performed during the previous seven days with self-administered format. The results of the physical activity questionnaire were then classified into low physical activity, moderate physical activity, and high physical activity. Body mass index data were collected by measuring body weight and height and then recorded on a physical examination form. Fluid consumption was taken with a 1x24 hour fluid record and the fluid consumption pattern was obtained from a 7x24 hour fluid record. Retrieval of hydration status data was taken using a urinometer to obtain the specific gravity value of urine. The urine used is the first urine expelled immediately after waking up before breakfast and before doing activities and has been stored in the bladder for no less than four hours.

Descriptive data analysis was used to identify gender, age, physical activity, body mass index, fluid consumption, fluid consumption patterns, hydration status in students. Chi-square test was used to analyze the relationship of hydration status with gender, physical activity and fluid consumption. Fisher's exact test was performed to analyze the relationship of hydration status with body mass index because it did not meet the Chi-

square test requirements. Pearson Correlation was used to analyze the correlation of fluid consumption with urine specific gravity test.

Results

Of 120 subjects, 27 subjects were not enrolled as they dropped out or met the exclusion criteria. A total of 93 subjects completed 100% of the study. Data were analyzed. Most of the subjects (66.7%) were female and were ≥19 years (64.5%). **Table 1** shows general characteristics of subjects.

Specific characteristics of the subjects can be seen in **Table 2**. The majority of the subjects had low level of physical activity (52.7%), had nonobese body mass index (82.8%), and had not adequate fluid consumption (53.8%).

Table 3 reports the fluid consumption pattern of subjects in this study. The average fluid types majority consumed by subjects is water (4.2 ± 1.22) at room temperature (3.85 ± 1.53). The average of drink frequency is 5.21 times per day and the average of daily fluid consumption is 1789 mL.

The distribution of subjects by hydration status is presented in table 4. Among 93 subjects, majority were well hydrated, while 10.8% were slightly hydrated, 6.5% were moderately hydrated and 9.7% were severely dehydrated.

In **Table 5**, the result of Chi-square analysis of the association of subject's gender with hydration status was shown. Being male was more (PR 1.571) associated with being dehydrated compared to female, but this relationship was not found significant (p=0.282).

Table 6 showed that having moderate-vigorous level of physical activity were risk factor for being dehydrated although not statistically significant (p=0.433) by using Chi-square analysis.

The fisher's exact test analysis in **Table 7** pointed out that there is no significant relationship of body mass index with hydration status (p=0.355) though being obese was more associated with dehydration (PR 1.520) compared to non-obese.

Table 8 showed that there is negative strong correlation (r=-0.651) of fluid consumption with urine specific gravity.

Discussions

In this study, 33.3% subjects are male and 66.7% are female. This finding is analogous to the data of 2014-2017 year medical student in Universitas Sriwijaya that male to female ratio is 1 to 2.4. This study revealed that most subjects (64.5%) was ≥19 years old. The data from Universitas Sriwijaya also shows that dominantly student age is ≥19 years old. The age cutoff in this study is 19 years old, according to age cutoff of Indonesian recommended water intake.

From the International Physical Activity Questionnaire, this research shows that the majority of the subjects has low level of physical activity (52.7%) and the least (6.5%) has vigorous level of physical activity. The transportation of subjects in this study predominantly is motor vehicle (66.66%) and the least (3.23%) is bicycle. This research is not similar to the research by Bednarek et al.[10] that stated more than half (52%) of university students had moderate level of physical activity and only 11% had low level of physical activity.

Of all subjects in this study, 82.8% was nonobese. Research by Abdalla and Mohamed[11] and research by Rao et al.[12] also stated similar findings where the majority of medical students is nonobese. The majority (53.8%) of fluid consumption in this study is adequate. This result found out to be suchlike with the findings by Zhang[13] with subjects from medical students in China.

The fluid consumption counted in this study is provided by fluids (drinking water and beverages of all kind). According to EFSA Panel[13], fluid consumption is mainly provided by fluid or 80% from daily water recommendation. Indonesian recommended water intake is referring to Indonesian Dietary Recommendation 2019[14] that set 2.3L/day for male age 16-18 years old, 2.5L/day for male age 19-29 years old, 2.15L/day for female age 16-18 years old, 2.35L/day for female age 19-29 years old.

The average fluid types majority consumed by subjects is water 4 times/day. According to the research conducted by Bardosono[15], similar results were found. In that study, majority (75%) of the subjects consumed water and only 1% drink other beverages. Malik et al.[16] stated that intake soft drink and sugar-sweetened beverages is associated with weight gain. The average of daily fluid consumption is 1789 mL. This finding is higher than research conducted by Zhang[5] that showed average of daily

fluid consumption is 1342 mL among medical students in China.

Majority (73.1%) of the subjects were well hydrated. The research by Zhang[5] stated respectively 75% subjects was in optimal hydration state, which was similar to this research's finding. In this study, subjects that were in dehydration state can be caused by some factors including physical activity and ambient temperature. Furthermore, the hydration status is determined by urine specific gravity (USG) using urinometer. Whilst Proctor[17] stated that urinometer is the gold standard for the measurement of urine specific gravity, the research of Stuempfle dan Drury[18] found that urinometer has 88% sensitivity and 67% specificity. Subjects that were severely dehydrated may be caused by the urine collected in this study is first morning urine sample. First morning urine sample means that subject collected urine right after woke up, before drank and ate breakfast. When the subjects met researcher to collect the urine sample, subjects is assumed to have eaten and have drunk so that subjects did not have signs and symptoms of dehydration.

Chi square's analysis of the association between hydration status with gender. Prevalence ratio 1.571 means that being male was more (PR 1.571) associated with being dehydrated compared to female, but this relationship was not found significant (p=0.282). In line with the study of Sari[19] showing that there was no significant relationship (p>0.05) between hydration status with gender. According to Institute of Medicine (U.S) Panel (2005)[20] female has less turnover rate than male with the result that male is expected to be more dehydrated than female. But this result also can be different because of subject's fluid consumption. We propose future research to applicate multivariate analysis in consider to some other factors, including fluid consumption.

The hydration status showed no significant relationship with physical activity. Subjects with vigorous level of physical activity would be 1.417 times higher to become dehydrated than subjects with low-moderate level of physical activity. In contrast to this study, Aryani[21] research showed that theres no significant relationship (p>0.05) between hydration status with physical activity. Study of Rao et al.[12] in medical students showed that 45% subjects claimed to have low physical activity because lack of time (60.5%), laziness (61.8%), and exhaustion from academic activity (42%). In that research, the data of physical activity taken by questionnaire so that the results were very subjective. Nonetheless this research showed that moderate-vigorous activity is the risk of dehydration.

The result of fisher exact's test showed that there is no significant relationship (p=0.355) between hydration status with body mass index. Andayani et al.[22] research with subjects from industrial workers that there was no significant relationship (p=0,072) between hydration status with nutrition status. Dehydration state is not only found in obese subjects but also nonobese subjects. Theoretically, the percentages of water in adipocytes is less than the percentages of water in myocytes. By that reason, obese people has less total body water than nonobese people. Hence, obese people were more associated with dehydration than nonobese people. The theory is contrast with the result of this study. This can happen because the nutrition status in this study was assessed by body mass index, not by body fat mass. Still this study showed that obese people has risk to become dehydration 1.520 times than nonobese people.

There was negative strong correlation (r=-0.651) of fluid consumption with urine specific gravity. Fluid consumption was assessed by self-administered 7-day-24-hours fluid record and urine specific gravity was assessed by urinometer. This outcome was confirming the outcome of Zhang[5] research. The research of Zhang also showed strong relationship between urine biomerkers and fluid consumption. The different is Zhang used urine volume (r=0.76) and urine osmolality (r=0.76) as urine biomarkers. Subjects in optimal hydration state drank more fluid than subjects in another hydration state[5].

There were several limitations in this study: limited instruments, fluid consumption from food was not taken and fluid records was not explained by trained nutritionist. However, this had been anticipated by researchers by using household utensil and photographs to help the subjects to remember and estimate the number and type of beverages. Additionally, in this study we did not count the fluid consumption from food since the

food consumption can influence the total fluid consumption.

Conclusion

In summary, the majority subjects in this study were ≥19 years old, had low level physical activity, nonobese and had adequate fluid consumption. The fluid types majority consumed by subjects is water at room temperature. The average of drink frequency is 5.21 times per day and the average of daily fluid consumption is 1789 mL. Most subjects were in well hydrated state. Fluid consumption from beverages showed strong correlation with urine specific gravity. The hydration status showed no assciation with gender, physical activity and body mass index.

Table 1. General characteristics of subjects (N= 93)

Characteristics	n	%
Gender		
Male	31	33.3
Female	62	66.7
Age		
<19 years old	33	35.5
>19 years old	60	64.5

Table 2. Specific characteristics of subjects

Characteristics	n	%
Physical activity		
Vigorous	6	6.5
Moderate	38	40.9
Low	49	52.7
Body mass index		
Obese	16	17.2
Non-obese	77	82.8
Fluid consumption		
Not adequate	43	46.2
Adequate	50	53.8

Table 3. Fluid consumption pattern of subjects

Fluid consumption pattern	Mean ± SD
Type of fluid (times/day)	
Water	4.2 ± 1.22
Hot coffee and tea	1.05 (1.03- 1.1)*
Milk and derivatives	1 (0-2)*
Soft drinks	1 (0-2.6)*
Other beverages	0 (0-1)*
Temperatures (times/day)	
Chilled with ice cubes	1 (0-3)*
Chilled without ice cubes	1 (0-4.8) *
Warm	1 (0-3) *
Room temperature	3.85±1.53
Frequency(times/day)	5.21±1.16
Daily fluid consumption (mL)	1789.3(989-2930)*

* Median (Min-Max)

Table 4. Distribution of subjects by hydration status

Hydration status	n	%
Well hydrated	68	73.1
Slightly dehydrated	10	10.8
Moderately dehydrated	6	6.5
Severely dehydrated	9	9.7

Table 5. The relationship of gender with hydration status (N=93)

	Hydration status				Total	PR	*p*
	Dehydrated		Not dehydrated				
	n	%	n	%			
Gender							
Male	11	35.5	20	64.5	31	1.571	0.282
Female	14	16.7	48	77.4	62		

Table 6. The relationship of physical activity level with hydration status (N=93)

	Hydration status				Total	PR	*p*
	Dehydrated		Not dehydrated				
	n	%	n	%			
Physical activity							
Moderate-vigorous	14	31.8	30	68.2	44	1.417	0.433
Low	11	22.4	38	77.6	49		

Table 7. The relationship of body mass index with hydration status (N=93)

	Hydration status				Total	PR	*p*
	Dehydrated		Not dehydrated				
	n	%	n	%			
Body mass index							
Obese	6	37.5	10	62.5	16	1.520	0.355
Non obese	19	24.7	58	75.3	77		

Table 8. The relationship of fluid consumption with hydration status (N=93)

	Urine specific gravity	
	r	p
Fluid consumption	-0.651	0.000

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Conflict of Interest

No potential conflicts of interest to declare in relation to this publication.

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ORIGINAL ARTICLE

Nutritional status indicator and its correlation with mental health score among adolescents in Islamic boarding schools

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Abstract

Background: It has been estimated that about 10–20% of adolescents worldwide had experiences of mental health problems. Malnutrition, including overweight and obese, is one of the risk factors for mental health in adolescents. There is a knowledge gap regarding the nutritional status and its correlation with mental health among adolescents who live in boarding schools. This study aimed to determine nutritional status and its correlation with mental health among adolescents in Islamic boarding schools.

Methods: A cross-sectional approach was used in this study in which two schools in South Tangerang City of Banten Province were purposively selected and 302 of students aged 15–18 years were completed this study. BMI-for-age Z-scores (BAZ) was used as the nutritional status indicator, and the Strengths and Difficulties Questionnaire (SDQ) was used to determine mental health of the subjects. Spearman correlation was used to determine the correlation between nutritional status indicator and mental health score.

Results: Nearly 30% of the subjects were overweight and obese, and almost 20% had result of mental health score in categories "borderline" and "abnormal". There was a significant correlation between nutritional status indicator and mental health score among adolescents in Islamic boarding schools (r=0.157, P=0.006).

Conclusion: Adolescents who had higher BAZ, had higher total difficulties scores. The schools and policy makers should give attention to nutritional status of the students since it is correlated with mental health.

Keywords adolescents, nutritional status, mental health, boarding school

Introduction

Mental health is a fundamental and important component of health. World Health Organization defined mental health as a state of well-being in which the individual realizes his or her own abilities, can cope with the everyday stresses of life, can work productively and successfully, and can contribute to his or her community. Mental health is more than the absence of illness and is strongly connected with physical health and behavior. Mental health is the foundation for well-being and effective functioning for an individual and a community.[1]

Adolescence is an essential time for enhancing mental health behaviors and well-being. During adolescence, poor mental health can compromise adolescents' development and future potential, and

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can lead to both physical and mental health impairments in adulthood if they remain untreated.[2] Poor mental health in adolescents is strongly associated with lower educational achievements, substance abuse, violence, and poor reproductive and sexual health.[3] It has been estimated that about 10–20% of adolescents worldwide had experiences of mental health problems.[2] A high prevalence of depression and anxiety problems has been reported worldwide over recent years, and there is increasing concern regarding adolescents' mental health. Previous studies have found that adolescents are more vulnerable to traumatic and stressful events and are prone to developing mental health problems.[4]

Five of the ten leading causes of disability-adjusted life years (DALY) in people aged 15-44 years are mental disorders (unipolar depressive disorders, alcohol use disorders, self-inflicted injuries, schizophrenia, and bipolar affective disorder). A study in Australia has shown that mental disorders contributed to 60–70% of the total DALY in young people age 15–24 years, reinforcing the idea that mental disorders are the major contributor to disease burden in this age group. Aside from disability, mental disorders might also contribute a substantial burden on mortality in young people. In many communities, a period of the heightened risk of suicide is increased in youth, where suicide is a leading cause of death in young people in China and India.[5]

Data from Basic Health Research 2018 in Indonesia showed that the prevalence of households whose member(s) were diagnosed with schizophrenia was 6.7‰, while the prevalence of population aged 15 years and above with depression and emotional disorders was 6.1% and 9.8%, consecutively. The prevalence of households whose member(s) were diagnosed with schizophrenia was increased nearly 4 times from 2013, while the prevalence of emotional disorders among population aged 15 years and above was almost doubled. The prevalence of depression is not available in 2013. Female showed higher prevalence in both depression and emotional disorders in Indonesia.[6,7]

Malnutrition, including overweight and obesity, is one of the risk factors for mental health in adolescents.[8] Previous studies have found the association between body weight status and mental health in adolescents. A study amongst children and adolescents found that depression and separation anxiety was mostly seen among underweight group.[9] Another study found that compared with normal weight adolescents, overweight/obese adolescents had lower self-esteem, higher overall depression scores, and severe anhedonia.[10] Several studies also mentioned the association between overweight or obesity with suicide ideation and attempts, anxiety, behavioral problems, and poor self-image.[11] Indonesia's National Basic Health Research in 2018 reported that 13.5% of adolescents age 16-18 years were overweight and obese, and the trend was increasing where the prevalence has risen tenfold between 2010 and 2018.[6,7] An observational study of overweight in Indonesia suggested the urgent program and policy action to reduce and prevent overweight among all ages, including adolescents.[12]

Islamic boarding school or known as *pesantren,* is the oldest Islamic educational institution in Indonesia.[13] It is an intensive form of education, in which students reside at school and visit their families only for weekends and vacations.[14] Boarding school can cause a sense of alienation since students are physically and emotionally isolated from their families and communities that may affect their mental health.[15] There is a knowledge gap regarding the nutritional status and its correlation with mental health among adolescents in Islamic boarding schools. It is crucial to measure nutritional status and mental health to identify the problems, and then develop and implement effective interventions. This study aimed to determine the correlation between nutritional status and mental health among adolescents living in Islamic boarding schools.

Methods

Study design

A cross-sectional approach was used in this study, where both independent and dependent variables are collected at the same time. Data collection was done in July–August 2020 at two Islamic boarding schools, located in South Tangerang City, Banten Province. South Tangerang was purposively selected since it is located in Banten Province, which was the 2nd province with largest number of Islamic

boarding school, and it had more Islamic boarding schools compared to other cities nearby, such as Jakarta, Depok, or Bekasi. The selection of the schools was based on the presence of the students in boarding school since the data collection was conducted during Covid-19 pandemic in which only small number of boarding schools had resumed their activities starting on July 2020. Both of schools selected were private Islamic boarding schools, which had formal education curriculum equal to senior secondary school.

Subjects

The subjects in this study were the students grade 11th and 12th aged 15–18 years in Islamic boarding schools. Students grade 10th were not included since the data collection was done during the process of new student recruitment in the new academic year 2020/2021. Therefore, the students grade 10th were not staying in the boarding school yet. Students who were not present during data collection, or refuse to participate in the study were excluded. The sample size was calculated using correlation coefficient formula, resulted in 264 minimum samples. There were 306 students voluntarily participated in this study.

Anthropometry and measurement

Body weight and height was measured using calibrated tools by well-trained school's staff due to the restriction on direct encounter with the students in regard to Covid-19 prevention. Previous study found that the results of school staff measured weight/height using similar protocol to the study should validly reflect weight/height status for almost all students.[16] Body weight was measured using SECA weighing scale. This measurement was following the standard method of body weight measurement: (1) placing the scale on the flat surface, (2) positioning the subjects in straight position, (3) bare feet, light clothes and taking off anything that can alter the result. Height was taken using Shorr Board according to the standard method: (1) doing the measurement on the stable surface, (2) the subjects should take off any accessories that can interfere the measurement, (3) head, shoulders, buttocks and heels should touch the board.

Nutritional status indicator

BMI-for-age Z-score (BAZ) was used as nutritional status indicator in this study. After body weight and height was measured, the body mass index (BMI) of the subjects was calculated by dividing body weight (kg) to height (m^2). The BAZ was calculated using software WHO AnthroPlus which is the global application of the WHO Reference 2007 to monitor the growth of children and adolescents aged 5–19 years.[17]

Mental health score

The Strengths and Difficulties Questionnaire (SDQ) was used to determine mental health of the subjects. The self-report questionnaire was used in this study. The SDQ has been adapted and translated into Indonesian language, and also been tested for validity and reliability.[18] It is made up of a total 25 statements distributed across five subscales: (1) emotional problems, (2) conduct problems, (3) hyperactivity, (4) peer problems, and (5) prosocial behavior. There were three option of response in each statement, "not true", "somewhat true", and "certainly true". "Somewhat true" is always scored as 1 but the scoring of "not true" and "certainly true" varies with the item. The score on each subscale ranges from 0-10 points. The first four subscales (emotional problems, conduct problems, hyperactivity, and peer problems) yield a total difficulties score.[19] The total difficulties scores were categorized into three categories which are normal, borderline and abnormal, which is shown in **Table 1**.

Statistical analysis

Before running the analysis, we excluded cases with incomplete data. Data was analyzed using software IBM SPSS Statistics for Windows version 25. Univariate analysis was used to describe the characteristics of the subjects, nutritional status, and mental health. The data was interpreted in both numerical and categorical data. Numerical data was analyzed using mean and standard deviation if the data was normally distributed, or median (25th – 75th percentile) if the data was not normally distributed. Categorical data was analyzed using

frequency (n) and percentage (%) distribution. Bivariate analysis was used to see the relationship between two variables. The Spearman correlation test was used to see the significant association between nutritional status indicator and mental health score. The results were considered significant if the p-value is less than 0.05.

Ethical consideration

This study was conducted after receiving an approval from Ethical Committee of Faculty of Medicine, Universitas Indonesia No. KET-246/UN2.F1/ETIK/PPM.00.02/ 2020, signed on March 2nd 2020, with the amendment of the protocol due to the adjustment of data collection method during Covid-19 pandemic situation (ND-709/UN2.F1/ETIK/PPM.0002/2020 signed on June 29th 2020). Permission before data collection was also obtained from the institutions where the study conducted. Before the data collection, all of the subjects received detail information regarding the study purpose and all of measurements. All of the subjects selected were voluntarily participated in this study. All of the information collected during the study was treated as confidential.

Results

In total, there were 302 students of Islamic boarding school aged 15–18 years completed the study and included in data analysis. The subjects' mean age was 16.8 ± 0.7 years, and the majority of them were girls. The subjects' parental education level was mostly moderate, which indicated the completion of junior or senior secondary school education. The details on subjects' characteristics was shown in **Table 2**.

The prevalence of thin, overweight, and obese in subjects were 3.3%, 14.9%, and 7.3%, respectively, as shown in **Figure 1**. This indicated that overweight and obese were more serious problem among the subjects in this study. The categories of nutritional status were reduced into two categories, which were overweight and non-overweight, for further analysis.

The mean value of the subjects' BAZ was 0.19, and it was not showing any significant difference between boys and girls (P>0.05). After being categorized, the proportion of overweight among the subjects was 22.2% (**Table 3**). The proportion of overweight was higher in boys than girls, but the difference was not statistically significant based on the chi-square test.

Table 4 showed that the total difficulties score presented a median value of 11, with the first and third quartiles of 8 and 14 respectively. When distributed in categories, most of the subjects had a "normal" results. The majority of them were also categorized as "normal" in all dimensions of emotional problem, conduct problem, hyperactivity, peer problem, and prosocial.

The proportion of subjects categorized as "abnormal" was mostly found in the dimension of emotional problem (9.6%). The scores of emotional problem was significantly different between boys and girls. The proportion of girls with "abnormal" results in emotional problem dimension (13.5%) was much higher than boys (4%). The conduct problem scores were not showing any significant difference between boys and girls, but the significant difference was found when it was categorized. The proportion of boys categorized as "abnormal" in conduct problems (12.1%) was much higher than girls (0.6%).

The Spearman's rho correlation test resulted in significant correlation between total difficulties, emotional problem, and hyperactivity scores with BAZ (**Table 5**). This suggested that the higher BAZ would result in the higher problem in terms of total difficulties, emotional problem and hyperactivity. However, the correlations were considered as weak since the correlation coefficients were all below 0.3.

Table 6 showed the comparison of mental health score by nutritional status. The result suggested that total difficulties and hyperactivity scores were significantly higher in overweight subjects. However, there were no significant difference between emotional problems, conduct problem, peer problem and prosocial scores among overweight and non-overweight subjects.

Discussion

Our results indicated that overweight and obesity were more serious health concerns than thinness in this study population. The findings also confirmed previous study that found a high prevalence of

overweight and obesity among the students who lived in Islamic boarding schools.[20] This finding was in line with the results of Basic Health Research Indonesia in which 13.5% of adolescents aged 16–18 years were overweight and obese in 2018, and the trend was increasing where prevalence of overweight and obesity had risen almost tenfold between 2010 and 2018. Meanwhile, the prevalence of thin adolescents was decreased in 2018. The high and increasing prevalence of overweight and obesity in adolescents is a major global public health problem since it will affect adolescents' health in later life, not only physical, but also psychological health. Studies found that overweight was associated with comorbidity conditions, such as hypertension, hyperlipidemia, diabetes, sleep apnea, poor self-esteem, and even depression. In addition, if the condition followed-up to adulthood, adolescents with overweight or obesity much more likely to suffer from cardiovascular and digestive diseases.[21]

There are overwhelming studies regarding factors associated with overweight and obesity among adolescents. Genetic factors, socioeconomic status, dietary intake, physical activity, sedentary behavior, screen time, sleep duration, food store environment, and school food environment are the factors found to be associated with overweight or obesity among adolescents.[22] Adolescents in this study were living in boarding school which have same environment, including food environment and physical activity environment. The schools provided meals three times a day, a mandatory physical education class once a week, and recess twice a day that can be used for students to do physical activity (e.g., sports, games, or cleaning activities). However, the students still had control regarding their food intake and physical activity. They were allowed to buy and consume snacks available in school canteen. Their parents were also allowed to send foods and snacks for the students. Snacking is a great contributor to energy intake among adolescents where a study among adolescents aged 12-19 years found that daily snacks consumption, which resulted in higher intake of added sugar, saturated fat, and sodium, were associated with overweight and obesity among adolescents. The finding suggested that approaches targeting snacking behavior are relevant to prevent overweight and obesity among adolescents.[23]

The result of this study revealed that the prevalence of overweight among boys was higher than girls. However, there was no statistically significant difference between them. This finding was different from the previous study, which found that the prevalence of overweight and obesity among girls in Islamic boarding school was higher than boys.[24] Data of Basic Health Research Indonesia 2018 also showed same pattern where the prevalence of overweight among girls (11.4%) were higher than boys (7.7%).[6] Decreasing participation in physical activity and sports, particularly for girls, may explain the differences.[25] On the contrary, a cohort study of United States adolescents revealed that gender norms were positively associated with weight loss attempts and behaviors for girls, while in boys, gender norms were positively associated with weight gain or muscle building behaviors. Gender norms are defined as societies' rules and standards that guide and constrain social behaviors for boys and girls regarding how they are supposed to act, think, and feel.[26] All these findings may suggest that the prevalence of overweight in adolescents is a concern, regardless the gender.

This study found that most subjects were not having problems in all subscales of the SDQ (emotional problem, conduct problem, hyperactivity, peer problem, and prosocial). However, there were almost 20% of the subjects that need further investigation and diagnosis by professionals. The lower score was found in peer problems and conduct problems, which indicated the lower problems in those subscales. A previous study mentioned that the students in Islamic boarding school were usually having close relationships with their peers since they lived and spent most of their time with them. Thus, it may explain the lower peer problems among them. The students in Islamic boarding school must follow the rules of the school, including daily activities, such as studying, praying, reciting Al-Qur'an, and participating in extracurricular activities. This condition may be associated with lower conduct problems among them.[27]

The differences between gender were found in emotional and conduct problems. Girls were more likely to have emotional problems, while boys were more likely to have conduct problems. This pattern was similar to previous study among Norwegian

adolescents that found higher emotional problems in girls and higher conduct problems in boys.[28] Girls were more likely to have emotional problems, especially related to internalizing problems, such as depression and anxiety, while boys were more likely to have externalizing problems, including conduct problems.[27] Literature mentioned that hormonal changes during menstruation may be associated with emotional problems among girls.[29]

This study found that nutritional status, which is defined as BAZ, was correlated with mental health. The higher BAZ would result in higher total difficulties, emotional problems, and hyperactivity scores. This result was in line with previous studies that found higher BMI (body mass index) was predictive of higher total difficulties and emotional scores.[30,31] Adolescents with overweight will attract attention to their surroundings and often develop a poor self-image, which can lead to being bullied by their peers.[11] Thus, it may result in emotional problems among them. Moreover, overweight subjects were more likely to have higher total difficulties scores that indicated poorer mental health, compared to non-overweight subjects. Overweight adolescents have been shown to be at higher risk of poor psychological health in general. Likewise, this study also found that overweight subjects were having higher scores in the hyperactivity subscale. This was aligned with previous study that found a significantly higher prevalence of Attention-Deficit/Hyperactivity Disorder (ADHD) for overweight children and adolescents aged 11-17 years. Children and adolescents with ADHD more frequently reported eating problems and were less likely to engage in physical activity. Hence, it may lead to overweight.[32,33]

There were some limitations to the current study. First, there is a possibility of random errors due to self-reported questionnaire. However, the SDQ is a brief, widely used, valid, and reliable instrument to determine mental health of adolescents. Second, the direction of nutritional status and mental health relationship may be bidirectional, but it cannot be determined in this study due to the cross-sectional design. Third, the Islamic boarding schools in this study were purposively selected. Thus, precautious should be taken in generalizing the results.

Conclusion

Nutritional status, determined by BMI-for-age Z-scores, was significantly correlated with mental health in terms total difficulties score, emotional problem, and hyperactivity. Adolescents with overweight showed higher total difficulties score and hyperactivity. Gender differences was found in mental health where girls were more likely to have emotional problems, while boys were more likely to have conduct problems. We suggest that the schools should give more attentions regarding the nutritional status and mental health of the students. Nearly 30% of the students were overweight and obese, which should be taken seriously since it will affect their health in later life. Investigating the health behavior associated with nutritional status in the schools is recommended since boarding schools play an important role in promoting healthy behavior. Developing and implementing school-based mental health promotion and interventions are recommended since almost 20% of the students were indicated a need to further diagnose of mental health problems by professionals. Further study is needed to investigate other potential factors associated with mental health among adolescents.

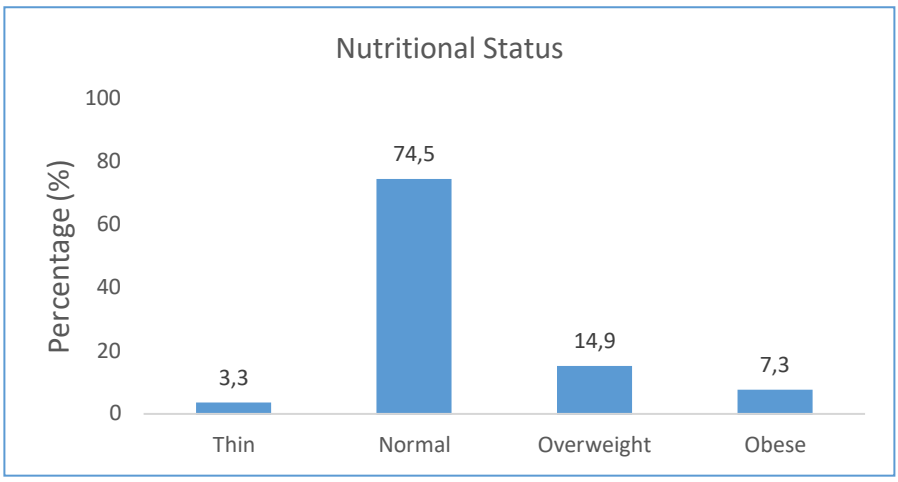

Figure 1. Nutritional status of the subjects

Table 1. The SDQ scores categories

Subscales	Normal	Borderline	Abnormal
Total difficulties score	0–15	16–19	20–40
Emotional problems	0–5	6	7–10
Conduct problems	0–3	4	5–10
Hyperactivity	0–5	6	7–10
Peer problems	0–3	4–5	6–10
Prosocial behavior	6–10	5	0–4

Table 2. Characteristics of the subjects (n=302)

Characteristics	Results
Age, years, mean±SD	16.8±0.7
Gender, n (%)	
Boys	124 (41.1)
Girls	178 (58.9)
Father's education level, n (%)	
Low (illiteracy-primary school)	18 (5.9)
Moderate (junior-senior secondary school)	176 (58.3)
High (diploma-doctorate)	108 (35.8)
Mother's education level, n (%)	
Low (illiteracy-primary school)	24 (7.9)
Moderate (junior-senior secondary school)	181 (60.0)
High (diploma-doctorate)	97 (32.1)

Table 3. Nutritional status of the subjects

Nutritional Status	Total (n=302)	Boys (n=124)	Girls (n=178)	p-value
BMI-for-age Z-scores[a]	0.19±1.1	0.12±1.3	0.25±0.9	0.322[b]
Non-overweight, n (%)	235 (77.8)	90 (72.6)	145 (81.5)	0.091[c]
Overweight, n (%)	67 (22.2)	34 (27.4)	33 (18.5)	

[a]Result presented in mean±SD since the data was normally distributed (tested by Kolmogorov-Smirnov with P value>0.05), [b]Continuous variable significance was tested by the Student's t-test, [c]Categorical variable significance was tested by chi-Square test

Table 4. The subjects' scores of total difficulties, emotional problem, conduct problem, hyperactivity, peer problem and prosocial

Mental health measured by SDQ	Total (n=302)	Boys (n=124)	Girls (n=178)	p-value
Total difficulties score[a]	11 (8-14)	10 (8-13.75)	12 (9-14)	0.022[be]
Normal, n (%)	255 (84.4)	107 (86.3)	148 (83.1)	0.750[c]
Borderline, n (%)	32 (10.6)	12 (9.7)	20 (11.2)	
Abnormal, n (%)	15 (5.0)	5 (4.0)	10 (5.6)	
Emotional problems score[a]	4 (2-5)	2.5 (1-4)	5 (3-6)	<0.001[be]
Normal, n (%)	244 (80.8)	116 (93.5)	128 (71.9)	<0.001[de]
Borderline, n (%)	29 (9.6)	3 (2.4)	26 (14.6)	
Abnormal, n (%)	29 (9.6)	5 (4.0)	24 (13.5)	
Conduct problems score[a]	2 (1-3)	2 (1-3)	2 (1-3)	0.105[b]
Normal, n (%)	258 (85.4)	100 (80.6)	158 (88.8)	<0.001[de]
Borderline, n (%)	28 (9.3)	9 (7.3)	19 (10.7)	
Abnormal, n (%)	16 (5.3)	15 (12.1)	1 (0.6)	
Hyperactivity score[a]	3 (2-4)	3 (2-4)	3 (2-5)	0.668[b]
Normal, n (%)	272 (90.1)	113 (91.1)	159 (89.3)	0.404[d]
Borderline, n (%)	23 (7.6)	10 (8.1)	13 (7.3)	
Abnormal, n (%)	7 (2.3)	1 (0.8)	6 (3.4)	
Peer problems score[a]	2 (1-3)	2 (1-3)	2 (1-3)	0.047[be]
Normal, n (%)	245 (81.1)	94 (75.8)	151 (84.8)	0.117[d]
Borderline, n (%)	51 (16.9)	26 (21.0)	25 (14.0)	
Abnormal, n (%)	6 (2.0)	4 (3.2)	2 (1.2)	
Prosocial score[a]	9 (7-10)	9 (7-10)	9 (8-10)	0.151[b]
Normal, n (%)	285 (94.4)	113 (91.1)	172 (96.6)	0.108[d]
Borderline, n (%)	14 (4.6)	9 (7.3)	5 (2.8)	
Abnormal, n (%)	3 (1.0)	2 (1.6)	1 (0.6)	

Table 5. Correlation between nutritional status indicator and mental health score (n=302)

Variable	Mental health score (correlation coefficient)					
	Total difficulties	**Emotional problem**	**Conduct problem**	**Hyperactivity**	**Peer problem**	**Prosocial**
Nutritional status indicator (BAZ)	0.157**	0.166**	0.018	0.170**	-0.033	0.015

**Statistical analysis used Spearman correlation test with significance level of p-value<0.01

Table 6. Comparison of mental health score by nutritional status indicator

Nutritional status indicator	Mental health score (median, Q1–Q3)					
	TD	**EP**	**CP**	**H**	**PP**	**PS**
Non-overweight (n=235)	11 (8–14)	3 (2–5)	2 (1–3)	3 (2–4)	2 (1–3)	9 (7–10)
Overweight (n=67)	12 (10–15)	4 (3–5)	2 (2–3)	4 (3–5)	2 (1–3)	9 (8–10)
p-value	0.005**	0.079	0.281	<0.001**	0.511	0.841

**Statistical analysis used Spearman correlation test with significance level of p-value<0.01
TD: Total difficulties, EP: Emotional problem, CP: Conduct problem, H: Hyperactivity, PP: Peer problem, PS:Prosocial

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ORIGINAL ARTICLE

Iron intake and its correlation to ferritin and hemoglobin level among children aged 24-36 months in Jakarta in 2020

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Abstract

Background: Iron is essential for child's development and growth. Children's iron requirements are secured from daily food intake that might be affected by Covid-19 pandemic. This study aims to determine iron intake and its association with ferritin and hemoglobin levels as indicators of iron status among children in Jakarta.

Methods: This cross-sectional study was conducted in Kampung Melayu, Jakarta from September to October 2020. Seventy seven healthy children aged 24–36 months were taken using total population sampling method. Interviews were conducted to obtain characteristics data and iron intake using a semi-quantitative-food frequency questionnaire (SQ-FFQ). Blood tests were performed to check the levels of ferritin (controlled by hs-CRP value), and hemoglobin. Pearson's/Spearman's correlation test was performed using SPSS version 20.0.

Results: Median of iron intake was 9.6 (1.5–40,7) mg/day, in which 33.8% of subjects was below the Indonesian Recommended Dietary Allowance (RDA) recommendation. The median ferritin value was 18.1 (1.4–91.1) μg/L and the hemoglobin was 11.8 (6.6–15.2) g/dL, in which 40.3% and 27.3% subjects with iron insufficient-deficient and anemia, respectively. There were positive correlations between iron intake and ferritin ($r = 0.328$, $p = 0.002$) and iron intake and hemoglobin ($r = 0.308$, $p = 0.003$). A strong positive correlation was found between ferritin and hemoglobin ($r = 0.769$, $p < 0.001$).

Conclusions: Iron intake of children aged 24–36 months had a weak positive correlation with ferritin and hemoglobin level.

Keywords children aged 24–36 months, ferritin, hemoglobin, iron intake, Jakarta

Introduction

Iron is an essential nutrient needed for the growth and development of children. Iron in the body is used for various cellular processes, including the formation of red blood cells, muscle cells, gene transcription, and nerve and brain development.[1] Iron deficiency persists to be the most common nutritional problem in children.[1] This can be caused by low iron intake, poor food quality and eating habits, gastrointestinal disease or parasite infection.[2] A continuous lack of iron intake can lead to a decrease in body's iron stores, iron deficiency erythropoiesis, to iron deficiency anemia.

The body's iron can be determined through a bone marrow biopsy examination. However, this is considered to be invasive and not commonly done. Blood ferritin test is the most frequent examination to determine body iron store.[3] Ferritin is an acute phase protein whose levels increase when inflammation occurs.[4] Inflammation can be assessed

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by examining high sensitivity-C reactive protein (hs-CRP).[5] The CRP levels ≥ 10 mg/L are associated with infection.[6] In children under 5 years of age without infection, ferritin levels < 12 μg/L indicates insufficient body iron store. Decrease in ferritin levels generally does not show symptoms, hence rarely realized. If the decrease in ferritin levels continues, a decrease in hemoglobin levels may occur, leading to anemia (hemoglobin levels < 11 g/dL)[7].

In children, fulfillment of iron requirements is secured from daily intake or supplementation. Iron is found in red meat, fish, poultry, vegetable sources, and iron fortification products in which their availability might be affected due to Covid-19 pandemic. Provision of adequate iron-rich intake is expected to meet the body's iron requirements. From the Indonesian RDA, the recommended iron intake for children aged 24–36 months is 7 mg/day.[8]

Herawati et al. found that 50.5% of Indonesian children under five years of age had iron intake below 77% Indonesian RDA.[9] The rapid growth of children occurs in the first 2 years of life, but high iron requirements are still needed until the age of 3 years.[10] In Europe, even though average iron intake in children is close to the daily recommendation, there is still high levels of insufficient in intake and iron levels.[11] In Indonesia, Herawati et al found 36.8% of children aged 24–35 months had less than required ferritin and hemoglobin levels.[9] Therefore, it is important to pay attention to iron intake at this age bracket to support optimal child development as a good provision before entering the preschool age.

The Covid-19 pandemic that occurred in 2020 caused economic impacts, including reduced economic growth and an increase in the unemployment rate. There are 29.12 million people of working age who have been affected by Covid-19.[12] This economic impact can affect the purchasing power and fulfillment of children's iron needs. This study aims to determine iron intake and its association with ferritin and hemoglobin levels in children aged 24–36 months in Jakarta.

Methods

This cross-sectional study was carried out during the Covid-19 pandemic, from September to October 2020 in Kampung Melayu Sub-district, Jakarta. This place was chosen because it was the only limited resources eligible that provided permission to do data collection due to the Covid-19 pandemic. This study was approved by the Health Research Ethics Committee of Faculty of Medicine, Universitas Indonesia(No. 441/UN2.F1/ETIK/PPM.00.02/2020, protocol number 20-04-0460).

Subjects

The study subjects were healthy boys and girls aged 24–36 months, with their parents provided permission to participate in the study. Subject selection was carried out by total population sampling. The subject's parents were explained about the purpose, benefits and the examinations to be carried out. Parents who agreed to take part in the research were asked to sign a consent form. Children with acute infections, fever, cough, colds, congenital diseases and syndromes, epilepsy, cerebral palsy, and mental disorders were excluded from the study. Of the total 87 subjects, 5 subjects did not complete the study procedure, 2 blood samples were lysis, and there were 3 subjects with elevated hs-CRP level (≥ 10 mg/L), therefore only 77 samples were furthered analyzed.

Characteristic data

Data on subjects' characteristics include: age, gender, gestational age, birth weight, maternal education, and family income were obtained from interviews. Maternal education was categorized into high (high school education and above) and low (below high school education). Family income was categorized based on the value of minimum wage (UMP) DKI Jakarta 2020 (Rp. 4,276,350) to be more or equal to the UMP and less than the UMP.

Iron intake and anthropometric measurement

The assessment of iron intake was taken using a semi quantitative-food frequency questionnaire (SQ-FFQ). Interviews were conducted to determine the subjects' iron intake during the last 1 month. Interviews were conducted using a food photo book. Anthropometric measurement includes body weight and height. The subjects' body weight was measured using the SECA digital scale, to an accuracy of 0.1

kg. The subjects' clothes and accessories were removed or only wore minimal clothing and the subjects stood on the scale. The subjects' height was measured using a SECA stadiometer with an accuracy of 0.1 cm. The subjects looked forward at the Frankfort horizontal plane, the heel, buttocks and back of the head touching the stadiometer. Each measurement was carried out twice and the average value was taken. Nutritional status was determined based on the Z-score weight/height in the WHO 2006 growth chart.[13]

Laboratory examination

Blood tests were performed to check the levels of ferritin, hemoglobin, and hs-CRP. The blood tests were conducted in collaboration with Prodia Laboratory. The subjects' blood was drawn in the Kampung Melayu Sub-district office by laboratory personnel. Prior to drawing blood, the subjects' cubiti area was disinfected with an alcohol swab. A total of 6 ml of blood was drawn in the cubiti area by laboratory personnel. Then the blood samples were taken to Prodia Laboratory for analysis. Ferritin examination was performed with the immunochemiluminescent method[14] using Immulite 2000, hemoglobin examination was performed with the cyanmethemoglobin-oxyhemoglobin method[15] using XN-series (Sysmex), and hs-CRP was performed with the immunoturbidimetric method[6] using the Architect C System.

Data analysis

Data were analyzed using IBM Statistical Package for the Social Sciences (SPSS) version 20.0. The normality of the data distribution was determined by the Kolmogorov Smirnov test. The data distribution was considered normal when the p value > 0.05. Categorical data were presented in the form of a frequency distribution (n, %). Continuous data were presented in the form of median (minimum-maximum). The Pearson's /Spearman test was used to determine the correlation of iron intake with ferritin levels and hemoglobin levels. The correlations were considered significant if the p value ≤ 0.05. Nutrisurvey 2007 was used to perform analysis of iron intake.

Results

From the 77 subjects, the median age was 30 (24–36) months. The majority of subjects had normal nutritional status and family income below UMP DKI Jakarta 2020. Data on subjects' characteristics can be seen in **Table 1**.

In this study, the median value of iron intake was 9.6 (1.5–40.7) mg/day. When compared with the 2019 Indonesian RDA adequacy, it was found that 33.8% of the subjects had insufficient iron intake. The results can be seen in **Table 2**. The median (minimum-maximum) ferritin value was 18.1 (1.4–91.1) μg/L and hemoglobin was 11.8 (6.6–15.2) g/dL. When compared with the cut value of ferritin (< 12 μg/L), there were 40.3% subjects with insufficient ferritin values. There were 27.3% subjects with insufficient hemoglobin (< 11g/dL) or anemia. The adequacy of ferritin and hemoglobin can be seen in **Table 3**.

The correlation between iron intake and ferritin levels and hemoglobin levels can be seen in **Table 4**. There were a weak positive correlation between iron intake and ferritin levels (r = 0.328, p = 0.002) and iron intake with hemoglobin levels (r = 0.308, p = 0.003). There was a strong positive correlation between ferritin and hemoglobin levels (r = 0.769, p < 0.001).

Discussion

This study showed a positive correlation between iron intake and ferritin levels (r = 0.328, p = 0.002) and iron intake with hemoglobin levels (r = 0.308, p = 0.003). This result is similar to the study of Herawati et al,[9] which found a positive correlation between the adequacy of iron intake and hemoglobin level in Indonesian children (r = 0.219; p = 0.041). This indicates that the amount of iron intake plays a role in the formation of ferritin and hemoglobin. This is similar to a study by Thompson et al that found an increase in ferritin and hemoglobin in children aged 2–5 years who received iron supplementation.[16] There was a strong positive correlation between ferritin and hemoglobin levels (r = 0.769, p < 0.001). This indicates the needs for adequate body iron store to support optimal hemoglobin formation. This is similar to the study of Herawati et al which obtained a positive

correlation between ferritin and hemoglobin concentrations ($r = 0.447$, $p < 0.05$).[9]

Iron is required for various processes in the body, such as deoxyribonucleic acid (DNA) biosynthesis, oxygen transport, energy metabolism, the formation of red blood cells, muscle cells, and brain development[1] hence when iron needs are not met, it will affect optimal child growth and development. In children, iron intake is secured from daily food. Based on the Indonesian RDA, the recommendation of iron consumption in children aged 24–36 months is 7 mg/day.[8] It is hoped that iron needs can be fulfilled from a variety of foods that are rich in iron.[1] Iron is obtained from food sources of heme and non-heme iron. Sources of heme iron come from red meat, poultry, and fish. Meanwhile, non-heme iron sources come from vegetable sources and fortification products. Most foods are sources of non-heme iron. However, the absorption of non-heme iron sources is lower, namely by 2–20% compared to heme iron sources of 15–35%.[17] Although the median iron intake of subjects in this study (9.6 mg/day) was higher than the recommendation in Indonesian RDA, however one-third of subjects did not have sufficient iron intake. Continuous lack of iron intake will cause a decrease in the body's iron reserves. Reduced body iron reserves can be detected from low serum ferritin levels, which can lead to decreased hemoglobin levels (anemia).[3] A study by Timmer et al[18] in the Netherlands on adult blood donors, found that higher hemoglobin levels were associated with a high intake of heme sources and a low intake of non-heme sources.[18] The similar thing was found in a study by Cox et al[19] on children aged 12–36 months in Canada, who found that consumption of heme iron from red meat reduces the risk of iron deficiency.

In this study, 40.3% of the subjects had insufficient ferritin levels. The percentage of ferritin insufficiency in this study was higher than the study by Herawati et al in children aged 24–35 months in Indonesia, namely 36.8%.[9] In this study, hemoglobin insufficiency was present in 27.3% of subjects. This result is lower than the study by Herawati et al, namely 36.8%.[9] If the children's ferritin level was not corrected, the hemoglobin insufficiency will also increase.

The balance of body's iron is regulated by absorption and transportation systems. Iron from food will be absorbed in the small intestine, stored in ferritin, used for cell needs, and brought into the circulation to meet the needs of the body's cells.[20] The amount of iron that is absorbed depends on the physiological needs and the body's iron reserves.[21] When the body's iron reserves are low, the absorption in the intestine will increase. Iron that is not used will be stored in ferritin. Most of the body's iron is found in erythrocytes, as part of the heme in hemoglobin.[22] When erythrocytes are senescent, they were recycled by macrophages. The degraded heme releases iron, biliverdin, and carbon monoxide. Iron will be transported to the cytoplasm, stored in ferritin as the body' iron reserves, used for cellular process, or transported out by ferroportin.[22] Maintaining iron intake is important to support the ferritin and hemoglobin adequacy.

There were some limitations of this study. It was carried out during the Covid-19 pandemic, thus resulting in limited time and available resources in the field. In addition, the parents of the prospective subject were also afraid to participate to avoid meeting activities during the Covid-19 pandemic. Limitations of the study included the possibility of memory bias in assessing the iron intake of children with the SQ-FFQ, even though food photo books had been used to reduce the bias.

Conclusion

From this study it can be concluded that iron intake had a positive correlation with ferritin and hemoglobin levels. One third of the subjects still had iron intake below the daily requirement. Iron is needed in the development and growth of children aged 24–36 months, thus it is important to pay attention to the adequacy of iron intake. By educating mothers about iron sources in food related to child feeding, it is hoped that the iron intake will be increased, thus increase the optimal iron status i.e. ferritin and hemoglobin

Table 1. Subjects' characteristics

Characteristics	Results
Age (months)	30 (24–36)†
Gestational age (weeks)	39 (32–42)†
Birth weight (grams)	2985 (1200–3900)†
Gender, n (%)	
Male	41 (53.2)
Female	36 (46.8)
Nutritional status, n (%)	
Obese	3 (3.9)
Overweight	1 (1.3)
Normal	66 (85.7)
Wasted	7 (9.1)
Severely wasted	-
Maternal education, n (%)	
High	45 (58.4)
Low	32 (41.6)
Family income, n (%)	
≥ UMP	19 (24.7)
< UMP	58 (75.3)

†: median (minimum-maximum)

Table 2. Subjects' iron intake

Variables	Results
Iron intake (median; minimum-maximum)	9.6 (1.5–40.7)
Adequacy of iron intake, n (%)	
Sufficient	51 (66.2)
Insufficient	26 (33.8)

Table 3. Subjects' adequacy of ferritin and hemoglobin levels

Variables	Results
Ferritin adequacy, n (%)	
Sufficient	46 (59.7)
Insufficient	31 (40.3)
Hemoglobin adequacy, n (%)	
Sufficient	56 (72.7)
Insufficient	21 (27.3)

Table 4. Correlation of iron intake with ferritin and hemoglobin levels

	Ferritin		Hemoglobin	
Nutrient	**r**	**p (1-tailed)**	**r**	**p (1-tailed)**
Iron intake	0.328	0,002*	0.308	0,003*

*: statistically significant

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ORIGINAL ARTICLE

The correlation between body mass index and the risk of osteoporosis in Acehnese adult females in Zainoel Abidin General Hospital

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Abstract

Background: Osteoporosis is a condition in which bone become weak and brittle characterized with lower bone density and quality causing increased risk of fracture. The elderly is the most common group to be affected and female is more prone compared to male. One of modifiable risk factors of osteoporosis is low body mass index or underweight. This study aimed to investigate the correlation between body mass index and the risk of osteoporosis on Acehnese adult females in RSUDZA.

Methods: This was an analytic observational-cross sectional study which was completed at the Internal Medicine and Orthopedic Policlinic at Zainoel Abidin General Hospital Banda Aceh from August 27th to September 13th 2019. The sampling method used was nonprobability sampling with accidental sampling technique. The body mass index was obtained by measuring respondents' height and weight while the risk of osteoporosis was assessed by measuring OSTA Score.

Results: Results showed that most of respondents was aged between 40-45 years old (55.4%) and there are 62 respondents (74.7%) with abnormal body mass index consisted of 9 underweight respondents (10.8%), 11 overweight respondents (13.3%), and 42 obese respondents (50.6%). The risk of osteoporosis was dominantly mild (69.9%). There were 7 underweight respondents (77.8) had moderate risk of osteoporosis while 2 underweight respondents had severe risk (22.2%). Meanwhile, 41 obese respondents had mild risk of osteoporosis (97.6%). Correlation test using Spearman showed *p* value 0.000 ($p < 0.05$) and rs = -0,731 which means that there is a strong correlation between body mass index and the risk of osteoporosis.

Conclusions: Lower body mass index is directly proportional with higher risk of osteoporosis.

Keywords body mass index, risk of osteoporosis, OSTA score, Acehnese

Introduction

Osteoporosis is a condition in which bone become weak and brittle characterized with lower bone density and quality causing increased risk of fracture.[1] Osteoporosis is mainly found on elderly because of decreased bone tissue associated with \ aging process. In menopause female, the process become quicker due to lower estrogen hormone.[2]

Asians commonly had lower bone mass compared to other population. The bone density on Cambodian, Lao and Vietnamese female in Rochester, United States of America, were lower compared to the white ethinicity.[3] An Asian statistic according to *International Osteoporosis Foundation* (IOF) estimated that there will be more than 50% hip fracture cases due to osteoporosis in Asia in 2050. This is resulted by low calcium intake of all Asian

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countries population which is only 1000-1300 mg/day.[4]

International Osteoporosis Foundation (IOF) mentioned that 1 out of 4 Indonesian 50-80 years of age females has the risk of osteoporosis.[5] This is supported by *Perhimpunan Osteoporosis Indonesia* (PEROSI) in 2007 which stated that the proportion of population with osteoporosis was 32.3% on female and 28.8% on male.[5] Data from Zainoel Abidin General Hospital also showed that the number of osteoporotic patients visit on Internal Medicine Policlinic in 2018 was 586 patients consisted of 394 females and 192 males.

The risk factors of osteoporosis are age, gender, history of fracture, lifestyle (alcohol consumption and smoking behavior), and low body mass index (underweight).[5] A study by Sri Prihatini et al[6] in three provinces which are North Sulawesi, Yogyakarta, and West Java showed that body mass index lower than 18.5 kg/m^2 is the predisposition risk which has significant correlation with the risk of osteoporosis.

Many instruments had been developed to predict low Bone Mineral Density (BMD) including Osteoporosis Self Assessment Tool for Asian (OSTA). This instrument is simple and easy to use for clinician in measuring the risk of osteoporosis in female. (7) This study will explain the correlation between body mass index and osteoporosis in Acehnese adult females at Zainoel Abidin General Hospital.

Methods

This is an analytic observational study with cross sectional design. The study was conducted at Internal Medicine and Orthopedic Policlinic of Zainoel Abidin General Hospital Banda Aceh from August 27th to September 13th, 2019.

Participants

The population of study are Acehnese adult females treated at Internal Medicine and Orthopedic Policlinic of Zainoel Abidin General Hospital. Samples were part of population fulfilling inclusion and exclusion criteria. The inclusion criteria are: 1. Patients of Internal Medicine Policlinic of Zainoel Abidin General Hospital, 2. Patients of Orthopedic Policlinic of Zainoel Abidin General Hospital, 3. Aged 35-45 years old, and 4. Agreed to be respondent. While the exclusion criteria are: 1. Previously diagnosed with osteoporosis, 2. Active smoker, 3. History of alcohol consumption, and 4. Currently menopause.

Measurements

Samples were taken using non probability sampling with accidental sampling method. The size of samples were determined using Slovin Formula. As there were 394 patients with osteoporosis at Zainoel Abidin General Hospital in 2018, samples needed with 10% inaccuracy tolerance were 80 respondents. Weight and height were measured using weight scale and height measurement tools GEA SMIC ZT-120. Data collection procedure were as follow:

1. Researcher completed administration procedure at Zainoel Abidin General Hospital, Banda Aceh.
2. Research collected data of female patients aged 35-45 years old at Internal Medicine and Orthopedic Policlinic of Zainoel Abidin General Hospital Banda Aceh.
3. Patients were classified based on inclusion and exclusion criteria to determine the number of samples.
4. Researcher asked for respondents' permission by signing an informed consent page.
5. Researcher interviewed the respondents regarding general information and measured respondents' weight and height. There were 7 enumerators supported the study which were medical students of Syiah Kuala University with similar perception.
6. The weight measurement was done as follow:
    a. Respondents wore casual wear without any accessories nor foot cover,
    b. Weight scale was put on flat surface,
    c. The scale was calibrated until the needle pointed to zero "0",
    d. Respondents were instructed to stand on the weight scale in which feet were positioned in the center,
    e. Respondents were instructed to stay calm and stare straight to the front,

f. Wait until the needle showed the fixed weight result,
g. The result of measurement was noted and recorded,
h. Respondents were asked to get back from the weight scale,

7. The height measurement was done as follow:
   a. Socks, hats, and any head covers were removed from respondents,
   b. Respondents stood under head ruler with straight position, staring to the front, straight knee, and head on Frankfort horizontal plane,
   c. Height was measured from ankle to the crest of the skull using measurement stick,
   d. The result of measurement was noted and recorded.

Body Mass Index (BMI) was measured using the formula = weight (kg) / height (m^2). The result was then classified into underweight (<18.5 kg/m^2), normal (18.5-22.9 kg/m^2), overweight (23.0-14.9 kg/m^2), and obesity ≥25.0 kg/m^2. Weight and height were measured using weight scale and height measurement tool SMIC ZT-120. The measurement of OSTA Score was done by inputting the data into OSTA formula = (Weight – Age) x 0.2. The result is collected in integer numbers. (8) The result is then categorized into mild risk (≥ 3), moderate risk (-1 to 2), and severe risk (≤ -2). (9) Data was analysed with univariate and bivariate analysis using spearman Rank Correlation Test. The study has been approved by Ethic Committee, Faculty of Medicine Syiah Kuala University and Zainoel Abidin General Hospital Banda Aceh: 179/EA/FK-RSUDZA/2019.

Results

Data was collected from August 27th to September 13th 2019 at Internal Medicine and Orthopedic Policlinic of Zainoel Abidin General Hospital with 83 respondents fulfilling the criteria. The characteristics of respondents included were age, occupation, and education history. Distribution data of respondents' characteristics can be seen on **Table 1.** Data on Table 1 showed that the majority of respondents were aged between 40-45 years old which were 46 respondents (55.4%). The occupation was dominated by housewife (74.7%) while the majority of respondents had an education history of senior high school (39.8%).

The body mass index of respondents can be seen on **Table 2**. It is shown that most of respondents had body mass index of obesity (50.6%) while there were 9 respondents with body mass index of underweight (10.8%).

Based on data from **Table 3**, most of respondents had mild risk of osteoporosis which were 58 respondents (59.9%) while respondents with moderate risks were 23 (27.7%) and 2 respondents with severe risk (2.4%).

Data from **Table 4** showed that underweight respondents (22.2%) had severe risk of osteoporosis while the whole obese respondents had mild risk of osteoporosis (97.6%). The result of statistical analysis using Spearmen Correlation Test showed that there is a correlation between Body Mass Index and the risk of osteoporosis with p value 0,000 (p value<0.05). The correlation between both variables was negative (-) and the correlation strength with r_s = -0.731 which means that lower body mass index is proportionally significant with higher risk of osteoporosis.

Discussion

The majority of respondents were aged between 40-45 years old which were 46 respondents (55.4%). This result is proportional with study by Prihatini *et al*[5] in North Sulawesi, Yogyakarta, and West Java in which older respondents (46-55 years old) were 554 respondents (22.8%) compared to younger respondents (25-35 years old) which were 452 respondents (18.6%). The bone turnover rate will increase similar with age because of disrupted bone remodeling process.

Respondents were dominated by housewife (74.7%) with history of senior high school (39.8%) education. This result is supported with the study by Setyawati *et al*[11] on 25-35 years old female in Bogor in which housewife was also dominated the study (87.9%). Occupation is associated with daily physical activity. According to Widyanti in Laras *et al*,[12] the physical activity of housewife is mainly categorized as mild based on International Physical Activity Questionnaire (IPAQ).

A study by Regina *et al*[1] on reproductive age female in the subdistrict of Babakan Ciparay, Bandung, West Java, Indonesia, showed that most respondents' last education was senior high school (35.9%). There is an association between history of education towards knowledge level especially in medical sector. Subject with high education level tends to understand medical information better compared to subjects with lower education level.[13]

Data from Indonesian Basic Health Research/*Riset Kesehatan Dasar* (RISKESDAS) 2018 showed that the prevalence of obesity on adult in Indonesia was 21.8% and Aceh Province is one of provinces with higher prevalence of obesity compared to national (24.4%). Factors of obesity includes: limited physical activity, higher energy intake compared to outtake, carbohydrate intake, and the use of hormonal contraception.[16] Based on the interview with the study respondents, it can be understood the majority of housewives had unhealthy lifestyle including food and limited routine physical activities resulting in obesity.

Menopause is one of osteoporosis risk factors because of decreased estrogen level stimulating the bone remodeling.[16,17] During pre-menopause period, the decreased of estrogen level was not so significant so that the influence towards bone density is also not significant.[16]

The result of this study shows there was a correlation between body mass index with the risk of osteoporosis with *p* value of 0.000 (*p* value<0.05). This result is supported with the study by Montazerifar[16] on 80 post menopause females at Zahedan Rheumatology Clinic, Malaysia, which showed that there is correlation between body mass index and lumbal Body Mass Density (BMD) with *p value* of 0.002 and correlation coefficient of 0.31 inferring weak correlation. In the newest systematic review, the annual global incidence of hip fracture was higher in Hongkong, Japan, South Korea, and Taiwan, compared to United States of America and Europe. The prevalence in Taiwan was categorized as high incidence country (>300/100,000) which was on the 9th position compared to other 61 countries, while Hongkong, Japan, and South Korea was listed on moderate incidence countries (200-300/100,000).[18]

A study by Widyanti[7] in 2017 showed that there is a correlation between total body fat with the bone density on reproductive women (15-49 years old) in Bandung with p value 0.006 and correlation coefficient of 0,327 inferring lower correlation and higher total body fat is proportional with higher bone density.

Balanced diet is crucial for the bone development and maintenance as also for the general health. Certain population such as women above 65 years old, women with decreased appetite due to several reasons, or women with food disruption might not consume vitamin and mineral in optimal amount for bone mass. Older women who lost weight has the risk of osteoporosis and hip fracture.[20]

Based on a Food Consumption Survey in Aceh (2014), the average consumption rate of soy and its product was 12.7 grams per person per day in which groups of 13-18 years old dominated the consumption (13.7 grams). Other than that, the average consumption rate of milk was the highest which is 1.5 grams per person per day. However, the lowest consumption rate of milk was on age group of above 55 and 19-55 years old (0.2 and 0.3 mL, respectively).[17] This result indirectly showed the deficiency of calcium intake of Acehnese especially adults so that the risk of osteoporosis is increased.

Lower body mass index (BMI) or underweight is one of osteoporosis risk factors. Nutrition status is associated with protein and calcium reserve for bone metabolism.[17] BMI <20 kg/m^2 is associated with decreased bone density and higher fracture risk. Subjects with higher BMI have better bone mineral content (BMC) and bone mineral density (BMD) on the lower extremities. The result of an observation study showed that the phenomenon is not only associated with the mechanical effect but also the consumed intake calories.[22] More weight will give more burden to the bone so that the bone density will be increased because of the accommodation process.[23,24] Mechanical burden of the bone will increase the bone remodelling process and decrease the bone turnover process resulting in stronger bone.[12]

Body fat is essential as protective agent towards fracture. Adipocyte cells are important source of estrogen hormone in which higher hormone level will cause increased other hormones such as leptin, preptin, and amylin. These hormones influences the activity of osteoblast and osteoclast both directly and indirectly in the bone remodeling process.[25]

Estrogen is one of sex hormones which plays role in the bone metabolism process by regulating osteoblast and osteoclast activity to balance the remodelling and destruction process. This is caused by the presence of osteoblast receptor on the estrogen hormone, they are alpha and beta receptor (ERα dan ERβ).[12]

Subcutaneous and visceral fact have contradicted effects on bone structure. Subcutaneous fact is crucial for bone mass because of its protein as the protective agent in bone growth, that is high amount of adiponectin on subcutaneous fat.[25] Excessive fat mass will not protect bone from osteoporosis. In subjects with obesity, body visceral fact will increase the bone resorption process via upregulation of proinflammatory cytokines such as IL-6 and TNF- α. Produced proinflammatory cytokines will stimulate the bone resorption process via RANKL/RANK/OPG pathway regulation.[26]

Central obesity and inflammation also affect the metabolic syndrome in female. A study by Muherdiyatiningsih[27] in 2008 on female adult aged 30-55 years old in Bogor, West Java, Indonesia showed that female above 44 years old had twice the risk of developing metabolic syndrome. Metabolic syndrome is a predictor of degenerative diseases such as diabetes melitus and coronary heart disease. Obese subjects will also have a difficulty in the daily activities because of limited movements causing balance problem and increased risk of injury. Therefore, it is important to maintain ideal body weight.[28]

The result of this study is different with the study by Martanti[29] in 2015 to 81 female adults in Tengaran which showed that there is no correlation between body mass index and osteoporosis with p value 0.708. The result also contradicted with Humaryanto[14] in 2019 in 347 female adults in Jambi which stated that there is no correlation between body mass index and bone mineral density. The difference of result is caused by the dominance of normal body mass index causing the tendency of similar result and interval. Other factors such as genetic and ethnicity also influence the bone density, fat mass, and muscle mass.[30] Factors such as ethnicity, genetic, smoking, excessive alcohol consumption, limited physical activity, low calcium intake and vitamin D, as also endocrine and metabolic disruption will also increase the risk of osteoporosis. Therefore, the identification and modification of risk factors are needed to decrease the incidence of osteoporosis and fracture in the near future.

Conclusion

The majority of respondents have abnormal body mass index which were 62 respondents (74.7%) consisted of 9 underweight respondents (10.8%), 11 overweight respondents (13.3%), and obese respondents (50.6%). It is also noted that 58 respondents had mild risk of osteoporosis (69.9%), 23 respondents with moderate risk (27.7%), and 2 respondents with severe risk (2.4%). In conclusion, there was a correlation between body mass index and the risk of osteoporosis in Acehnese adult females at Zainoel Abidin General Hospital with p value of 0.000 ($p<0.05$) and $rs = -0.731$ with strong correlation. This implies that lower body mass index is proportional with higher risk of osteoporosis. It is recommended for the next study to use Mini Nutritional Assessment (MNA) as the nutritional measurement method and to explore more information regarding to the subjects' nutrition intake.

Table 1. General characteristics of respondents (n=83)

General Characteristics	Frequency (n)	Percentage (%)
Age		
35-39 years old	37	44.6
40-45 years old	46	55.4
Occupation		
Housewife	62	74.7
Civil servant	15	18.1
Non-civil servant	6	7.2
History of education		
Primary School	9	10.8
Junior High School	20	24.1
Senior High School	33	39.8
College	21	25.3

Table 2. Distribution of body mass index

Body mass index	Frequency (n)	Percentage (%)
Underweight	9	10.8
Normal	21	25.3
Overweight	11	13.3
Obese	42	50.6

Table 3. Distribution of osteoporosis risk in subjects

Risk of osteoporosis	Frequency (n)	Percentage (%)
Mild	58	69.9
Moderate	23	27.7
Severe	2	2.4

Table 4. The correlation between body mass index and the risk of osteoporosis

Body mass index	Risk of Osteoporosis								r_s	p Value
	Mild		Moderate		Severe		Total			
	n	%	n	%	n	%	n	%		
Underweight	0	0	7	77.8	2	22.2	9	100	-0.731	0.000
Normal	8	38.1	13	61.9	0	0	21	100		
Overweight	9	81.8	2	18.2	0	0	11	100		
Obesity	41	97.6	1	2.4	0	0	42	100		

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ORIGINAL ARTICLE

Food avoidance behaviour among children aged 2-6 years in North Jakarta and its correlation with weight and energy intake

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Abstract

Background: Children generally facing food avoidance or food refusal behaviour and it may affect their food consumption. But there is limited information on food avoidance behaviour among Indonesian children. Therefore, this study aimed to assess whether energy intake and body weight are influenced by food avoidance behaviour in children aged 2-6 years in North Jakarta.

Methods: Participants (N=168) were recruited between February – March 2020. Data collection was obtained via interviews with the mother or caregiver of the children. Food avoidance behaviour consisting of satiety responsiveness, slowness in eating, emotional under-eating, and food fussiness was measured with the Child Eating Behaviour Questionnaire. The child's weight and dietary intake were assessed using a digital weighing scale and 2 x 24 hours food recall. Spearman test was performed to analyse the correlation between these variables. Multivariate analysis was done using linear regression to determine predictors of a child's body weight and energy intake.

Results: Energy intake among children was below the recommendation, and it was significantly correlated with the child's body weight. Satiety responsiveness was negatively correlated with the child's body weight ($r = -0.166$; p-value < 0.05) and energy intake ($r = -0.210$; p-value < 0.05). After running a linear regression test, we found that satiety responsiveness along with family income and child's age was a significant predictor of energy intake among children.

Conclusions: Children who are more responsive to satiety had lower body weight and energy intake. Understanding the child's food avoidance behaviour is useful for designing intervention programs related to optimizing intake in children and malnutrition.

Keywords children, food avoidance behaviour, energy intake, body weight

Introduction

Currently, Indonesia is facing the double burden of malnutrition, where the prevalence of undernutrition remains high, but the prevalence of overweight and obesity at all ages is increasing over time, particularly in DKI Jakarta province.[1] Malnutrition is linked to other health problems, such as infectious diseases and developmental disorders in children, and this can lead to an increase in child mortality. One of the factors contributing to this malnutrition problem is dietary intake. Along with infectious diseases, maternal health, feeding practice, dietary intake was a factor that related to wasting, overweight, and stunting among children.[2,3] In Indonesia, a study from South East Asian Nutrition Survey (SEANUTS I) showed that the nutrient intake of Indonesian children was below the Indonesian Recommended Daily Allowance (RDA), and the major problem among Indonesian children was stunting and underweight.[4] The results of the

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SEANUTS study in Malaysia also showed that 30% of the children there could not meet their energy requirement, but the prevalence of overnutrition was still higher than undernutrition in Malaysian children.[5]

Children's diet is influenced by multiple factors, including mother's education, mother occupation, family income, parental feeding practice, and children eating behaviour.[6,7] Studies showed that mother nutrition knowledge and occupation were related to dietary adequacy among children because a mother have a big influence on determining what, when, and how much food is provided to their children directly.[8,9] In addition, family income was related to the family's ability to access food.[10] Parental feeding practices have a bidirectional relationship with child eating behaviour. The practices can influence and/or respond to child eating behaviours, which in turn affects the child's food intake. For instance, the pressure to eat practice was associated with increased food avoidance and decreasing preferences on the consumption of the to-be eaten foods.[11,12] While responsive feeding including modelling healthy eating and involved with children during meals can contribute to healthy eating behaviour as well as promote optimal food intake among children.[13]

In this study, we try to focus on children eating behaviour, particularly food avoidance behaviour, that may influence dietary intake and diet quality. Food avoidance behaviour refers to the child's tendency to avoid or reject certain foods. Children generally facing food avoidance or food refusal behaviour, especially children aged 2-6 years and this behaviour was associated with lower fruit and vegetable intake and less dietary variety.[14] The Child Eating Behaviour Questionnaire (CEBQ) was used to measure food avoidance behaviour. Food avoidance behaviour consists of four scales, namely satiety responsiveness, slowness in eating, emotional under-eating, and food fussiness. A high score on food avoidance behaviour indicates a high tendency to avoid or refuse foods.[15]

The relationship between the food avoidance scale and children's diet is often stated. Previous studies showed that higher score on food avoidance behaviour was associated with lower meal size and higher intake of snack food and less intake of fruits and vegetables.[7,16,17] Moreover, a study among school children in the UK reported that satiety responsiveness, slowness in eating, and food fussiness was negatively associated with child weight.[18] This is supported by findings in children under-five in Australia, where satiety responsiveness and slowness in eating were inversely correlated with energy intake of lunch meal and child's BMI.[19] Thus, assessing food avoidance behaviour in children may help identify children who are at high risk of becoming obese or underweight. To our knowledge, a study on eating behaviour especially for food avoidance scale in Indonesian children is still limited. Then, exploring the association between food avoidance with dietary intake and body weight might contribute to strengthening programs or interventions to prevent nutritional problems among children. This study aimed to assess whether energy intake and body weight are influenced by food avoidance behaviour in children aged 2-6 years in North Jakarta.

Methods

Study design

The study is a cross-sectional study. Data collection of this study was done from February until March 2020 in Jakarta Province. Jakarta, as one of the most densely populated provinces with many slum areas, was chosen purposively. Then, through multistage random sampling, Pejagalan village located in North Jakarta was selected as the study area.

Subjects

In Pejagalan village, four child health care *posyandu* was randomly selected. *Posyandu* is a community-based integrated health post providing some basic health and nutrition services mainly for young children and pregnant women, such as growth monitoring, nutrition supplementation, immunization, and antenatal care. Using the list of children in *posyandu* and family registered certificate (*kartu keluarga*) in the selected *posyandu* area, consecutive sampling was carried out to select subjects who meet the inclusion criteria. The inclusion criteria for subject selection were male or female children aged 2.0 – 6.9 years and were healthy, the mother agreed to sign informed consent

and were able to communicate in Bahasa Indonesia. While, mothers who report that their children had a food allergy or food intolerance were excluded from this study. For bivariate analysis, the sample size was calculated by using the formula of correlation estimation for cross-sectional survey, and for multivariate analysis sample size was calculate based on the rule of thumb of 10 subjects for each variable in the model. After calculating the sample size for bivariate and multivariate analysis, a total minimum sample needed for this study was 168 of the children.

Child's weight

It was measured by a qualified enumerator using SECA 876 digital weighing scale to the nearest 0.1 kg. According to the standardized procedure, children were asked to remove shoes and heavy clothing before the measurement.[20] Measurement were taken twice, and the third measurement was taken when the difference between the two measurements was more than 0.1 kg.

Questionnaire

Data collection was obtained via interviews with the mother or caregiver of the children by trained enumerators. The time needed to interview each respondent during the survey was approximately 45–60 minutes. Mother or caregiver reported their sociodemographic information, such as child's birth date, sex, mother education, mother occupation, caregiver relationship, and family income. Mother education was categorized into low education (≤9 years of schooling, e.g., Junior High School and below) and high education (≥10 years of schooling, e.g., Senior High School and above). While mother occupation was categorized into unemployed (housewife), partially employed (a mother who works less than 30 hours in a week), and fully employed (a mother who works at least 35-40 hours in a week or 8 hours in a day). Then, family income was divided into three categories; low income (below the first quartile), middle income (between first to the fourth quartile), and high income (above the fourth quartile).

Child eating behaviour questionnaire

Food avoidance behaviours were assessed using the CEBQ. In this study, the 15 items questionnaire consist of four food avoidance subscales: satiety responsiveness (5 items; e.g., my child has a big appetite), slowness in eating (3 items; e.g. my child eats slowly), emotional under-eating (3 items; e.g. my child eats less when angry), and food fussiness (4 items; e.g. my child refuses new foods at first). Mothers were asked to rate their children's behaviour related to food avoidance on a 5-point Likert scale ranging from "never" to "always" and each item will be scored 1 (Lowest) to 5 (Highest). The mean score (range 1 – 5) was calculated for each subscale. Internal reliability (Cronbach alpha) was calculated for each subscale of CEBQ, and after deleting four items on CEBQ, good internal reliability was found in four subscales with values of Cronbach alpha ranging from 0.711 – 0.751. The deleted items are "My child takes more than 30 minutes to finish a meal" from slowness in eating scale, "My child eats more when he/she is happy" from emotional under-eating scale, "My child enjoys a wide variety of foods" and "My child is difficult to please with meals" from food fussiness scale.[15]

Dietary assessment

Children's dietary intake was assessed using 2 x 24 hours food recall. Mothers were asked to recall all foods and beverages consumed by their child during the previous day (00:00- 24:00). During the dietary assessment, an error might occur due to memory bias or inaccurate estimation on the portion size and cause misreporting data. In this study, under/overreport energy intake was calculated through the ratio of reported energy intake to BMR. Basal Metabolic Rate was estimated from the Schofield equation, and the cut off for under-, plausible, and overreport energy intake was based on Börnhorst et al. 2012.[21] Energy intake was categorized into two categories, adequate and risk of inadequate. Adequate energy intake refers to the proportion of subjects that consume amounts of energy above the recommendation. The following formula of EER was used to determine the

individual energy requirement based on age, sex, body weight and height, and also physical activity level.

Statistical analysis

Before running the analysis, we excluded cases with incomplete data and under/overreport energy intake. All the collected data obtained from the questionnaire were entered in SPSS software version 20.0, and dietary assessments were entered and transformed into energy intake using NutriSurvey software program. After combining data from energy intake, data analysis was continued with SPSS software to run the univariate, bivariate, and multivariate analysis. Univariate analysis was used to describe socio-demographic and economic characteristics, children's food avoidance behaviour score, child's body weight, and energy intake. Numerical data are presented as mean ± SD or median (IQR) depend on the distribution of the data and categorical data are presented as a proportion (%). Normality test was conducted using Kolmogorov test and coefficient of variance. For Kolmogorov test, significance was set at p-value > 0.05, and for coefficient variance, data was normally distributed if the value was ≤ 20 percent. Since the food avoidance behaviour data were not normally distributed, we ran Spearman test to assess the correlation between food avoidance score with child's body weight and energy intake. While multivariate analysis was done using linear regression to determine predictors of a child's body weight and energy intake. These analyses were considered significant if the p-value < 0.05.

Ethical consideration

This study was conducted after receiving approval from the Ethical Committee of Faculty of Medicines, Universitas Indonesia No. ND-6/UN2.F1/ETIK/PPM.00.02/2020. Before data collection, approval was also obtained from the local authority, health district office, and Primary Health Care. During data collection, the mothers independently signed informed consent before the interview.

Results

The final total sample of this study was 168 children. Table 1. shows the sociodemographic characteristics of the subjects. The majority of the children were boys (63.1%). The median of child's age was four years old and there was similar distribution in children aged 3 years old (22.6%) and 4 years old (24.4%). According to mother education and occupation, 67.3% of the mother have low education and the majority of the mother were unemployed (66.7%). Most of the children were taken care of by their parents (91.1%). The median household income was IDR 3.05 million and the majority of children lived in households that had a lower middle income (76.2%). Table 1. also presents the distribution of a child's body weight and energy intake. Children's body weight showed the median of 15.3 kg, and the median of energy intake for all children was 1307.3 kcal, and both of these variables were not normally distributed. Energy intake data obtained from multiple food recall 24-hours was categorized as adequate and risk of inadequate. These findings suggest that more than half of our subjects had a risk of inadequate energy intake. Further analysis showed that body weight and energy intake among children have a significant correlation with their age, and a child's body weight also differ significantly by mother's education level. The higher median of body weight was found among children with mother who has low education.

Table 2. shows the distribution of food avoidance behaviour scores among our subjects. From the table, we can see that the median scores for food avoidance scales range from 2.6 to 3.3. The emotional under-eating scale has the highest median, followed by satiety responsiveness at the second. Further analysis showed that the satiety responsiveness scale had a significant association with the family income, in which the median satiety responsiveness scale was higher among children from higher-income families.

Bivariate analysis was performed to determine the correlation between the food avoidance behaviour scale with a child's weight and energy intake. Table 3 displayed the correlation between these variables using the Spearman test. All of food avoidance scales were positively correlated with one

another, except the correlation between food fussiness scale with slowness in eating and emotional under-eating. Overall, the result showed that satiety responsiveness had a negative correlation with child's body weight (r = -0.166; p-value < 0.05) and energy intake (r = -0.210; p-value < 0.05). Moreover, energy intake also positively correlated with child' body weight (r = 0.354; p-value < 0.01).

Table 4. displayed the summary of multiple linear regression analysis. A significant predictor of a child's body weight was the child's age (β = 1.370, p-value <0.01), in which, an increase of one unit on child's age corresponds to an increase of 1.370 units on body weight. While, significant predictors of energy intake were child's age (β = 0.715, p-value <0.05), family income (β = 0.000, p-value <0.01) and satiety responsiveness (β = -1.736, p-value <0.01). For every unit increase in satiety responsiveness score, energy intake among children decreases 1.736 times.

Discussion

This present study reveals that energy intake among children in Jakarta was below the recommendation. This is similar to the study of SEANUTS I that showed the percentage of Indonesian children who have dietary intake below the recommendation was high (21% – 63%).[4] Childhood is a period of rapid growth and development. Nutritional needs during this period increased as the child gets older, and in line with our finding, the older the children the greater their energy intake, and the energy intake significantly correlated with their body weight. For a long time, a child's inadequate body weight can trigger various health problems.[2] Study among Indonesian pre-school children showed that inadequate energy intake was also related to an increased risk of developmental delay.[22]

This study hypothesizes, there is a correlation between food avoidance behaviour with a child's body weight and energy intake among children aged 2-6 years. In this study, food avoidance related to eating behaviour was represented by satiety responsiveness, slowness in eating, emotional under-eating and food fussiness. Based on the result of our study, the children seem to have an emotional tendency to eat less and be more responsive to satiety. The result also showed that satiety responsiveness had a significant correlation with a child's body weight and energy intake. The higher the score on the satiety responsiveness scale, the lower the child's body weight and energy intake. This finding is in line with previous researches that showed four scales of food avoidance behaviour were negatively correlated with body weight and dietary intake and it was usually related to obesity-reducing behaviour, such as lower meal size.[7,16]

In the final regression model, a child's age, family income, and satiety responsiveness were a significant predictor of energy intake and the significant predictor for a child's weight was only found on child's age. Family income was found as a predictor of energy intake. Increasing family income contributes to greater energy intake among children. A previous study showed families with low socioeconomic status tend to have a weaker purchasing power to provide enough food in their home.[10] They also have difficulty in accessing healthy food. Study in Swedish, healthy eating was associated with higher diet costs due to the different prices between healthy food and unhealthy food. Thus, families with high income are more likely to access adequate and healthy foods.[23]

In this study, satiety responsiveness appeared to be the strongest predictor of a child's energy intake. Satiety responsiveness defines as a child's response to satiety or internal signal to finish eating, and the more responsive the child to satiety the more likely the child to leave their food.[24] This finding supports the crucial role of parents in improving a child's self-regulation ability, particularly responsiveness to satiety cues. Satiety responsiveness among children is also related to the type of food preference and food consumption. Previous studies have found that children who are more responsive to satiety tend to have a lower preference for fruits and vegetables,[25] lower consumption of vegetables, cheese, and meat, and higher consumption of energy-dense foods such as, candies and chocolate.[26] Satiety was related to the diet composition and consuming high-energy foods that were relatively satiating can provide pleasant feeling of fullness.[27] This is in line with our finding which showed children get full up easily.

Supporting the hypothesis, evidence from the previous studies showed that satiety responsiveness and slowness in eating were related to dietary intake

among children.[19,26] In our finding, satiety responsiveness was related to slowness in eating. Slowness in eating refers to the reduction of a child's speed in eating and is caused by a lack of interest and enjoyment of food. The child who has a higher score of slowness in eating scale will be taking a long time to finish their meals.[28] Previous study expected that the eating rate among children will be getting slow when they are more responsive to satiety.[29] Children with this behaviour are more likely to have inadequate intake of food, and then it will put them at risk of underweight and undernutrition.[26] Moreover, several studies have shown a relationship between eating behaviour with child's body weight. Satiety responsiveness and slowness in eating were inversely related to the child's BMI.[7,18,19,30] On the contrary, our finding shows that slowness in eating was a positive predictor of energy intake, but the association was not significant.

In contrast with our hypothesis and finding from the previous studies, the significant correlation between emotional under-eating and food fussiness with energy intake and body weight were not found in this study. Whereas several studies showed that these behaviours are also related to a child's dietary intake and body weight.[7,18] Emotional under-eating refers to children who will eat less in response to their emotions, such as angry, tired, happy, upset, etc.[28] While food fussiness refers to the rejection of unfamiliar and/or familiar food and children with food fussiness are more selective about which foods they want to eat.[31]

Despite our strength by measuring a child's eating behaviour, dietary intake, and body weight in one study, there are several limitations in our study that need to be considered. First, we use the reference height in the Indonesian RDA, not the actual height of each child in categorizing children's energy intake. Second, the CEBQ used in this study was modified from its original version for better reliability. It might impact the interpretation of the food avoidance results of the study. Third, given the characteristics of the subjects, this study cannot be generalized to Indonesian children living in different socio-demographic and economic characteristics. Finally, other potential confounding such as child's food preferences and food availability in the household were not measured in this study.

Conclusion

Among the four food avoidance scales assessed in this study, satiety responsiveness was found to be negatively correlated with the child's body weight. Along with the child's age, family income, and slowness in eating, satiety responsiveness was also a significant predictor of children's energy intake, which was significantly correlated with the child's body weight. Parents and nutrition practitioners may find that early assessment of a child's food avoidance behaviour, especially the satiety responsiveness, could be used to identify children at risk of malnutrition. Therefore, encouraging mothers to apply responsive feeding practices, such as feed the child directly, slowly, and patiently in response to child eating behaviour as well as providing nutrition education that suggests adequate food and recommended portion sizes may have an impact on improving child diet and nutrient intake.

Table 1. Characteristic of children aged 2–6 years old in Pejagalan, North Jakarta (n=168)

Variables	n (%) or Median (IQR)
Sex	
Boy	106 (63.1)
Girl	62 (36.9)
Age	4 (2)
2 years old	29 (17.3)
3 years old	38 (22.6)
4 years old	41 (24.4)
5 years old	35 (20.8)
6 years old	25 (14.9)
Mother Education	
High	55 (32.7)
Low	113 (67.3)
Mother Occupation	
Unemployed	112 (66.7)
Partially employed	33 (19.6)
Fully employed	23 (13.7)
Caregiver relationship with child	
Mother/father	153 (91.1)
Others (Aunt, grandmother or grandfather)	15 (8.9)
Family Income Level	3.05 million (2.2 million)
Low (< 2 million)	24 (14.3)
Middle (2 – 4.2 million)	104 (61.9)
High (>4.2 million)	40 (23.8)
Body weight (kg)	15.3 (4.1)
Energy intake (kcal)	1307.3 (509.9)
Adequate	80 (47.6)
Risk of inadequate	88 (52.4)

Table 2. Distribution of food avoidance behaviour score among the subjects (N=168)

Food Avoidance Scale	Median (IQR)
Satiety Responsiveness	**3.2 (1.2)**
My child has a big appetite*	3 (2)
My child leaves food on his/her plate at the end of a meal	3 (2)
My child gets full before his/her meal is finished	3 (2)
My child gets full up easily	4 (1)
My child cannot eat a meal if s/he has had a snack just before	4 (2)
Slowness in Eating	**2.6 (2.4)**
My child finishes his/her meal quickly*	3 (2)
My child eats slowly	3 (3)
My child eats more and more slowly during the course of a meal	3 (3)
Emotional Under-eating	**3.3 (1.7)**
My child eats less when angry	3.5 (3)
My child eats less when s/he is tired	3 (2)
My child eats less when upset	4 (2)

Table 2. Distribution of food avoidance behaviour score among the subjects (continued)

Food Avoidance Scale	Median (IQR)
Food Fussiness	**2.75 (1.5)**
My child refuses new foods at first	3 (3)
My child enjoys tasting new foods*	3 (2)
My child is interested in tasting food s/he hasn't tasted before*	3 (2)
My child decides that s/he doesn't like a food, even without tasting it	3 (2)

Scoring of the child eating behaviour questionnaire (Never = 1; Rarely = 2; Sometime = 3; Often = 4; Always = 5)
*Reversed score

Table 3. Correlation between food avoidance scales with child's weight and energy intake

Variables	Body weight	Energy intake	SR	SE	EUE	FF
Body weight (kg)	1					
Energy intake (kcal)	0.354**	1				
Satiety responsiveness (SR)	-0.166*	-0.210*	1			
Slowness in eating (SE)	-0.096	-0.037	0.615**	1		
Emotional under-eating (EUE)	-0.056	-0.048	0.466**	0.390**	1	
Food fussiness (FF)	0.008	-0.105	0.200**	0.144	0.057	1

*Statistical analysis used Spearman correlation test with significance level of P-value<0.05
**Statistical analysis used Spearman correlation test with significance level of P-value<0.01
SR: Satiety responsiveness, SE: Slowness in eating, EUE: Emotional under-eating and FF: Food fussiness

Table 4. Multiple linear regression analysis for CEBQ subscale on child's weight and energy intake

Variable	Child's weight[e]			Energy intake[f]		
	B	SE	P value	B	SE	P value
Child's age	1.370	0.158	<0.001**	0.715	0.274	0.010*
Child's sex[a]	-0.186	0.412	0.652	-0.905	0.715	0.207
Mother education[b]	0.181	0.449	0.687	1.043	0.779	0.182
Mother occupation[c]	0.332	0.323	0.306	-0.910	0.561	0.106
Caregiver relationship[d]	-0.719	0.784	0.361	0.622	1.361	0.648
Family Income	0.000	0.000	0.676	0.000	0.000	0.006**
Satiety responsiveness	-0.325	0.343	0.345	-1.736	0.595	0.004**
Slowness in eating	-0.048	0.212	0.823	0.713	0.368	0.055
Emotional under-eating	-0.044	0.223	0.845	0.212	0.387	0.584
Food fussiness	-0.131	0.209	0.534	-0.569	0.363	0.119

Unstandardised regression coefficients (B) are from multiple linear regression models with enter method.
* Significance level at P-value <0.05
** Significance level at P-value <0.01
[a] Child's sex (1 = boys; 2 = girls)
[b] Mother education (1 = high education; 2 = low education)
[c] Mother occupation (1 = unemployed; 2 = partially employed; 3 = fully employed)
[d] Caregiver relationship (1 = mother/father; 2 = others (aunt, grandmother or grandfather)
[e] R square = 0.373
[f] R square = 0.153

Conflict of Interest

The authors declared no conflict of interest regarding this article.

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NARRATIVE REVIEW

The importance of school snacks for primary school-aged children nutritional support as the foundation of *Sekolah Generasi Maju* in Indonesia

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Abstract

As a developing country, Indonesia is still burdened with high prevalence of child malnutrition including those in primary school. One of the main factors affecting nutritional status of children is snack consumption in school. School snacks are expected to be able to contribute to nutritional requirements. This narrative review is written to collect information and knowledge regarding nutritional status, nutritional requirements, factors determining nutritional status of primary school children and, lastly, recommended school snacks. This review also acts as a basic information for school snacks program establishment.

Keywords Indonesia, nutritional status, school-aged children, snacks

Background

Primary school age acts as the continuation from toddler to the next phase of children's growth, development, and learning. In this phase, nutrition is one of the most important aspects. Nevertheless, high numbers of malnutrition in school-aged children remains a national problem.

Despite of its economic growth, Indonesia suffers from high prevalence of undernutrition, obesity and micronutrient deficiency in children (commonly known as the triple burden).[1] According to Basic National Health Research/*Riset Kesehatan Dasar* (Riskesdas) 2013,[2] as much as 11.2% of primary school-aged children were underweight, 26.4% were anemic and 18.8% were obese. Prevalence of stunted school-aged children was still high (30.7%), regardless of its decline from 35.8% in year 2010 Riskesdas data. Regionally, data from West Java Riskesdas 2018[3] showed 16.43% of primary school-aged children were stunted, 6.45% were severely stunted, 5.16% were underweight, 1.88% were severely underweight and 8.9% were obese. In Bandung, the capital city of West Java, 20.64% school-aged children were classified as stunted, 6.51% were severely stunted, 4.54% were underweight, 0.47% were severely underweight and 7.95% were obese. Malnutrition in children may affect physical and mental development. A research regarding a relationship between nutritional status and learning performance in Nairobi, Kenya, Africa, shows that children with low nutritional status or obese demonstrated poor learning performance, poor classroom and out-of-class activity, and low attendance.[4] In addition, several studies indicate that children with short stature (stunting) suffered from

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impairment in brain and motor development, lower levels of intelligence, and learning difficulties.[5–7]
The reason behind the underweight status in school-age children is the lack of fulfilment of nutritional requirements. This involves the interaction between the lack of nutrition intakes from food and impaired absorption of nutrients. On the contrary, the cause of overweight in school-aged children is the interaction between the excessive calorie intakes and the lack of physical activity. To overcome this, it is necessary to ensure children have appropriate food intakes according to the recommended dietary allowances/*angka kecukupan gizi* (AKG) for 7 to 12-year-old children.[7] Supports from various parties such as local governments, teachers, parents, and school cafeteria managers are crucial to the sustainability of the school's nutritional support program. Programs and facilities that are applicable in accordance with the school conditions are also necessary. School of advanced generation/*Sekolah Generasi Maju* is a school that will provide facilities for children to gain the best nutritional support as well as knowledge improvement. Through nutritional support programs and facilities in school cafeteria, schoolchildren are expected to gain proper knowledge on nutrition and health, as well as to secure healthy nutritional status that will improve their learning potential at schools. Therefore, this narrative review is compiled as a guideline on various important nutritional requirements of school-age children and food ingredients that can be made into healthy and nutritious snacks sold in the school cafeteria.

Nutritional status of primary school-age children in various cities in Indonesia

Researches conducted in Indonesia have shown varying numbers on the nutritional status of primary school-aged children. One of them is a study in Tangerang Regency, West Java, where the figure shows that 17.8% of school-aged children were underweight and very underweight, while 7.3% of them were overweight.[8] A study on 50 primary school children in Serang City, Banten, West Java, shows that 3% of them were very underweight, 6% were underweight, 13% were overweight, and 8% were very overweight.[9] Another study in a primary school in Surakarta shows that 6.59% of the schoolchildren were underweight and 21.97% were overweight.[10]
A Study by Yurni et al.[11] on a primary school in Bogor city, West Java, concluded that out of 52% of primary school children, 3.8% were underweight, 11.5% were overweight, and 11.5% were obese. Another study by Sekiyama et al.[12] on a primary school in a village in West Java shows that out of 68 children, 2.9% were underweight, while 17.6% of them were overweight and very overweight. A research conducted in Makassar, the capital city of South Sulawesi, by Syahrul et al.[13] on 877 primary school children shows that 14.5% of them were overweight and 20.4% were underweight. Jahri et al.[14] conducted a research on 350 primary school children in Bengkalis Region, Riau, Sumatra and found 1.7% of the children were very underweight, 12% were underweight, 5.7% were overweight, and 4.6% were obese.

What about Bandung city? A cross-sectional study by Yulia et al.[15] on 7 public schools in Bandung shows that 21.7% of the children were overweight and 19.7% were very overweight. Another study by Riana et al[16] in a primary school in Bandung shows that out of 145 schoolgirls, 2.1% of them were very underweight, 6.9% were underweight, while 11.7% were overweight, and 4.8% were very overweight.

Unfortunately, there have not been many studies that uncover the problem of micronutrient deficiency in primary school-age children. A study by Bardosono et al[17] on 245 primary school-age children with underweight status in Jakarta and Surakarta shows that about 12% of the children had iron and zinc deficiencies. Southeast Asian Nutrition Survey (SEANUT)[18] research in 48 cities in Indonesia on children aged 0—12 years shows that 55% of the children were anemic, 4.1—8.8% of children suffered from iron deficiency, and 25.2—39.2% of children were stunted. This condition indicates that school-age children are not different from toddlers, who experience the triple burden of malnutrition, with undernutrition, overnutrition, and micronutrient deficiency.

The energy and nutritional requirements of Indonesian primary school-aged children

In the primary school-age period (7—12 years), children's physical growth occurs gradually and continuously. However, their cognitive, emotional, and social development happen very rapidly. Appropriate nutritional intakes are essential for the children to achieve optimal growth, development, and health, as well as to prepare themselves for changes in the body during adolescence.[19]

Nutrients particularly required by primary school-aged children are carbohydrates, proteins, fats, vitamins, iron, zinc and iodine. Carbohydrates are important sources of energy for the body and brain. Proteins are necessary for cell growth and brain development. Fat is a source of energy that helps with the absorption of vitamin A, D, E and K, and brain development, as well as provides good taste in food. Unsaturated fats, which are omega 3 and 6 fatty acids, help with brain development, learning concentration, allergy prevention, as anti-inflammatories, and brain cells protection. Vitamins, especially vitamin A and C, help to maintain immunity. Vitamin D helps with calcium absorption, which is important for bone and teeth growth. Vitamin D also plays as an anti-inflammatory and improves immunity. Minerals, such as calcium, iron, zinc and iodine, are important for bone, muscle, dental, and cell growth, anemia prevention, as well as brain development. Fibers help to maintain gastrointestinal health and help to facilitate bowel movements.[19–21] Energy and nutritional requirements for primary school children must correspond with Indonesian AKG, as stated in **Table 1.**

Regarding special nutrients to support school-age children's physical growth and cognitive development, research by Bardosono et al.[17] on 245 primary school-age children shows that milk supplementation fortified with iron and zinc for 6 months has improved the scores of fast thinking compared to the control group. A systematic study by Falkingham et al.[22] shows that iron supplementation improved children's attention and learning concentration, as well as improved the intelligence quotient (IQ) in school-age children with anemia.

Food that contain both nutrients are listed in **Table 2**. Those special nutrients can be obtained from basic food ingredients or fortified food (e.g. milk or flour).

Factors determining primary school children's nutritional status

The nutritional status of school-age children is affected by several factors, such as adequate nutritional intake, parents' level of education, breakfast habits, and homemade meals they bring to school. According to Riskesdas 2010,[23] 44.4% of primary school-age children consumed food with inadequate energy. About 30.6% of them had protein intake below minimal requirement. There is no national data available on excessive consumption of energy and protein on school-age children.

Study by Syahrul et al.[13] conducted in Makassar, found that there was a significant correlation between mothers' level of education to undernutrition status (*underweight*) in school children. Meanwhile, mothers with a high level of education were significantly correlated to overnutrition status (*overweight*). This suggests that a highly educated mother tends to prevent undernourishment while simultaneously increases their children's risk of having overnutrition since every mother plays a vital role in their child's dietary intake. Wolde et al.[24] indicated that parents with lower level of education tend to have children with undernutrition due to the lack of a healthy lifestyle, including the absence of healthy breakfast with balanced nutrition. Therefore, addressing the level of education alone is not sufficient to overcome nutritional problems. It must be accompanied by an improvement in health and nutrition knowledge.

Concerning breakfast, research by Anzarkusuma et al.[8] indicates that 94.4% of the children stated that they always have breakfast before going to school. Similarly, a study by Nuryani et al.[25] shows that 64.9% of the children always eat breakfast before school. Breakfast supposedly contributes 20–30% of total calorie requirement for a day, or about 300–600 kcal, which in balanced nutrition composition consists of 50–65% carbohydrate, 15–20% protein, and < 30% fat.[20] In general, schoolchildren consume rice, bread, instant noodles, or fried rice as breakfast,[26] of which appear to be lacking in protein,

fiber, iron and vitamins. An example of breakfast menu that fulfills school children's nutritional needs is a portion of fried/uduk/turmeric/white rice, with egg side dish, slices of tomato, carrot, and cucumber, and a glass of milk or fruit juice; or 2 pieces of bread filled with omelette and a slice of cheese, tomato, and cucumber.

To help fulfilling daily nutritional requirements, lunch box meals or snacks sold in school should contribute about 10% of total calorie needs in a day, or about 160–200 kcal. However, research by Anzarkusuma et al.[8] indicates that 79% of school children do not have the habit of bringing their own meals from home. This is similar to a study of school children Serang City that shows only 25% of the children have the habit of bringing homemade meals and only 54% are accustomed to bring their own drink to school. This study also revealed that the common content of their lunch boxes are rice, a side dish, and water. While the 5 preferred types of snacks to buy in school are bread, biscuits, wafers, packaged snacks, and sausages. For drinks, the 5 most preferred types are ice cream, bottled water, bottled tea, carbonated drinks, and unpackaged fruit juice/drink.[9]

The small number of children who bring their own homemade meals to school indicates that they need snacks at school as breakfast substitute in order to be able to meet 20% of their total daily calorie needs (300 kcal). Schools need to provide or sell food with balanced nutrition that can fulfill the calorie needs. Some good examples would be fried/uduk/turmeric rice with side dishes like eggs, fried chicken/nuggets, sausages, sauteed tempeh, sauteed anchovies and peanuts, as well as urap veggies/sauteed kangkung/sauteed carrot and green beans, or fried noodle/vermicelli with side dishes of eggs/nuggets/sausages and vegetables. Examples of snacks are rice cake/rice/pastry/rissoles/fried bread filled with minced vegetable (carrots, beans, etc.), milk and fruit egg pudding, mambo ice with fruit or milk and mung beans, fruit soup with milk and mung beans/chocolate sprinkles/kidney beans topping, or fresh fruit juice with milk and no sugar.

Based on the observation in some schools, school cafeterias and hawkers outside the school sell similar types of food: unhealthy snacks with questionable hygiene that contain food additives (dyes, preservatives, seasoning, etc.). As a result, those food only fulfill the calorie needs but lacking in nutrients, thereby negatively impacting the health and nutritional status of school children. The existence of school cafeteria is expected to help addressing this problem by exclusively providing affordable, healthy and nutritious snacks that the children would like. Healthy means free from various biological contamination (germs and dust) and chemical contamination (food additives),[27] as well as nutritious as it is made from food ingredients that contain complete nutrients required by school-age children. The cafeteria manager can also educate schoolchildren on how to select healthy and nutritious snacks, so they will gradually prefer to buy snacks only from the school cafeteria/canteen.

Conclusion

Primary school-aged children in Indonesia are experiencing triple burden of malnutrition, with undernutrition, overnutrition and micronutrient deficiency. Such problems are due to their lack of appropriate nutritional intakes, parents' poor knowledge on children nutritional needs, absence of breakfast, as well as the availability of unhealthy food and snacks sold at school. Therefore, there is an urgent need to immediately continue the nutritional improvement program in schools that are more practical, independent, and sustainable in order to support the foundation of *Sekolah Generasi Maju* in Indonesia. Recommended activities would be introducing healthy and nutritious ingredients to make snacks sold in the school cafeteria that schoolchildren will like, as well as nutrition education activities for school children and cafeteria/canteen managers.

Table 1. Recommended dietary intakes for school-age children

Age Group (year)	Energy (kcal)	Protein (g)	Total Fat (g)	Unsaturated fat (g)		Carbohydrates (g)	Calcium (mg)	Iron (mg)	Zinc (mg)	Iodine (mcg)	Fiber (g)	Vit A (mcg)	Vit C (mg)	Vit D (mcg)
				Omega 3	Omega 6									
7—9	1650	40	55	0.9	10	250	1000	10	5	120	23	500	45	15
Male														
10–12	2000	50	65	1.2	12	200	1200	8	8	120	28	600	50	15
Female														
10–12	1900	55	65	1.0	10	280	1200	8	8	120	27	600	50	15

Source: Regulation of Minister of Health of the Republic of Indonesia (Permenkes RI) No. 28 of 2019 on the Recommended Dietary Allowances (AKG) recommended for the people of Indonesia[28]

Table 2. Iron and zinc content in food ingredients

Nutrients Nutrient	Recommended intakes based on AKG		Food Ingredients	Household Measurements	Measurement in grams	Nutrient per Household Measurement	Nutrient per gram	Calories
Nutrients Iron (mg)	7—9 yo	10	Chicken liver	1 medium piece	30	2.2	0.07	75
	Male		Tuna fish	(canned)	200	1.5	0.01	116
	10–12 yo	8	Ground	3 ounces	85	2.2	0.03	180
	Female		Spinach	1 cup	30	0.8	0.03	6
	10–12 yo	8	Beet root	3/4 Cup	100	0.8	0.01	43
			Clams	1/2 Cup	90	3.6	0.04	150

Nutrients Nutrient	Recommended intakes based on AKG		Food Ingredients	Household Measurements	Measurement in grams	Nutrient per Household Measurement	Nutrient per gram	Calories
			Mackerel	1 whole piece	90	0.9	0.01	150
			Shrimp	5 medium shrimps	35	0.9	0.03	50
			Mackerel Tuna	1 ounce	100	0.7	0.01	30
			Kidney Beans	2 tablespoons	20	1.5	0.08	75
			Kangkung	1 ounce	100	1.1	0.01	25
			Long beans	1 ounce	100	1.3	0.01	25
			Red spinach	1 ounce	100	3.1	0.03	50
			Katuk leaf	1 ounce	100	2.3	0.02	50
			Snow peas	1 ounce	100	1.5	0.02	50
Zinc (Zinc, mg)	7—9 yo	5	Oyster	1 whole piece	28	12.8	0.46	30
	Male		Clams	1/2 Cup	90	1.4	0.02	50
	10–12 yo	8	Crab	1 medium chicken	30	3.8	0.13	50
	Female		Shrimp	5 medium shrimps	30	1.8	0.06	50
	10–12 yo	8	Skinless chicken	1 medium chicken	40	2.4	0.06	50
			Ground beef	3 ounces	30	3.8	0.13	75
			Kidney Beans	2 tablespoons	20	0.6	0.03	75
			Katuk leaf	1 ounces	100	0.5	0.01	50
			Snow peas	1 ounces	100	1.2	0.01	50

Source: reference no.28–30

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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