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Editorial

How COVID-19 pandemic affect nutritional status

Community Nutrition: Nutrition Through Life Cycle

- Pattern of fiber intake in different socio-demographic settings among elderly in Jakarta, Indonesia and its associated factors
- Investing in adult nutrition to reduce mobility problems in ageing population
- Protein and iron intake adequacy among high school girls in Depok, Indonesia
- Dietary intake and obesity in oil and gas workers: A literature review

Clinical Nutrition : Critical Care Nutrition

- Energy target achievement and its determinants in critically ill COVID-19 patients in Indonesia
- Effects of enteral glutamine supplementation on intestinal permeability in acute pancreatitis: A literature review

Clinical Nutrition : Nutrition & Metabolism

- Effect of intermittent fasting on fat mass and fat free mass among obese adult: A literature review
- The effect of dietary fiber on insulin resistance in obesity: A literature review
- Association between apolipoprotein B and dietary fibers

Clinical Nutrition

- The role of nutrition and pancreatic enzyme replacement therapy in children with cystic fibrosis
- A diagnostic test for malnutrition in adults: mid-upper arm circumference towards body mass index: A literature review
- Probiotics administration as a prevention for postoperative infectious complications in colorectal cancer patients: A literature review

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EDITORIAL

How COVID-19 pandemic affect nutritional status

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The outbreak of COVID-19, a disease caused by SARS-CoV-2, has subsequently forced partial lockdowns in many countries. In the past two years, most preschool, school-aged, and young adults have to do online classes, courses, colleges, jobs and meetings, which may alter their daily life. This include changes in nutritional intakes and physical activities. These changes may result in either increased of obesity or malnutrition. It is well known that obesity and malnutrition may worsen the outcomes of COVID-19 infection. If not infected, they may also worsen quality of life.

Many studies have been done in the past year regarding nutritional behaviors during the COVID-19 lockdowns. A study in Germany to 1964 young adults reported 31.2% of participants had increased the amount of food intakes.[1] In Spain, a study resulted that people consumed 539 kcal more than the recommendation during lockdown.[2] Similar to these studies, a study in Poland showed that 43% and 52% of the participants reported eating and snacking more, respectively.[3]

In Indonesia, COVID-19 has primarily affected food access and causes drop of income. The poor and vulnerable groups have difficulties in affording high nutritional value food thus resulting in, not only decline of food intake, but also lower dietary quality.[4]

Regarding physical activity, a survey study showed 45.6% of 90 participants had low physical activity during the quarantine.[5] On the contrary, a comparative study to 147 Malaysian and 107 Indonesian students showed increased of physical activities in 79.6% Malaysian and 77.6% Indonesian.[6]

In relation to Indonesian children's nutritional status, COVID-19 pandemic disturbs *Posyandu* (small integrated healthcare center for mother and children) activities. This results in delay in detection of malnutrition in children.[7–9] There is also concern regarding the increased of micronutrient deficiencies among children, mainly iron.

Currently, it is still a long journey until the end of COVID-19 pandemic. Global strategy of intervention may be required to combat detrimental nutritional status due to the quarantine.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ORIGINAL PAPER

Pattern of fiber intake in different socio-demographic settings among elderly in Jakarta, Indonesia and its associated factors

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Abstract

Introduction Despite many health benefits from dietary fiber, inadequate intake is prevalent among elderly population. This study aims to obtain the pattern of fiber intake in different socio-demographic backgrounds among elderly in Jakarta area, Indonesia and its' associated factors.

Methods: A cross-sectional study was conducted among elderly aged ≥ 60 years in 5 community health center across Jakarta province. A total of 126 elderly were interviewed using two non-consecutive 24-h dietary recall methods to obtain dietary intake data. Socio-demographic backgrounds on age, sex, education, income, marital status, and energy intake were assessed using structured questionnaire. Mann-Whitney or independent t-test was performed to measure the different of fiber intake in each socio-demographic variable. Linear regression test was performed to analyze the variables that associated with fiber intake.

Results: Majority of 98.4% of elderly have total fiber intake <80% of Indonesian Recommended Dietary Allowance (RDA) with average intake of 6.6 g/d. Lower fiber intake was significantly found in females, widowed/separated, have lower education and income, and have inadequate energy intake. Factors associated with total fiber intake were income (adjusted β=0.20, p=0.01) and energy intake adequacy (adjusted β=0.65 p=0.00).

Conclusion: Fiber intake among elderly in urban area is inadequate and the pattern was worse in the low socio-demographic settings. By this finding, it is important to give priority to the socially disadvantages group when formulating nutrition intervention policy in this population setting.

Keywords dietary fiber, socio-demographic, elderly, Jakarta, Indonesia

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Introduction

Numbers of elderly around the world are rapidly growing. The share on prevalence of this population in the low-middle income country like Indonesia was among the highest. Ministry of Health Indonesia reported that there were 9.03% elderly live in Indonesia in 2017 and projected to reach about 12.9% in 2030.[1] As the capital city of Indonesia, Jakarta province has the second highest life expectancy among other province which was 73.56 years in 2015.[2] In the other hand, social inequity gap in this area was high. Indonesian National Statistic Agencies reported that income per capita inequity in Jakarta was higher than the national number since 2014 indicated by *Gini* coefficient that accounted as much as 0.39 in 2018.[3] Due to many factors affecting health status of elderly that contributed not only physiological factors, but also social determinants, social inequity in urban area could affect health status of elderly living in this area.[4]

Dietary factors play significant roles in the prevention and management of diseases among elderly population. Due to gradual changes in metabolic and physiological function in older age, higher risk to chronic diseases among elderly occurs. Common conditions such as hearing loss, osteoarthritis, lung disease, type-2 diabetes, and neuro function decline were prevalent.[5] In the other hand, dietary fiber intake has been studied to be part of important components in balance and healthy diet practices that support the prevention of chronic diseases among elderly population. Consumption of dietary fiber proven to be associated with the lower risk to cardiovascular risk factors such as type-2 diabetes and chronic kidney disease.[6] In addition, lower risk to depression, constipation, and obesity were also observed to be associated with high intake in dietary fiber in daily basis.[7,8]

The role of dietary fiber in body function was crucial due to its physicochemical components that take part in the digestion processing time and viscosity. The function includes as an effective stool bulkers, modulator of blood glucose level, and lowering blood cholesterol levels.[9] Sources of dietary fiber are commonly found in cereals, vegetables, fruits, and nuts with various range of fiber content. Food sources such as corn, wheat (whole grain), and soy were reported to have high fiber content with more than 10 g fiber in 100 g of edible portion. While among fruits and vegetables group that has high fiber content in 100 g edible portion were bitter gourd (16.6 g), beetroot (7.8), eggplant (6.6), kiwi (3.39), pear (3.0), and strawberry (2.2).[10]

In contrast with the important role of dietary fiber in many metabolic processes, inadequate intake of this nutrient component was found to be prevalent especially among elderly population. Indonesian Dietary Guideline (IDG) gives a recommendation of fiber intake about 25 g/day for men and 22 g/day for women aged 65 – 80 years old.[11] However, previous studies among outpatient elderly in multicenter study and urban elderly in Yogyakarta province showed the average intake of fiber intake was 9 g/ day.[12,13] This number was contributed only around 37% of the Indonesian Recommended Dietary Allowance (RDA). Factors such as education and income have been reported to be correlated with the intake of fiber among elderly.[14–16] However the data on pattern of this food group intake in different socio-demographic settings among elderly in low middle income settings such as Indonesia is still lacking. Information on the fiber intake based on socio-demographic and economic backgrounds are needed to support development that targeted elderly population with specific and appropriate strategies needed. Therefore, this study was conducted to obtain the profile of fiber intake among urban elderly in different socio-demographic factors in Jakarta, Indonesia.

Methods

Subject and study design

The study was designed as a cross-sectional study and participants were recruited from the sub-district community health center. The selection of subjects using community health center was on the basis of that the community health center as the first front line of National Health Insurance (NHI/JKN) program. Thus, elderly that become the member of the program should have register and have regular check up in this facility.[17] We selected five sub-district level of health center (Tanjung Priok,

Palmerah, Johar Baru, Matraman, Jagakarsa) from five urban municipalities based on cluster sampling method.

Participants' recruitment and screening were conducted from July – August 2020 that based on the following criteria: aged ≥ 60 years, residents of DKI Jakarta, and able to follow study protocols. Screening were conducted among 450 elderly from five community health center and 138 subjects were selected, however 12 of them were excluded due to unavalability for the second food recall. Final subjects participated in the study was 126. Minimum total sample size needed was 65 based on calculation to compare differences in fiber intake between two group in several socio-demographic backgrounds using mean and standard deviation (alpha = 0.05, 0.8 power, with reference to previous study by da Silva[18]). Correlation estimation formula was performed to analyze association of independent variables with the fiber intake (alpha of 0.05, 0.8 power, and correlation estimation was 0.3 based on Monsivais and Drewnoski[19]) and minimum sample needed was 85. Therefore, total of 126 subjects participated in the study have fulfilled the required minimum sample size. All subjects have signed a written informed-consent before the start of the study. Ethical permission of the study obtained from by Research Ethics Committee, Faculty of Medicine, Universitas Indonesia and Dr. Cipto Mangunkusumo General Hospital. Additional study permission also obtained from Department of Health and *Pelayanan Terpadu Satu Pintu* (PSTP) of Jakarta province.

Data collection

Field enumerators were recruited to conduct data collection in the field. Selection criteria of the enumerators were based on academic backgrounds and experiences in the field data collection. Training of enumerators was also conducted to standardize the interview protocols and measurement procedures. Before data collection, pre-testing was conducted to give better understanding in each items questionnaire and avoiding leading questions. Revision to interview flow and adjustment with field conditions were taken into the final study protocols.

Dietary assessment

Main variable of fiber intake of the respondent were assessed based on 2 days repeated 24-hour food recall measured on non-consecutive days include weekday and weekend. The first dietary recall was conducted in face to face interview in the health center and food photograph book were used to help subjects remembering and estimating the portion consumed. Second dietary recall was performed by phone in non-consecutive day. Analysis on total number of dietary intakes consumed was conducted using Nutrisurvey version 2007 and Excel Office 2010. Database of the fiber content were derived from US Department of Agriculture (USDA), Food and Agriculture Organization (FAO), and Indonesian food database from SEAMEO-RECFON food database. Using similar databases, vegetable fiber and fruit fiber intake were calculated manually using Excel Office 2010. Vegetable and fruit group classification were obtained based on USDA food group components.[9] Current study also measure total energy intake of the subjects and presented based on percentage of adherence to the Indonesian RDA.

Socio-demographic characteristics assessment

Socio-demographic characteristics measured were age, sex, marital status, education, and income that were interviewed based on structured questionnaire. Age variable were categorized as early elderly (60 – 75 years) or older elderly (> 75 years). Sex measured based on identification card (ID) classified as male or female. Marital status was classified as married/ lives with partner or widowed/ separated. Education were measured based on the last diploma obtained by subjects and classified using indicators of nine years compulsory education by Indonesian government. Income was categorized based on provincial minimum wage in Jakarta in 2020 (4.2 million Rupiah, currency level at USD 1 = IDR 14,732).[20]

Statistical analysis

Data analysis performed using SPSS Statistic ver. 20.0 (IBM Corporation, Armonk, NY, USA). Data on fiber intake in different socio-demographic group

presented presented as mean (standard deviation) for normally ditributed data, while those without normal distributions were presented as median (25th percentile – 75th percentile). We analyzed the difference amount of total fiber, vegetable fiber, and fruit fiber intake in different socio-demographic settings using Mann-Whitney or independent t-test with CI 95% and significant level $p<0.05$. Correlation between continues variable were analyzed using Spearman's correlation. Association of independent variables with total fiber, vegetable fiber, and fruit fiber intake analyzed using linear regression test with CI 95% and significant level at $p<0.05$.

Results

Dietary fiber intake in different socio-demographic settings

Total fiber intake among study subjects were 6.6 g/day (4.5 – 10.1). The average score was not accomplishing the RDA for elderly population group. Number of subjects that have at least 80% adherence with the RDA were only 1.6% (2 subjects), while intake of total fiber 98.4% (124) subjects were below 80% RDA. Intake of vegetable and fruit fiber among subjects was 2.5 g/day and 1.1 g/day respectively. Based on the socio-demographic backgrounds, lower total fiber intake was found among female, widowed/divorced subjects, lower education and income group, and have <80% RDA of energy intake ($p<0.05$ or $p<0.01$). The pattern on vegetable fiber showed similar result with the total fiber intake. While for fruit fiber, significant higher intake was found among high educated and income level group only ($p<0.01$). Distribution of dietary fiber intake based on socio-demographic background of the subjects was presented in **Table 1**.

Factors associated with dietary fiber

Using Spearman's correlation test, we found that income and energy intake variables were correlated with total fiber intake among subjects. The coefficient correlation for income was 0.34 ($p=0.00$) and energy intake was 0.65 ($p=0.00$). After adjustment with sex, marital status, and education in linier regression analyses, the association were remained with adjusted β for income was 0.20 (95% CI 0.00 – 0.00, $p=0.01$ and adjusted β for energy intake was 0.65 (95% CI 0.00 – 0.00, $p=0.00$). For vegetable fiber intake, income and energy intake were variables that showed significant correlation and the correlation coefficient was 0.22 ($p=0.01$) and 0.43 ($p=0.00$) respectively. However, in the linear regression analyses, association of income variable was change (adjusted with age, sex, marital status, and education), thus energy intake was the only variable remained associated with vegetable fiber intake (adjusted β 0.47, 95% CI 0.00 – 0.00, $p=0.00$). Variable of fruit fiber showed significant correlation with income ($r=0.3$, $p=0.00$) and energy intake ($r=0.29$, $p=0.00$) in the bivariate analyses. Variable of income was the only factor remained associated with fruit fiber intake in the linier regression analyses (adjusted β 0.41, 95% CI 0.00 – 0.00, $p=0.00$) after adjustment with marital status and education. Analyses of associated factors with total fiber, vegetable fiber, and fruit fiber intake were summarized in **Table 2**.

Discussion

Dietary fiber intake among subjects in current study was lower compare to study by Setiati et al among outpatient elderly in 15 referral hospital across Indonesia with average fiber intake was about 9 grams.[12] The result were also lower compare to study among rural elderly in Yogyakarta and community elderly in Hong Kong that showed dietary fiber intake was around 8 grams/ day.[13,21] Average intake of total fiber among subjects were only accomplishing 34% than recommended intake in male subjects and 26.3% among female subjects. Inadequate intake of fiber among elderly were faced both in developing and developed country. Country such as Canada and US reported that average intake of fiber among elderly was 14–15 g/ day and thus still not met it's country dietary recommendation.[11] It is suggested that high intake of low fiber content grains such as rice and cooking method like frying would related to the lower intake of total fiber.[10,18] Majority of total fiber intake were contributed from grains, especially whole grains (50%), while vegetables were contributed around 30–40%, then followed by fruit (16%), and 3% were from other

minor sources such as nuts and seeds.[10] However, as most of Indonesian people were using rice as main staple grains, thus contribution to total fiber intake resulted as poor due to low fiber content in this food source.

Regarding gender differences in total and vegetable fiber intake, this study findings were contrary compare to study among elderly in Lebanon that reported that women showed significant better dietary fiber intake than men (9.6 vs 11.6 g/1000 kcal).[22] However, study among high income settings among elderly in UK Biobank data reported similar findings with current study where dietary fiber intake were found to be higher in male subjects. It was reported that women consume more fat, saturated fat, and carbohydrate as the contribution to total energy, thus it could dominating the contribution of fiber sources food consumption in the diet.[23] Another similar result were reported among adults in Philippines where deficiency in dietary fiber and important nutrients (vitamin C, vitamin A, calcium, iron) was higher among females. Food pattern such as low consumption in nutrient-dense food like fruit and vegetables were being highlighted need to be improved especially among elderly, females, and those in low SES.[24] In addition, women were reported have lower diet quality score that mainly contributed from lower variety score and adequacy to dietary fiber, iron, and calcium intake.[25] Similar gender difference was found in vegetable fiber intake among subjects. The possible explanation was contributed from higher adherence in fruit and vegetable intake recommendation in males than females especially among adults population that were maintained into dietary habit in older life.[26]

A social and psychological factor contributes to many health outcomes among elderly population. Dietary pattern was reported to be influenced by factor such as support from family member and feeling of being wanted in the community and the family.[27] In current study, elderly that live with partner or married had better total and vegetable fiber intake than those live single/divorced/widowed. This result was compatible with study among Hong Kong Chinese elderly. It was suggested that having partner or family member at home contributes to better control of nutrition intake such as fiber, calcium, and vitamin D in relation with controlling possible existing diseases condition.[21]

Studies reported that socioeconomic factors such as education and income positively associated with fiber intake both in adult and elderly population.[18,21,28] According to socioeconomic backgrounds, better income and educated subjects showed higher mean of dietary fiber consumption. The condition was similarly reported among Malaysian urban elderly where nutrition knowledge and purchasing choices in low SES settings could attenuated the dietary pattern intake and resulted in decrease consumption of high fiber food consumption such as fresh fruit and vegetables.[29] Current study findings were in accordance with previous study where higher education and income were the factors that showed significant difference in total, vegetable, and fruit fiber intake. Better education were associated with access to information level and better lifestyle choice that resulted in higher total energy and fiber intake among individuals.[12,28] In addition, this study reported that income was variable that associated with total and fruit fiber intake among subjects in the linier regression analyses. There were similar concern reported among adults in Boston, USA study where subjects with higher income reported have higher purchasing power in fiber food sources from fresh products.[30] This findings emphasize that better access in higher income settings could contributed in better fiber intake among individual.

In addition, better adherence to energy intake among subjects reported to be associated with higher total and vegetable fiber intake in current study. It was contributed from better adherence to energy intake could indicates good compliance with dietary recommendation of the subjects, thus better diet quality that high in fiber consumption could positively affected.[26] Higher risk to inadequate energy intake were commonly found among elderly.[12,21] The factors were associated with decrease in several body function such as loss in appetite, difficulties in swallowing, and reduction in nutrient absorption in the body.[27] These condition might lead to decrease in food intake and weight reduction that usually undetected and could cause serious health problems such as decrease in lean body mass (*sarcopenia*) or malnutrition.[31]

The study reported the most recent evidence of dietary fiber pattern in different socio-demographic backgrounds among elderly live in urban area. By these study findings, appropriate public health intervention in nutrition aspect could be developed in relation to rapid changing in social structure that happen in the urban area. The study performed by validated measurement tools and standardized data collection procedures to ensure data quality administration.

However, there were limitations needed to be considered in current study. First, the using of 24-h recall to measure diet quality might not be representative of dietary intake at the individual level. Despite this limitation, the using of the 24-hour dietary recall has been studied to have good reliance to provide accurate estimates of energy and nutrient intake in the population level.[32] In addition, data collection were administered during COVID-19 pandemic, thus behavioral and dietary changes might occurred. Study conducted in Mainland China sample during lockdown period reported that there were reduction of consumption of fresh food such as fruit and vegetables and physical activity level.[33] Thus, it may affect to lower the dietary fiber intake compare to general situation before the pandemic. Considering this effect during pandemic situation, comparison of fiber intake with previous studies among Indonesian elderly have showed that prevalence was commonly low. Therefore, the need of improvement in such an emergency situation should be in higher priority.[12,13]

Conclusion

Low dietary fiber intake was prevalent among subjects in urban area of Jakarta with average intake was 6.6 g/d. The pattern showed that lower intake found in female, widowed/separated, low education and income, and have inadequate energy intake. Income and energy adequacy were factors that associated with fiber intake among study subjects. By these findings, the study highlighted the need for dietary fiber intake improvement among urban elderly in Jakarta and priority should be considered for those among socially disadvantages group. Further investigation in a larger population need to be conducted in the future studies.

Table 1. Pattern of fiber intake in different socio-demographic backgrounds of the subjects[a]

Variables	Total fiber *(g/day)*	p-value	Vegetable fiber *(g/day)*	p-value	Fruit fiber *(g/day)*	p-value
Fiber intake	6.6 (4.5 – 10.1)		2.5 ± 1.6		1.1 (0.0 – 2.8)	
≥ 80% RDA (n,%)	2 (1.6)					
< 80% RDA (n,%)	124 (98.4%)					
Age						
Early elderly	6.6 (4.5 – 10.0)	0.74[§]	2.2 (1.4 – 3.3)	0.17[§]	1.1 (0.0 – 2.7)	0.91[§]
Older elderly	6.4 (2.4 – 11.7)		3.1 ± 1.9		0.7 (0.0 – 3.4)	
Gender						
Male	8.5 ± 3.5	**0.00****[§]	2.9 ± 1.6	**0.01***[†]	1.1 (0.0- 3.3)	0.27[§]
Female	5.8 (3.8 – 8.1)		2.2 ± 1.5		0.9 (0.0 – 2.3)	
Marital status						
Married/live with partner	8.2 ± 3.9	**0.00****[§]	2.5 (1.6 – 3.6)	**0.01***[§]	1.1 (0.0 – 3.2)	0.16[§]
Widowed/divorced	5.8 (3.8 – 7.4)		2.0 ± 1.2		0.7 (0.0 – 2.4)	
Education						
≤ 9 years	6.4 ± 3.3	**0.00****[§]	2.2 ± 1.3	**0.03***[†]	0.7 (0.0 – 2.0)	**0.00****[§]
> 9 years	7.5 (5.5 – 12.1)		2.8 ± 1.8		1.5 (0.0 – 4.4)	
Income[b]						
Minimum wage or higher	11.5 ± 4.4	**0.00****[§]	3.7 ± 2.1	**0.00****[†]	4.4 ± 3.5	**0.00****[§]
Below minimum wage	6.3 (4.2 – 9.3)		2.3 ± 1.4		0.9 (0.0 – 2.4)	

Variables	Total fiber *(g/day)*	p-value	Vegetable fiber *(g/day)*	p-value	Fruit fiber *(g/day)*	p-value
Energy intake[c]						
≥ 80% RDA	10.6 (8.1 – 12.3)	**0.00****[§]	3.9 ± 2.3	**0.00****[†]	1.1 (0.7 – 3.5)	0.28[§]
< 80% RDA	6.0 (4.0 – 8.6)		2.2 ± 1.2		1.1 (0.0 – 2.6)	

[a]Data presented as mean ± standar deviation; median (25th percentile – 75th percentile); or n(%). [b]Provincial minimum wage of Jakarta in 2020 is IDR 4,267,000 (USD 300; currency level at USD 1 = IDR 14,732). [c]Based on Indonesian Dietary Guideline (IDG) for age 65 – 80 years. [†]Independent t-test. [§]Mann-Whitney test. *significant level at p<0.05. **significant level at p<0.01.

Table 2. Associated factors of fiber intake among study subjects[d]

Variables	Unadjusted β[††]	p-value	Adjusted β	95% CI	p-value
Total fiber					
Sex			0.09	-0.52 – 2.02	0.24
Marital status			-0.09	-1.99 – 0.47	0.22
Education			0.06	-0.65 – 1.66	0.39
Income[c]	0.34	**0.00****	0.20	0.00 – 0.00	**0.01***
Energy intake[d]	0.65	**0.00****	0.56	0.00 – 0.00	**0.00****
Vegetable fiber					
Age[b]	0.10	0.25	0.11	-0.01 – 0.08	0.13
Sex			0.09	-0.32 – 0.93	0.34
Marital status			-0.14	-1.04 – 0.17	0.16
Education			0.02	-0.47 – 0.65	0.75
Income[c]	0.22	**0.01***	0.07	0.00 – 0.00	0.41
Energy intake[d]	0.43	**0.00****	0.47	0.00 – 0.00	**0.00****
Fruit fiber					
Marital status			0.03	-0.5 – 0.88	0.66
Education			0.10	-0.03 – 1.17	0.25
Income[c]	0.30	**0.00****	0.41	0.00 – 0.00	**0.00****
Energy intake[d]	0.29	**0.00****	0.09	0.00 – 0.00	0.25

[a]Linear regression analyses were performed with 95% CI. [b]Presented as continues variable age in years. [c]Presented as continues variable in IDR. [d]Presented as continues variable in kkal. [††]Spearman coefficient correlation. *significant level at p<0.05. **significant level at p<0.01.

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Conflict of Interest

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LITERATURE REVIEW

Investing in adult nutrition to reduce mobility problems in ageing population

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Abstract

As people age, most body organs deteriorate. Osteoporosis, arthritis, sarcopenia, muscle aches, low back pain and neuropathy are common mobility issues in the elderly. Body mass index (BMI), physical inactivity, and having comorbidities increase the likelihood to have mobility health problems. One in every ten adults over the age of 45 years in Indonesia develops these mobility problems, and one in every fifteen adults has difficulty in walking/stepping before entering the elderly age. Nutrition has been reported to have important role in controlling weight and physical locomotive organs. Generally, 46% adults in Indonesia have vitamin A deficiency, 70% vitamin C deficiency, 77% vitamin E deficiency, and inadequate calcium intake. Low nutrition intake can result in increasing mobility problems that lead to health issues in the aging population. Dietary strategies are necessary to achieve healthy ageing. Currently, no standardized guideline has been developed for preventing mobility health problems in Indonesia. This calls for urgent need to hinder poor quality of life in elderly population.

Keywords mobility health, nutrition, healthy ageing

Introduction

Ageing is a lifelong accumulation of diverse deleterious changes of physiological functions that are responsible for the increased risk of age-related diseases. Despite genetic factor, having morbidities, poor nutrition, and unhealthy lifestyles contribute to the ageing process.[1] In addition, understanding health status and social service use can predict the levels of disability in the aging population.[2] Strategies to achieve healthy ageing should be performed far before the individuals enter the elderly age, and should take into account the nutrition, lifestyle, and health status in the adult stage.

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Indonesia is one of the world's largest populations and projected to have more than 30% of population above the age of 50. In the current health system, only 25% of these senior adult population are included in the public health programs, and even less (12%) in private insurance policies.[3] Consequently, these increase the likelihood of impairment in the aging population.

Changes in aging body is inevitable. This include loss of muscle mass, reduced bone mineral density and water, reduced function of musculoskeletal and neuromotor. Previous research highlighted the importance of promoting physical activity that would improve the musculoskeletal and neuromotor function in the aging population, compared to those inactive.[4] Starting at the age of 35, joint and muscle pain appears slight, and increases with age. While sarcopenia and osteoporosis are more common in older age, above 50. Indonesian elderly frequently encounter arthritis, osteoporosis, sarcopenia, muscle

ache, and neuropathy.[3] Having muscle and bone problems are linked with mobility issues in the elderly population. Impairment can lead to fatigue, muscle weakness, lower motion, and balance. With poor mobility, people will have difficulty in doing daily activities, resulting in higher independence in elderly age and reduce quality of life.[5]

Most of the times, people with metabolic syndrome and poor diet would also develop mobility disorders. Studies have shown the association between protein, vitamin A, vitamin C, vitamin E, vitamin D, calcium, and omega-3 with mobility problems in later life.[6] Understanding factors contributing to these mobility-related diseases, prevention strategies that emphasizing the needs for dietary intervention would be vital to reduce the disease burden in ageing population.

Mobility problems in aging population

Mobility refers to the ability of an individual to move the body and perform daily tasks. Good mobility is a characteristic of healthy ageing, as described by the World Health Organization (WHO). Lifestyle, climate, diet, and exposure to health hazards would reduce the functional capacity, and eventually affect the mobility.[7] Mobility system consists of bone, muscle, joint, cartilage, tendons and ligaments, supported by the central and peripheral nervous systems. These organs will deteriorate as humans get older. Bone mass decreases after reaching its peak bone mass at 30 years of age and loses approximately 0.3% and 0.5% in women each year. Muscle mass also decreases by approximately 3–8%.[8]

Common mobility problems found in elderly people include osteoporosis (reduced bone mineral density), arthritis (the inflammation of joints), sarcopenia (loss of muscle mass and strength), muscle aches, low back pain and neuropathy. Patients with sarcopenia have higher risk of osteoporosis and lower mineral density, than general population. Osteoarthritis patients would have less muscle strength than normal people.

Locomotive dysfunction can also lead to muscle pain, reduced movement, loss of muscle strength and impaired balance. [9]

Older people experience physiological changes related to age, such as lower bone mineral density and loss of muscle mass. Lack of stamina, exhaustion, weakness, and lack of appetite are common complaints from older people that can lead to immobility and poor diet. Diet and micronutrient status have been extensively studied in the impact of physical and cognitive function. The relationship between micronutrient insufficiency and physical function has been a vicious cycle. It might have short-term and long-term impact on physical well-being, including immobility.[10]

Additionally, chronic diseases, such as hypertension, diabetes, heart disease, and chronic kidney disease are prevalent among elderly people. These conditions are considered as comorbidities that need to be addressed. Nutrition intervention is not only important for preventing mobility problems, but also for improving the overall physical well-being.

Role of nutrition in mobility

Mobility health is not a common term for Indonesians. It is reflected by the mobility-related diseases, such as arthritis, osteoporosis and sarcopenia. The result from Basic Health Research (2018) identified that the incidence of osteoporosis and sarcopenia in people aged between 45 and 60 years old is associated with joint and muscular problems in adults (35 to 45 years). In addition, the number of chronic illness is prevalent among adults and must be treated in older ages (55-64). The disease burden will be higher as mobility issues increase.[3]

In Indonesia, physical activity among adults is relatively poor and trends in adequate physical activity are shown to be steadily declining by age. About 78% of the population between 35 and 39 years was considered physically active, but the percentage fell into 69% in the 60-64 age group. The most popular activity in the 31–59 age group is biking (46%). While walking and jogging opportunities are more favoured in the elderly (60+) population. [3] A study revealed that physical inactivity for two weeks would lower muscle strength by 30%.[11] This also supports the reason why mobility problems arise at 45+ population, and increases with age. [3] The risk of mobility issues in elderly people could also be attributed to insufficient calcium intake and vitamin D deficiency, which is

high prevalent in Indonesia.[6] **Table 1** listed the relationship between nutrients and its function in mobility.

Data in Indonesia revealed that about 34% of both male and female adults in their productive age, and 46 % of those above 55 have protein deficiencies that can affect muscle and bone health. [3] Higher protein intake than recommended daily intake (0.8 g protein/kg body weight per day) can increase the muscle mass, strength, and function in older people. Moreover, it can improve immune status, wound healing and blood pressure.[12] The European Society for Clinical Nutrition and Metabolism (ESPEN) generate recommendations for health care professionals to maintain muscle strength and function in elderly population. It recommends that the diet should contain at least 1.0-1.2 g protein/kg body weight/day for healthy older people, or 1.2-1.5 g protein/kg body weight/day for older people who are malnourished or at risk of malnutrition due to acute or chronic illness. This recommendation should even be higher for individuals with severe illness or injury. In addition, daily physical activity or exercise (resistance training, aerobic exercise) should be performed by all older people, for as long as possible.[16] Protein deficiency has been found to cause several clinical syndromes, but mainly affects skeletal muscles, physical exhaustion, calcium and bone mineral density, and weakness among elderly population. This nutritional problem can occur at any age in any group due to disease or poor diets and is often aggravated by a lack of energy intake. Protein deficiency can also exacerbate other nutrient deficiencies (including vitamin A and iron) and induce metabolic syndromes (diabetes, dyslipidemia, etc.).[17]

About half adult females in the age between 45 and 55; and more than one-third of females aged 60+ had vitamin D deficiency. Vitamin D is important element for calcium absorption and bone mineralization, that positively correlated with bone mineral density (BMD). Age-related reduced bone mineral density begins around the fourth decade, resulting in a steady decline in BMD. This trend is exacerbated even more among females during and up to 10 years after menopause due to estrogen deficiency. Vitamin D deficiency leads to lower absorption of calcium, that eventually would release calcium from the bones. This would increase the risk of fracture, osteomalacia, osteoporosis, diabetes, cardiovascular disease, and rheumatoid arthritis.[13,18] Older people's dietary requirements for vitamin D are higher due to reduced skin development, reduced exposure to sunlight and thinning of the skin. Untreated vitamin D insufficiency increases reduced bone mineral density and thus increases the risk of fracture, but this is exacerbated by aging. Vitamin D and calcium are essential to the mechanical and structural integrity of the skeleton. Calcium metabolism homeostasis is closely regulated by many hormones, of which parathyroid and vitamin D play a key role. Calcium supplementation will not be useful without sufficient vitamin D. [18] More than half of the adults and female had calcium deficiency.[6] An analysis of 20 prospective studies concluded that in postmenopausal women, calcium supplementation decreased the probability of reduced bone mineral density on average by about 1% per year. The combination of vitamin D and calcium supplement would significantly reduce the risk of fractures. This showed that vitamin D and calcium are essential for bone health.[18]

Although Indonesian adults consume a variety of foods, it is not sufficient to meet the micronutrient requirements. This can be explained by lack of nutritional awareness, poor eating habits, low income or low capability to purchase foods.[6]

A research in Indonesia shows that overall nutrient adequacy of micronutrients was less than 100%, with the exception of iron and vitamin A, this might be due to low fruits and vegetable intakes. [3] Male adult nutrient intakes were higher than female, with the exception of vitamin C. Men aged 30-49 years had higher intakes of nutrient than men aged 19-29 years, excluding vitamin A. Women aged 19-29 years of age had higher nutrient intakes than women aged 30-49 years of age, excluding calcium and vitamin A. The nutrient density of calcium, zinc, vitamin C and vitamin A in Indonesian adults falls below guideline, classified as inadequate. The research also shows an adult calcium deficiency prevalence of 54.2%, iron deficiency of 36.4%, zinc deficiency of 74.3%, vitamin A deficiency of 44.8%, and vitamin C deficiency of 71.4%. [6] These deficits are significantly higher in older populations. Calcium and iron deficiency are higher in women than in men. Inversely, the prevalence of zinc,

vitamin A and C in women was lower than men. Zinc deficiency is evident in Indonesian adults. Indonesian study found that 7 in 10 adults have insufficient intake of zinc and vitamin C. This finding was also seen in other developing countries, such as Mali, Africa, which concludes that micronutrient deficiencies are more prevalent in developing countries than in developed countries.[19]

In Indonesia, 46% of adults have vitamin A deficiency, 70% have vitamin C deficiency and 77% have vitamin E deficiency. [3] Vitamin A, C, and E are excellent antioxidants that protect cells from oxidative damage and are primarily determined by dietary intake. Antioxidants can help with inflammatory reactions by inhibiting the development of reactive oxygen species (ROS), by scavenging free radicals, or by eliminating ROS derivatives. Free radicals, ROS and their derivatives may accumulate substantial structural damage, inflammation, and cell death in the synovial joint. Vitamin C (ascorbic acid), vitamin E, thiol (glutathione) or a variety of plant polyphenols may neutralize ROS in the joints and minimize oxidative stress associated with the progression of arthritis.[20] The effects of antioxidants in muscles and joints examined in a cohort study of Framingham Osteoarthritis (OA) with vitamins A, C and E decreased OA progression in the knee. Another Australian study shows that the beneficial impact of vitamin C intake on the reduction of bone size and bone marrow lesions, both of which are significant in the pathogenesis of the knee.[21] Antioxidant vitamins have essential functions to modulate oxidative stress, to participate in immune responses and to contribute to cell differentiation. The potential of antioxidants to neutralize reactive oxygen species (ROS) and oxidative stress is not limited to joints, but cellular in general.[14]

Food plays an important role in controlling weight and physical locomotive organs. Risk factors such as age, low physical activity, comorbidities, and low BMI are contributing to the increase of mobility problems. [6] Polyunsaturated fatty acid (PUFA) intake is very low for adults in Indonesia with only 3.5 percent energy with 6-11 % recommendation. This is due to insufficient consumption of fish and other seafood [22]. Omega-3 have anti-inflammatory effects that protects cell from oxidative stress that has shown benefits for mobility organs. Moreover, The American Heart Association (AHA) recommends suggest replacing unsaturated fatty acids from vegetable oils, fish, nuts and legumes with saturated and trans fatty acids to prevent hypertension, heart disease and cardiovascular disease. [23] The use of PUFA may be beneficial for comorbidities prevention in mobility problems in elderly. [6] Some oligosaccharides, such as fructans, have a potential benefit to the lipid profile in the promotion of cardiovascular disease and other comorbidities. Fructans form of inulin has shown benefits in improving the lipid profile, glycemic levels, insulin resistance, and can be used as a substitute for fatty foods to improve satiety. [15]

Dietary strategies are urgently needed to improve the well-being of adults and older people. Increasing the knowledge, information and retention of healthy diets can improve future mobility outcomes. The study of mobility issues in Indonesia is not well established, and therefore, there are still rooms to explore supplements/medicine to support mobility.

Mobility assessment tools

There are many assessment instruments that commonly used to evaluate mobility and balance among elderly population, such as the Timed Up and Go (TUG) test, Short Physical Performance Battery (SPPB), Dynamic Gait Index (DGI), and Berg Balance Scale (BBS). In fact, these tools differ from each other with regard to their functional level, content, and characteristics. Additionally, the interpretation of results could vary depending on the methodology of recording outcomes. For instance, some tests analyse quantitative measurements, while others focus on qualitative aspects. The Asian Working Group for Sarcopenia 2019 consensus recommends the use of gait test and 5-time chair stand test to evaluate the patient's mobility. Nevertheless, the TUG test is not recommended in the consensus since there are differences in interpreting the etiologies.[24] It is crucial to select an accurate assessment tool in order to properly evaluate the health condition, precisely determine the plan of care, and monitor progress. In order to choose the appropriate assessment test in the research field and in practice, several factors have to be taken into consideration. The tests must be valid,

suitable for the target population, and easy to be implement. [25]

In general, the assessment or screening of mobility may be general or specific to an organ. Overall mobility assessment includes control, balance, durability and feature evaluation. General mobility assessment is good to increase public awareness of early symptoms. However, it might not suitable for clinical setting, which need physical assessment, laboratory investigations, and regular monitoring. General mobility measures such as one-leg steady-state testing, five chairs, regular gait speed testing, locomotive testing, 6-minute walking and rock-port testing are ground-breaking examples of non-course mobility testing, and failure to provide any value or below average indicates practical mobility issues. Nevertheless, we cannot determine the exact etiology of the problem if we used the general assessment tools.[25]

Assessment of mobility problems are based on the diagnosis such as osteoarthritis, arthritis or low back pain with rigorous organ testing or a series of comprehensive physical/radiologic test based on current guidelines available. Risk factor assessment is also performed to understand the likelihood of mobility problems. The risk factors include personal information, history, lifestyle and diet. This should be carried out by healthcare professionals.[30] There is one study in Indonesia that assessed frailty in elderly using hand grip strength and usual gait speed to asses disability but no consensus has been made. The results by Setiati (2019) clearly reaffirm that slow gait speed is closely related to frailty. Walking requires the coordination of various organ systems and consumes energy, thus decreased organ function and increased energy consumption for walking may be reflected through slowing gait speed. Slowing gait speed (<0.8m/s based on 15-ft walking test) is a promising prognostic factor for mobility problems in Indonesia elderly.[31]

Japanese has more awareness in mobility problems way before Indonesia. They conducted a locomo campaign and challenge in 2015 and 2018. Locomo campaign, derived from locomotive syndrome is a campaign to measure locomotion syndrome with serial of test. This campaign obtained the reference value from almost 9000 people in nationwide study. [8] Locomotive Syndrome Test is a series of approaches to the assessment of locomotive failure. It includes a sit-in test, a two-stage test and a self-reported questionnaire. The objective of the two-step test is to assess the weight, strength and balance of the lower limb. This test measures the probability of immobility separately at 70 years of age. In a stand-by test, people must stand on one or both of the four-height stools and stand for 3 seconds after standing up. Two-stage measures the total duration of the two-stage stage of the participant. Both approaches would require only a few seconds and minimal equipment, including an unarmed chair and a measuring device. These physical tests are combined with a self-reported Geriatric Locomotive Functional Scale (GLFS) questionnaire to assess mobility, body pain, daily activity and mental health status. With the national survey, Japan has recently acquired a benchmark of nearly 9,000 people at two risk levels; level 1 (decreased locomotive function) and level 2 (decreased locomotive function).

Sitting and Rest (SRT) is another early screening measure. In this test, stability, balance, motor control and the relationship between muscle power and body weight are measured in a short period of time. SRT is used to measure the number of supports needed to sit and rise from the floor (chest, knee, forearm, knee, thigh, and legs). The SRT score is considered to be correlated with all causes of mortality and relates to mobility of holistic strength, joint and balancing functions. This test may be able to screen Indonesia's population as soon as the movement in this test is surprisingly similar to everyday activities, including religious or religious meetings. The inability/difficulty of rising after sitting on the floor with a crossed leg is a symptom of a mobility problem.[27]

Learning from the Japanese locomotive campaign, the similarity of the movement in religious prayer or reunion can be a way to increase the sensitivity of mobility. Using general mobility tests such as the Sitting & Resting Test (SRT), early screening may involve a step closer to the flow of daily movements in religious prayer or gathering. [32] Early mobility problems may arise when lifting is not possible after sitting on the floor with a bent leg or prostrate position, and when some people prefer to pray with a chair. Hajj and Pilgrims are religious activities with active mobility; therefore, screening is important for health and mobility principles one year before departure, including multiple general

mobility assessments and regular weekly activity guidance. The role of health care practitioners in healthy aging also a critical point to be consider in promoting a favourable health environment and system in Indonesia.[33]

Conclusions

The healthy adult population of Indonesia must be informed and aware of the health benefits of mobility and its relationship with nutrition. Some dietary deficiencies found in Indonesian adults include protein, vitamin A, vitamin C, vitamin E, vitamin D, zinc and omega-3. This dietary deficiency will result in their well-being and impairment in the future. Mobility disorders are mostly the result of metabolic syndrome comorbidities in Indonesia, and food and lifestyle improvements are the only way to avoid them. Prevention and early screening are critical to improve the independence of older people in order to reduce the risk of harm and the potential inability to work. Disability can lead to a lower quality of life, and long-term care is needed to reduce the burden on families and the community by avoiding this impact.

Table 1. Nutrient's function in mobility

Nutrient	Function in Mobility	References
Protein	Promotes muscle protein synthesis and bone metabolism	3
Vitamin D	Enhanced calcium absorption in intestine and bone mineralization	12
Calcium	Important mineral for bone forming Reduce osteomalacia and osteoporosis	13
Antioxidant (Vitamin A, C, E)	Reduce oxidative stress that helps inflammatory reaction such as in arthritis, osteoarthritis	14
Polyunsaturated Fatty Acid (PUFA)	Omega-3 anti-inflammatory effect and reduce oxidative stress Reduce comorbidities that may increase mobility problem risk	6 15

Table 2. Mobility screening tools

Test	Objective	Equipment	Time	References
Two-step test	Locomotive syndrome risk level of 1 indicates that the decline of your locomotive functions has already begun	Distance measurement tool	1 minutes	26
Sit to stand test		Unarmed chair and stopwatch	Few seconds	
Geriatric locomotive function scale		Self assessment	1-5 minutes	
Sitting rising test	Evaluation of Physical Performance, strength, balance	No need	Few seconds	27
One-leg standing test	Evaluation of muscle strength and balance	stopwatch	<1 minute	22
Pick up weight test	Assessment of reach down and pick up	5 kg object	Few seconds	25
5 times sit to stand 5TST	Evaluation of lower limb strength, muscle forces, balance	Unarmed chair and stopwatch	In a short time	
Timed up and go	Assessment of balance and walking ability	Armed chair and stopwatch	Few seconds	
8 Foot up and go	Measurement of power speed, ability and dynamic balance	Armed chair, stopwatch and cone	Few seconds	
Usual gait speed	Evaluation of gait speed	Hallway and stopwatch	Depends on	

Test	Objective	Equipment	Time	References
			walking distance	
Short physical performance battery	Examination of gait balance, strength and endurance	Walkaway, unarmed chair and stopwatch	10-15 minutes	
Tinetti performance assessment	Measurement of balance and gait	Walkway, armless chair and stopwatch	10 to 15 minutes	
Backward walking	Evaluation of mobility sensitively	No need	Depends on distance	
Turn 180	Evaluation of balance and mobility	No need	Few seconds	
Rockport test	Evaluation of physical performance, endurance and mobility	1.6 km track, stopwatch	Depends on the endurance	28
6 minute-walk test	Evaluation of physical performance, endurance and mobility	Hallway and stopwatch	6 minutes	29
Fingertip to floor test	Evaluation of flexibility	Ruler/distance measurement	Few seconds	
Hand grip strength	Evaluation of muscle strength and endurance	Hand grip dynamometer	<1 minute	

Conflict of Interest

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ORIGINAL PAPER

Protein and iron intake adequacy among high school girls in Depok, Indonesia

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Abstract

Introduction: Iron deficiency anemia is the most common type of anemia among adolescent girls. The prevalence of anemia among pregnant women increased from 2013 to 2018, and females age 15-24 years had the highest prevalence of anemia. Therefore, knowing the baseline status of protein and iron intake —particularly animal-sourced protein as the main source of heme iron—is important to design future intervention program. Thus, this study was aimed to assess the protein and iron intake adequacy of High School girls in Depok, Indonesia.

Methods: 211 girls from Senior High School in Depok, Indonesia participated in this study. Subjects were selected using a multi-stage random sampling method. A questionnaire was administered to obtain general characteristics. Dietary intake data were obtained using a 3-day non-consecutive 24hr recall 1 weekend 2 weekdays interview. Anthropometric status was measured and calculated. Data were analyzed using IBM SPSS Statistics 20. Spearman's correlation (significance $p<0.05$) was used to determine the factors related to protein and iron intake.

Results: This population had inadequate intake of energy (97.2%), protein (59.7%), and iron (98.6%). However, intake of fat was higher than recommended in 59.2% of participants. Protein and iron intake were not correlated with age, father's education, mother's education, and the number of household member.

Conclusions: This population had low energy, protein, and iron intake adequacy while 59.2% had fat intake more than recommended. There was no relationship between protein and iron intake with age, father's education, mother's education, and the number of household member. Further studies on factors related to low protein and iron intake are needed to formulate a suitable intervention program.

Keywords protein, iron, adolescent girls, recommended nutrient intake

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Introduction

Adolescence is the period of growth spurt, a period in which the growth is faster than any period in an individual's life except during the first year. Although the rate of growth during adolescence is second to that in infancy, it is greater in duration, and therefore total nutritional requirements during puberty may be greater than during any other period in life[1]. Adolescent girls are particularly vulnerable to malnutrition because they need to meet the body's increased demand due to menstruation and future pregnancy[2].

Iron deficiency anemia is the most common type of anemia among adolescent girls. RISKESDAS results showed that the prevalence of anemia among pregnant women increased from 37.1% in 2013 to 48.9% in 2018. Among those pregnant in 2018, females age 15-24 years had the highest prevalence of anemia at 84.6%[6]. One of the many ways to improve anemia status is by improving the iron intake and protein intake especially animal-sourced protein as the main source of heme iron[19]. Low protein adequacy may also result in low lean body mass, which is associated with many adverse health outcomes in the future like metabolic syndrome and low immunity[2].

The adolescent period is a good opportunity to introduce health intervention to improve anemia status before pregnancy and prevent future health consequences. Therefore, it is important to know the intake of iron and protein of adolescent girls as a baseline for developing an educational intervention[19]. Thus, this study aimed to assess the protein and iron intake adequacy of high school girls in Depok, Indonesia

Methods

This cross-sectional study was a part of a joint study between Universitas Indonesia and RSUI for the development of healthcare in Depok City. Data collection was conducted from October until December 2018.

Participant and recruitment

Subjects of this study were adolescent girls enrolled in Senior High School in Depok. The inclusion criteria were female students attending Senior High School grade 10 and 11. Those with an apparent physical disability, those with medical conditions that cause them to follow dietary protein restriction (i.e. chronic kidney disease, phenylketonuria), and those who were unable to complete the study were excluded from the study. None of the participants were reported being vegan.

The subjects were chosen using multistage random sampling, where sub-districts in Depok City were randomly chosen, then continue the randomization into villages level, high school level, and classroom level. Female students from the chosen class were the subjects.

Instruments

Instruments used to collect the data for this study were 1) structured questionnaire with informed consent for parents or guardian and permission form for students to obtain general characteristics of participants; 2) 24Hr recall form to obtain 3-day 24hr recall 1 weekend 2 weekdays dietary intake data; 3) Food Photograph Book "*Buku Foto Makanan"* from Total Diet Survey of Indonesia 2013 by The Ministry of Health to help estimate the portion during 24hr recall interview; 4) SECA® 876 scale to measure participants' weight, and; 5) Shorr board to measure participants' height.

Procedures

Ethical clearance from the Ethical Committee of Faculty of Medicine, Universitas Indonesia number 999/UN2.F1/ETIK/VIII/2018 and permission letter from local government number 668/AF.1/31/-1.862.9/2018 were obtained before the study began. The data collection procedure started with delivering informed consent to participants and their respective parents or guardian after an explanation about the study. In the case where the subject's parent was not physically available to sign the form before data collection begins, the school teacher in charge of coordinating the study was appointed as the guardian and can give consent for the subject.

Data collection was conducted on sample population with interview using the structured questionnaire, continued with 3-day non-consecutive 24hr recall 1 weekend 2 weekdays and followed by anthropometric measurement of body weight and height.

Data analysis

Data was analyzed using IBM SPSS Statistics 20. General characteristics of the participants were presented in numbers and percentages. Descriptive statistics of macronutrient intake were expressed as median (min-max) and as proportions to total energy intake. Spearman's correlation was used to determine if there were relationships between protein and iron intake with participants' general characteristics. The level of significance was set at $p<0.05$.

Results

General characteristics

Among eight schools chosen to participate, one school refused to participate. Among 3 public schools and 4 private schools that agreed to participate, a total of 211 participants fit the inclusion criteria and agreed to participate in this study. Among all participants, 55% attended public school, 50.7% were in grade 10, and 57.8% were in the Natural Science program. The average first menstruation age of all participants was 12.2 ± 1 years old, with the earliest menstruation experienced at nine years old and the latest at fifteen years old.

Among participants, 73% had normal BMI, 0.9% were very thin, 4.3% were thin, 15.2% were overweight, and 6.6% were obese. Based on the calculation of Height-for-Age, 5.2% of participants were stunted.

Dietary intake was measured using 3 days non-consecutive 24Hr recall interview with one weekend and two weekdays. The median daily energy intake was 1185.8 (497.1-2861.5) kcal. After comparing with their energy requirement, only 2.8% of the population have adequate energy intake. Using the Goldberg cut-off ratio (EI_{rep}/BMR_{est}) of <1.01 for a 3-day 24Hr recall, this study found that 64.5% of participants were underreporting their energy intake.

Table 2 showed that the carbohydrate intake in this population was at the lower end of the recommended percentage of carbohydrate to total energy intake. Fat intake was slightly higher than the recommended percentage of fat to total energy intake. In this population, 59.2% had fat intake more than recommended percentage of total energy intake. Protein intake was within the recommended percentage of protein to total protein intake. Fiber intake was low since it is recommended to consume at least 25g of fiber per 2000 kcal consumed daily.

The recommended protein intake to fulfill maintenance and growth for adolescent girls age 15-18 years was 0.84g/kg body weight/day. In this study, it was found that 59.7% of participants have inadequate protein intake. In this population, calories from protein contributed to 12.8% of total energy intake.

Grains and cereals group (30%) was the highest source of total protein intake in this population, followed by white meat and its products (21.6%), egg and its products (12.1%), soy and its products (9%), red meat and its products (7.8%), aquatic meat and its products (7.5%), milk and its products (6.7%), vegetables (1.7%), nuts and seeds (1.4%), roots and tubers (1.2%), and fruits (1%).

Participants obtain their protein almost equally from both animal (55.7%) and plant (44.3%) sources. Protein intake from the animal source was mostly obtained from white meat and its products (38.2%), followed by the egg and its products (22%), red meat and its products (14.4%), aquatic meat and its products (13.6%), and milk and its products (11.8%) consecutively. Protein intake from plant source in this population was mostly obtained from grains and cereals (69.8%), followed by soy (18.6%), vegetables (3.9%), nuts and seeds (3%), roots and tubers (2.6%), and fruits (2.1%) consecutively.

Median iron intake in this population was 4.3 mg/day. Using MSM (Multiple Source Method) probability approach methods with 10% iron bioavailability for diets rich in cereals but including sources of vitamin C, the prevalence of iron intake inadequacy in this population was 98.6%.

In this population, only one participant (0.5%) reported consuming 2 iron supplementation tablets per day. Two participants (0.9%) reported consuming 1 iron supplementation tablet per week.

The iron supplementation tablets consumed by participants were purchased from a drugstore and the brand they consumed contains iron equal to 30 mg elemental iron per tablet.

In this study, protein intake was not correlated with age (r=0.059, p=0.393, N=211), father's education (r=0.069, p=0.333, N=201), mother's education (r=0.082, p=0.245, N=202) and number of household member (r=-0.062, p=0.366, N=211). Iron intake was not correlated with age (r=0.128, p=0.063, N=211), father's education (r=0.021, p=0.769, N=201), mother's education (r=0.003, p=0.966, N=202), and number of household member (r=-0.034, p=0.627, N=211).

Discussion

This study examined the nutrient intake of adolescent girls attending schools in an urban area of Indonesia. This population had inadequate intakes of energy (97.2%), protein (59.7%), and iron (98.6%). However, intake of fat was higher than recommended in 59.2% of participants.

This population tends to have a higher BMI compared to RISKESDAS 2018 data for adolescent girls age 13-15 years and 16-18 years in West Java Province and nationally and among those living in cities[6]. This population has a slightly lower prevalence of thin and very thin girls and a slightly higher prevalence of overweight and obese girls compared to the RISKESDAS 2018 data.[6]

Looking at the overall energy intake, it was found that only 2.8% of the population have adequate energy intake and 64.5% of participants were under-reporting their energy intake. The average energy intake in this population itself (1241 kcal) was lower than the national energy intake in Indonesian cities at 2108.52 kcal and specifically West Java at 2173.59 kcal, so it was predictable to also have low protein intake.[7]

The under-reporting of energy intake was likely due to the under-reporting of energy-source foods. In our study, we used food photographs to estimate portion size and studies have shown that pictures may lead to under-estimated portion as compared to weighing. A study by Valanou *et al* (2017) found that food pictures may not be appropriate to quantify the intake of amorphous solid foods (i.e pies and pastry fillings) and liquid or semi-liquid foods (i.e porridges)[8]. On the other hand, under-reporting of energy from fat is unlikely to cause energy under-reporting since we have taken into account fat absorption during dietary data entry.

Another explanation for the high number of under-reporting is the possibility that the cut-off used in this study might be inappropriate for this population. One of the limitations of the Goldberg cut-off is that it is only appropriate for individuals who are in energy balance. Therefore, they may not be useful for growing children or adults who are dieting to lose weight.[9]

In this population, more than half of the participants had fat intake contribution to total energy that was higher than recommended. Among the required 30% of fat contribution to total energy intake, it needs to consist of 7-10% of saturated fatty acids, 7- 8% of polyunsaturated fatty acids, 10-15% of single unsaturated fatty acids, and intakes of trans fatty acids must be restricted[11]. Long term high-fat diet might result in alteration of insulin function and obesity. Obese adolescents also tend to stay obese through adulthood. Therefore, fat needs to be consumed within the recommended limit.[12,13]

The average protein intake in this population was around 40.3g which was lower than the national protein intake in Indonesian cities at 64.09g[7]. There were only 40.3% of participants with adequate intake, which was also lower than the national protein adequacy in cities (64.09g) where all were reported to have adequate intake.[7] Despite the low adequacy, the average protein intake (40.3g) was not far from the average protein requirement (43.5g) and animal protein contributed more to the total protein intake in this population.

Adequate protein intake especially of the animal source is important for growth and immunity especially for females due to its micronutrient content that is needed during menstruation and pregnancy.[2,14] Inadequate protein during the adolescent period might put them at risk in later stages of life.[2]

Dietary fiber intake in this population was lower than recommended. Fulfilling fiber intake to a recommended amount is important in the era where adolescent obesity and chronic diseases keep increasing. However, an excessively high-fiber diet may inhibit micronutrient absorption like iron and can also cause inadequate energy intake, therefore

those with very poor diets with foods of low digestibility need to pay attention to their fiber intake.[10]

In this study, only 1.4% of this population have adequate iron intake. Adolescent girls are at risk for the development of iron deficiency anemia due to the high demand for iron during this period, the frequent losses during menstruation, disease-induced malabsorption, and possibly pregnancy[15]. A similar issue about iron was found in Cambodia where iron was the problem nutrient among adolescent girls aged 15 to 18 years, along with other animal-related nutrients like calcium, vitamin B_2, folate, and vitamin A.[16] A study among adolescent girls age 15-18 years in Malang, East Java found that iron and calcium were absolute problem nutrients in the population,[17] indicating the problem that adolescent girls tend to have with iron.

In Indonesia, one of the government's programs to improve anemia was to distribute iron supplementation tablets to female students. Each student receives 52 iron supplementation tablets to be consumed every week for a year. According to RISKESDAS 2018, the majority (77.6%) of adolescents age 16-18 years old received their iron supplementation tablets from school.[6] In contrast to that, in this population, only 3 participants (1.4%) reported consuming iron supplementation tablets, and all of them were purchased from the drugstore. Among these participants, only the participant who consumed iron supplementation tablets daily had adequate iron intake. This low rate of compliance might be due to the data collection method where iron intake data was obtained from 3-day 24Hr recall. Hence, complete history of iron supplementation tablets consumption and source during the past year was not assessed.

Adolescent girls with inadequate iron intake may add further burden to the risk of iron deficiency anemia. Iron deficiency may lead to growth disturbance, decreased cognitive performance, depressed immune function, and increased risk of pregnancy complication.[18]

Adolescents who become pregnant at this period or in the future are even at greater risk of various complications since they must compete with their fetus for nutrients and raising the infant's risk of low birth weight and early death. In Indonesia, pregnant females age 15-24 years had the highest prevalence of anemia (84.6%) compared to other groups.[6] Therefore, it is important to improve protein and iron intake and promote better eating habits among adolescent girls to reach optimal growth, improve cognitive performance, and prevent health risks in the future.[2]

In this study, protein and iron intake were not correlated with age, father's education, mother's education, and the number of household members. Economic status was not assessed in this study.

Protein foods, particularly of animal that is also rich in heme iron, are often linked to socioeconomic status. But regardless of income, Parents with better education tend to be able to provide more nutritious foods due to their ability to choose foods with good nutritional value. In terms of the number of household members, greater family size might decrease the food intake per capita in general, but in some situations, increasing family size itself may indicate higher socioeconomic status. In addition, instead of a total household member, dependency ratio plays a bigger role in determining food intake.[18]

Strengths and limitations

This study used 3-day nonconsecutive 1 weekend 2 weekdays 24Hr recall data which better reflect usual intake. Fat intake was well estimated due to the inclusion of fat absorption during data entry.

However, dietary intake data needs to be analyzed with caution due to the under-reporting of energy intake that was detected in more than 50% of the intake data. Thus, this is the limitation of this study

Conclusions

Due to the low adequacy of protein and iron, these adolescent girls might be at risk for iron deficiency and anemia. Inadequate protein and iron intake are worrying particularly among female adolescents due to the demand for rapid growth during puberty and the loss of blood experienced during menstruation. Further studies on the compliance of iron supplementation and factors related to protein and iron intake are needed to help formulate an accurate intervention program.

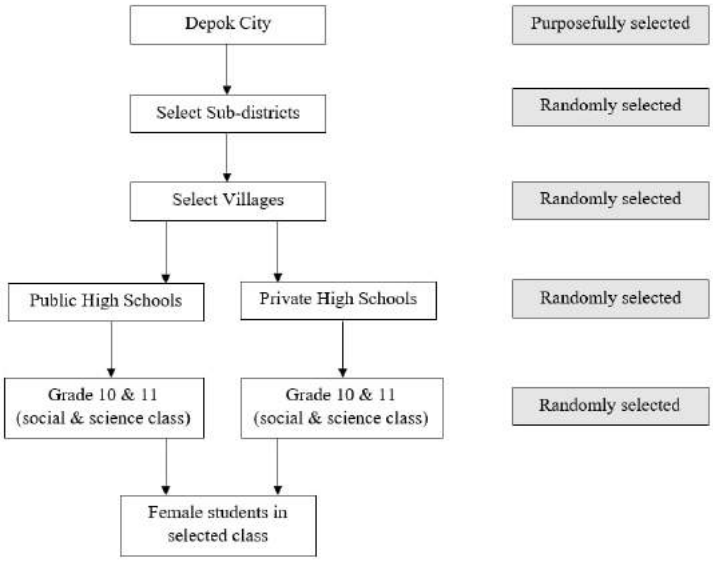

Figure 1. Sampling procedure

Table 1. General characteristics of the participants

Characteristics	n	%	N
Age			
15	130	61.6	
16	77	36.5	211
17	4	1.9	
Father's Education			
No education	1	0.5	
≤9 years	28	13.9	201
>9 years	172	85.6	
Mother's Education			
No education	0	0	
≤9 years	37	18.3	202
>9 years	165	81.7	
Father's Occupation			
Not Working	4	1.9	210
Working	206	98	
Mother's Occupation			
Not Working	12	5.8	206
Working	194	94.2	
Number of household member			
≤4 persons	112	53.1	211
>4 persons	99	46.9	

Table 2. Macronutrient intake of participants (N=211)

Macronutrient	Median (g)	Min-Max (g)	% contribution to energy intake	Recommended % to total energy intake
Carbohydrate	166.3	60.9-375	55	55-70%
Fat	41.2	13.3-121	30.6	15-30%
Protein	38.6	12.7-84.2	12.8	10-15%
Fiber	4.9	1.3-63.1	1.6	5%

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Dietary intake and obesity in oil and gas workers: A literature review

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Abstract

Introduction Working in oil and gas industries was found to be associated with unhealthy lifestyle, obesity, and non-communicable diseases (NCDs). This study aimed to systematically review the dietary intake, obesity status, and identify possible workplace health promotion strategies for oil and gas setting.

Methods: This literature review was conducted through a comprehensive search of Scopus database. Search terms included diet (and synonym), worker (and synonyms), oil and gas (and synonym). The search was limited to paper in English and Indonesian. Combinations of the keyword yielded 76 papers, of which 13 articles were relevant.

Results: Reviewed studies implied that diet consist high amount of fat, particularly saturated fat, and cholesterol, with low intake of dietary fiber. Fatigue, boredom, and inadequate sleep may influence unhealthy food choices. All studies revealed that mean BMI among oil and gas workers was found to be higher than general adult population, ranged from 24 to almost 30 kg/m^2. Possible health promotion components to be modified are knowledge and beliefs, self-care, peer support, food availability and time restriction at cafeterias.

Conclusion: It is confirmed that obesity and NCDs prevalence were high in oil and gas worker, however the updated studies addressing their dietary intake are needed. Health promotion initiative made by oil and gas company are unlikely to be found in scientific paper. There is a need for more health promotion program that scientifically designed so that the outcome and cost effectiveness can be measured properly

Keywords dietary intake, obesity, oil and gas worker

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Introduction

Oil and gas industries play an important role in world economic development. Crude oil and natural gas accounted for 32.0% and 22.2% of the world total primary energy supply in 2017. Industrial use, commercial and public services, transportation, and residential were several sectors of oil and gas consumption share.[1] Because of high demand for flexibility and productivity in oil and gas workforce, workers are usually engaged in 12-hour work schedule with 12-14 days of rotations.[2]

Engaged in shift work has long been identified as occupational hazard, with a rising body of evidence showing an association between shift work and adverse health concern that include metabolic disorder, obesity, and chronic diseases.[3–5] Due to unusual working schedule, shift worker may pose additional risk of unhealthy lifestyle habits, including poor diet.[6] Apart from most common risk of working on shift, they are exposed to stressor that are specific to the workplace setting, such as vibration, noise, adverse weather condition, confined living and working areas that may influence higher risk to metabolic disorder and unhealthy lifestyle.[7] Recent study found that oil and gas worker experienced heavy mental workload and even tends to very heavy.[8]

Study in Italian oil and gas workers showed that during ten years of follow-up, there were significant increase in cardiovascular diseases risk factors, including obesity and hypercholesterolemia.[9] Growing body of evidence revealed that it is easier to find obese worker in oil and gas population, compared to general adults' population.[10–12] Foods in oil and gas workplace are usually available at all hours throughout the days. Plentiful of pleasant energy-dense foods prepared with significant amount of salt and fat are served. Therefore, their diet are known to be high in saturated fat, cholesterol, and sodium.[10] However, studies regarding their eating habits and nutrition intake as the key aspect of obesity prevention were rather limited.

The consequences of unhealthy eating habits and obesity may influence working performance through back pain, stress, and non-communicable diseases.[13] Particularly in petrochemical industries, 80% of obese workers were more likely to have higher absences days per year compared to normal weight employees. This was attributable to illness due to cardiovascular diseases. Around 1.8 million USD of economic lost were attributable to obesity related illness in this population. These impacts will continue to increase unless actions are taken.[14]

Worksite as a place and environment where employees spend significant amount of time and engaged into several habits was a promising setting for health promotion. Workplace health promotion and primary prevention was found to be effective in improving worker health behaviors and clinical outcomes.[15] Moreover, it is positively associated with worker presenteeism[16] and productivity[17]. However, the results were varied based on the study population, study characteristic and methodological quality.[18]

As a leading industry in economic development, oil and gas companies are keen to improve the health of their employees.[14] Therefore, worksite health promotion supposed to be applicable. Furthermore, there were occupational doctor or occupational nurse within the working location[19], increasing the support system of health promotion in this industry.

This literature review aimed to systematically summarize and appraise the literature on eating habits, dietary intake and obesity in oil and gas workers, explore potential variables associated with those habits and identify possible workplace health promotion strategies in this population.

Methods

A systematic search was conducted on 29/07/2020 through Scopus website. The combination of keywords used were: *TITLE (worker OR employee OR workforce) AND TITLE-ABS-KEY ({oil and gas} OR petrochemical OR offshore OR onshore OR {oil industry} OR {oil refinery}) AND ALL (diet OR eating OR {food choice} OR nutrition OR nutrient OR nutritional).*

Studies were considered eligible if they were conducted in oil and/or gas workforce, if the study was targeted both oil and/or gas workers and other workers, only subgroup analyses of oil and/or gas workers included in this research. Studies should be an original research, including but not limited to randomized controlled trials (RCT), quasi-

experimental studies, longitudinal and cross-sectional studies. This review was limited to papers in English and Indonesian. Due to lack of references in the topics of eating habits among petrochemical worker populations, all study fulfilled inclusion criteria and published since the instinctive periods were included in analysis.

Identified studies was then screened based on its title and abstract. Full papers were obtained and assessed for eligibility in the second step of screening. Studies were excluded due to not measured dietary/nutrition outcome (18), not targeted oil and/or gas worker (2) and duplicate studies (6). Snowball checking on the reference list from included studies and manual search on Google Scholar was conducted to ensure that no applicable studies had been omitted.

The publications were classified to two main categories: 1) Studies exploring outcomes regarding dietary intake, 2) Studies exploring outcomes regarding obesity, 2) Studies exploring outcomes regarding the improvement of diet, eating habits and obesity among oil and/or gas workers. The following information was extracted: first author, year of publication, study design, study location, characteristics of participants, diet/obesity outcome and measurements, influencing factor, and key findings.

The methodological quality of each study was assessed using an Effective Public Health Practice Project (EPHPP) "Quality Assessment Tool for Quantitative Studies" that evaluates six main domains: (1) selection bias; (2) study design; (3) confounders; (4) blinding; (5) data collection method; and (6) withdrawals/dropouts, each of which can be rated as strong, moderate, and poor. An overall score was obtained for each study by adding up the separate section rating (see Additional file 1). The literature review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Results

The literature search through Scopus website yielded 76 papers, after first and second screening, 13 articles met the inclusion criteria. Most studies were cross-sectional (8), three longitudinal studies, one experimental study and one qualitative study. Studies were published between 1992 and 2020. The study populations came from different geographical regions: seven were European studies (UK=3, Norway=1, Finland=1, Italy=1, Brazil=1) five were Asian studies (Iran=3, Indonesia=1, Kuwait=1) and one study conducted in Australia. Sample size ranged from 16 to 3282 participants. The study participants were dominated by male with percentage of males ranging from 85 to 100%. The detailed characteristics of study assessing dietary intake shows in **Table 1**.

Dietary intake

Four studies explored dietary intake of oil and/or gas workers (Christina et al 2011; Hassani et al. 2020; Heath et al. 2016; Oshaug, Østgård, and Trygg 1992). Two studies are using one day 24-hour dietary recall (Christina and Sartika 2011; Oshaug, Østgård, and Trygg 1992) and two studies are using a validated semi quantitative Food Frequency Questionnaire (FFQ) (Hassani et al. 2020; Heath et al. 2016).

Regarding the type of foods consumed, the study by Oshaug and collagues [20] found that animal protein sources food, particularly high in meat and low in fish, dairy product and fried fries were important foods in worker's dietary pattern. Two studies (Hassani et al. 2020; Oshaug, Østgård, and Trygg 1992) identified that sweets and snacks, sweetened beverages, coffee, and tea with added sugars were snacking choices among oil and gas population.

The analysis of the diet implied high intake of fat, particularly saturated fat and cholesterol; with low intake of dietary fiber. In line with excessive intake of fats, the availability of fat sources foods in oil and gas setting was also high.[20] Study compared nutrient intake of oil and gas workers with other groups of workers found significant, positive association between job-related factor such as shift schedule, fatigue, and sleep duration with dietary fat intake of workers.[21]

Obesity

Eight studies reported mean Body Mass Index (BMI) and obesity status among oil and/or gas

workers (Al-Asi 2003; Baghshini et al. 2017; Christina, Ayu, and Sartika 2011; Heath et al. 2016; Mannocci et al. 2015; Parkes 2003; Poorabdian et al. 2013; Stewart et al. 2017). All studies revealed that mean BMI among oil and gas workers was found to be higher than general adult population, ranged from 24 to almost 30 kg/m^2. The study reporting lowest BMI was an observative cross-sectional study of UK offshore workers at baseline years of 1984 (24.9 kg/m^2)[10] and the highest reported average BMI was from Iranian male petrochemical workers (29.93±7.3 kg/m^2)[22]. Overall prevalence of obesity ranged from 12.7% from Italian oil and gas and energy company worker[12] to 49.5% from Indonesian onshore oil and gas workers[23]

Observative cross-sectional studies reported that mean BMI and obesity prevalence increased during follow-up period.[10,24] Variables found to be significantly associated with BMI among oil and gas worker were age, gender, marital status, level of education, employment status, type of work, job control, job demand, smoking, physical activity, and dietary intake, however the direction of these associations varied between studies.[12,22–25]

Two studies found that older workers were more likely to have obesity, when compared to younger worker (Christina et al 2011; Mannocci et al. 2015). Nevertheless, one study found distinct results, in UK offshore population, younger workers have higher risk to be obese. Additionally, this study by Parkes[24] also found that workers with lower education and involved in sedentary job were prone to be obese. These results were inconsistent with separates studies that found workers with higher level of education[23] and worked in the field[25] have higher risk of obesity, compared to workers with lower education and office workers, respectively.

Improvement of dietary intake and obese status

Three studies investigate the efforts to improve diet, eating habits and obese status among oil and/or gas workers were identified. All three intervention were formed nutrition education/consultation session in the workplace, but in different strategies (Hassani et al. 2020; Talvi, Järvisalo, and Knuts 1999; Viterbo et al. 2019).

The study by Talvi et al[26] gives a counselling session designed based on workers' health needs. This prospective cohort study was well received by the company, however for three years follow-up only physical fitness improved, there were no significant changes in dietary habits and obesity.

The study by Viterbo et al[27] aimed to increased health self-care of workers towards annual interdisciplinary health promotion sessions for four years. Groups receiving health promotion showed significant improvement in physical activity, the obesity prevalence was decreased, but not significant.

The study by Hassani et al[28] have shortest periods, three months. However, the quality of this study was better, since this study was developed as a randomized clinical trial study. Education sessions was not only targeted the workers, but also their family. Intensive meetings with nutritionist during that amount of time and massive follow-up resulting significant improvement in nutritional knowledge, dietary practices, body weight and BMI.

Discussion

Based on available literature found in this review, the population of oil and gas workers from both developed and developing countries were engaged into poor diet quality, high prevalence of obesity and high risks of NCDs. Included studies identified association between obesity and age, gender, marital status, level of education, employment status, type of work, job control, job demand, smoking, physical activity, and dietary intake, however, the direction of these associations varied between studies. Potential intervention to improve diet, eating habits and obesity among oil and gas workers consist of informational messages, behavioral and social skills, environmental changes, and policy.

Decades ago, study already predicted that dietary patterns of oil-worker may contribute to the development of coronary heart diseases.[20] Unfortunately, dietary assessment was not common to be assessed compared to BMI or anthropometric measurement, in spite of the close association between diet and BMI. Given that the most existing studies were cross-sectional, we assumed that the limited time and resources were obstacles to obtain a valid dietary data.

Nevertheless, from those limited data we managed to summarize similar patterns that the diet

of oil and gas workers consist of high intake of fat and low intake of fiber. Latest systematic review about shift work and eating habits corresponds these finding, additionally, this review managed to conclude that shift worker has poor diet quality with altered meal patterns such as skipping some meals and eat more food at unusual times.[6] However, another systematic review shows that the energy and macronutrient intakes of shift worker were not different with day workers. This review suggest that it could be the meal timing, food choice and energy distribution between meals that varies between shift workers and fixed day workers.[29]

Contribution of total fat (saturated fat) towards energy intake (%) from Norwegian oil-worker, Indonesian onshore oil and gas worker, and Australian oil and gas worker were 44.0 (17.0), 32.7, and 34.5 (14.1), respectively. Meanwhile daily cholesterol and dietary fiber intake were 755mg and 19g; 366mg and 13g for Norwegian and Indonesian oil and gas workers, respectively [20,21,23]. Intake of other nutrients may be unique and specific to the country characteristic, for instance most of the Norwegian oil-workers consumed calcium and vitamin D at its recommended amounts (or above), when it is not the case for other countries.[20]

Dietary fiber intake was half of the recommended value and percentage of saturated fat intake was exceeded its recommended intake (≤10% of energy).[30] While compared to other worker, this value was slightly lower than night shift worker. Oil and gas worker usually have 12-hour long working hours for 12-14 consecutive days, being attached to those shift and rotation found to be associated with adverse lifestyle habits such as lack of sleep and excess fatigue that resulting poor dietary intake.[21] Additionally, the results from qualitative study shows that workers were less likely to eat healthy food if they were tired or bored.[19] Moreover, this could be a two direction of association since a cohort study found that being overweight and obese were associated with higher job demand and low control towards their jobs (poor job strains) that linked with fatigue and depression.[22]

Recent systematic review revealed that engaged in shift work had negative association with nutritional intake.[3] It is increased the possibility of being overweight/obese with overall odds ratio was 1.23 and higher chances to develop abdominal obesity.[5] Probably due to unhealthy sleeping habits and eating at abnormal circadian times that resulting alteration in metabolism pathways, shift worker also has higher risk of diabetes and cardiovascular diseases.[31] Another systematic review also found significant relationship between obesity, binge eating and depression.[4] These findings, implied that when aiming to improve dietary habits of workers, it is important to maintain optimal sleep quality and physiological health of workers', for instance through fatigue and workload management.

The outcome measurement of obese status differed between one study that used BMI cut off for Asian population (Obese: BMI≥25)[23], while the rest of studies used BMI cut off for general population (Obese: BMI≥30). Measurement of central obesity was less discussed, although some studies measure workers waist-circumference. Several demographic variables were found to be significantly associated with BMI, non-communicable risk and its prevalence, indicated the needs of early and routine NCDs risk assessment among workers.[12,22–25] A systematic review and meta-analysis show that health checks are associated with little but significant improvement in total cholesterol, systolic and diastolic blood pressure, and body mass index, particularly among those who were high risk.[32]

In recent years, oil and gas companies were invested in worksite health promotion initiative aimed to improve workers' health and well-being including diet and nutrition. However, the evidence is rather limited. Some results published in projects book and reports[33–35], and other initiatives probably remain unpublished, therefore cannot be included in this review. There is a need for collaboration between the companies and academics to design the health promotion program based on evidence, so that the outcome and cost effectiveness can be measured properly.

Three papers investigated the effect of education/counseling in oil and gas workers was identified. A qualitative study on offshore oil and gas worker in Scotland highlighted that knowledge and beliefs about consequences of outcomes related with healthy eating may influence their food choices. For instance, when workers believe that poor sleep quality is related with unhealthy eating habits, it may increase the possibility of eating healthily.[19]

Among reviewed studies, two longitudinal studies found significant improvement in physical activity/physical fitness but not in dietary intake and obese status. These studies were provided counseling sessions that cover multiple aspect of health promotion, including nutrition and physical activity.[26,27] The third study was a randomized clinical trials (RCT) on nutrition education targeting workers and their family, after 3-month of follow-up there were significant improvement in dietary intake, body weight and BMI.[28]

The prospective cohort study in Finland oil refinery employees was give the intervention group 2-hour lecture session in energy intake and consumption, BMI, metabolism of macro and micronutrient, and healthy cooking methods delivered by occupational health nurse. Printed education materials were distributed after the course, however the monitoring of diet during 3-year of follow-up was not further discussed in the article. Compared to one shoot nutrition education, physical activity training in this study was more extensive, consist of 20 weeks of training guided by instructor at the beginning of the study and measurement of physical fitness every six months.[26]

Similar concern was identified from Brazilian oil workers cohort study. During the four-year of interdisciplinary health promotion strategies, each year, workers only received one consultation session with nutritionist on their food profiles and how to improve its quality. The counseling session was insisted to increase workers self-care towards their health.[27] Contrary to that, an RCT targeted Iranian oil and gas workers gives five nutrition education session through lecture and group discussions. The study was conducted for three-month period. When there was no education session throughout the week, question and answer sessions and telephone follow-up were conducted to strengthen workers understanding towards education materials.[28] This study resulted in significant improvement in nutrition knowledge and CVD risks related outcomes. However due to relatively short follow-up durations, the probability of weight regains, and relapse of unhealthy behaviors could not be identified.

The results from longitudinal and experimental studies indicated that worksite health promotion should not be established as one shoot projects, but to be inserted as a continuous process that attached to workers daily life. Aside from modifying workers knowledge and beliefs towards education and counseling, the finding from reviewed cross-sectional studies give hints on the modifiable worksite related factors that could be improved the diet, eating habits and obese status among workers, including peer influence, food availability, and self-care.

Social influence was one of the behaviors change domains identified in oil and gas workers. Both negative and positive influence from peers were affecting their exercise and eating habits. In the case of positive influence, motivation from colleagues, the availability of supportive partner while exercising and healthy eating play an important role.[19] A randomized controlled trial in Malaysian obese adults worked in the university show that compared to nutrition counseling, group support lifestyle modification was more effective in achieving weight loss, improving self-efficacy towards their weight, friend social support, and quality of life.[36]

Promotion of health self-care is suggested, particularly for offshore worker that live in remote or isolated environment. Workers willpower to eat healthily and to exercise regularly, including setting goals, planning and self-monitoring helps worker to be prepared and stay on track. For instance, bring their own healthy snack, records their calories intake and exercise history were found to be important in order to survive in the obesogenic environment of offshore lifestyle.[19]

Foods in oil and gas workplace are usually available at all hours throughout the days. Plentiful of pleasant energy-dense foods prepared with significant amount of salt and fat are served.[10] It is natural to grab the nearest available food when in hunger, therefore food provision is a key influence on workers healthy eating behavior. To make healthy food available and probably restrict eating times were suggested to positively impact eating behavior.[19] Improving healthier food choices at work found to be effectively increase fruit and vegetable consumption, reduce fat intake, promote weight loss and reduce blood cholesterol level.[37] However, changes in environmental conditions, both to make healthier food available and provide comfortable exercise facility are considered

expensive than informational and behavioral strategies. Therefore, cost-effectiveness analysis is needed prior to these environmental changes.[38]

Conclusion

To summarize, the analysis of the diet implied high intake of fat, particularly saturated fat and cholesterol; with low intake of dietary fiber. Type of food frequently consumed by workers were animal protein sources food, particularly high in meat and low in fish; sweets and snacks, sweetened beverages, coffee, and tea with added sugars. Fatigue, boredom, and inadequate sleep may influence unhealthy food choices. Potential intervention to improve diet, eating habits and obesity among oil and gas workers identified in this review consist of three main components[38]: (1) Informational messages, improve knowledge and beliefs through education, counseling, and other delivery methods; (2) behavioral and social skills, promote health-self-care, family and peer supports, (3) environmental changes and policy, provide healthy food options, cafeterias time restriction and exercise facility. Finally, it is worthy to note that worksite health promotions are potential to improve nutrition, physical activity, and health related outcomes.

This systematic review provides snapshots of diet, eating habits, and obesity among oil and gas worker, and its possible improvement strategies. Although there seems to be several studies reviewing diet and obesity in workers, we manage to emphasize the review of this aspects in rarely studied oil and gas population since the beginning of time until the recent published study. However, we must confirm that there are still many research gaps, including the lack of longitudinal studies on dietary patterns and nutrient intake and scarcity of RCTs in this populations. Ten from thirteen included studies focused on populations in developed countries, which may receive universal health coverage and better-quality health services that may be counteracted workers lifestyle habits. Other limitation relates to the screening, and language. Screening of articles was performed by one author. Several article in Italian and Chinese language was unable to review due to language restriction. Moreover, as in most review studies, publication bias might be an issue.

Table 1. Studies exploring factors influencing diet, eating habits in oil and gas workers

Author (year)	Study design (sample size)	Population	Assessment of dietary intake	Description of worker's dietary intake	Influencing factors
Oshaug *et al* (1992)	Cross-sectional (n= 203, 4% females)	Offshore worker in North Sea oil installations, **Norway**	standard 24 h dietary recall, and additional questions regarding underlying factors influencing the diet.	Type of food found to be important in workers diet were meat, vegetables, fresh fruits, seafood, fried fries, eggs, and ice-cream. Coffee, fruit juice and soft drinks were frequently consumed beverages. Workers average daily intake of energy was 2916±69 kcal, contributed from 44% of fat, 39% of carbohydrate, and 17% of protein intake. Workers diet was high in fat and cholesterol but low in dietary fiber.	High contribution of fat towards energy in the 5-month food stocks.
Christina and Sartika (2011)	Cross-sectional (n= 378)	Onshore oil and gas workers, **Indonesia**	One-day 24 dietary recall	More than half of workers consumed total fat higher than its recommended value, almost half respondents consume >300 mg of cholesterol/day and only 12.4% workers have adequate intake of dietary fiber.	Multivariate analysis showed that age, level of education, employment status, energy, carbohydrate, and dietary fiber intake were associated with obesity.
Health *et al* (2016)	Cross-sectional (n= 131, O&G worker=28 male and 4% female)	Workers engaged in shift work schedule, **Australia**	Validated semi-quantitative self-administered food frequency questionnaire (FFQ)	Contribution of fat and saturated fat towards energy intake among oil and gas workers were exceeded the recommended value (34.5 and 14.1%, respectively) however its slightly lower than other shift workers (printing, postal and nursing).	Multivariate analysis showed that sleep duration, fatigue, and shift schedule were associated with dietary intake of shift workers.
Smith *et al* (2018)	Qualitative semi-structured telephone interview (n= 16)	Offshore oil and gas workers, **Scotland**	Qualitative interview	Living in the offshore settings and attached to the unhealthy lifestyle habits was an automatic process, however workers perceived that eating patterns and physical activity were behaviors that required to change.	Knowledge, intentions, memory, attention and decision-making process, environmental context and resources, social influences, emotional and behavioral regulation were associated with those behaviors.

Table 2. Studies exploring obesity in oil and gas workers

Author (year)	Study design (sample size)	Population	Obesity prevalence	Findings
Parkes (2003)	Cross-sectional (n=1581) and longitudinal (n= 354)	Male offshore workers, United Kingdom (UK)	The prevalence of obesity and overweight in baseline were 7.5 and 47.3%, respectively. Mean BMI and obesity prevalence were significantly increased for 10 years follow-up. Baseline and end line BMI (kg/m^2) were 25.6±2.8 and 26.6±2.9, respectively.	Non-smokers, sedentary jobs, lower education, younger workers and those who are married have higher Body Mass Index (BMI).
Al-Asi (2003)	Cross-sectional (n= 3282, 15% female)	Oil workers, Kuwait	Overall prevalence of overweight and obesity among workers was 75%, based on gender, the prevalence was higher in male workers (79%) than females (56%).	Looking into the type of work, overweight and obesity level was higher in field workers (78%) than office workers (72%). Among those type of workers, field workers have higher prevalence of physical inactivity and diabetes (65% and 18%, respectively) than office worker (56% and 15%, respectively).
Poorabdian (2013)	Cohort (n= 500)	Male petrochemical workers, Iran	Mean BMI of workers was 29.93±7.3 kg/m^2	Overweight and obese workers were having higher job demand and low control towards their jobs. A significant association was found between job control and demand with cardiovascular risk factors including BMI, hypertension, hyperlipidemia, and smoking.
Mannocci *et al.* (2015)	Observative cross-sectional (n= 1073, 1% female)	Oil and gas and energy company workers, Italy	The prevalence of overweight and obesity was 49.7 and 12.7%; hypertension 35.5%, high Fasting Blood Glucose (FBG) 3.0%; high cholesterol and high triglycerides 24.3 and 29.7%, respectively. Mean BMI was 26.26±3.4 kg/m^2.	Major cardiovascular risk factors were significantly higher in older group and its worsened by age, shown the needs of early risk assessment among this population.
Stewart *et al* (2017)	Observative cross-sectional (n= 558)	Male offshore workers, **United Kingdom (UK)**	Compared to anthropometric surveillance data of UK offshore workers 30 years ago, today workers experienced increased body weight (+13.9 kg), body height (+3.1 cm) and mean BMI (kg/m^2) changes from 24.9 to 28.1, escalating obesity and overweight prevalence by 6 and 24%, respectively.	This could be contributed to the obesogenic environment of offshore workplace, including 24-hour availability of energy-dense and appetizing foods accompanied by mechanization at works.
Baghshini *et al* (2017)	Cross-sectional (n= 670)	Male gas refinery employees, **Iran**	It is easier to find gas refinery employees with Metabolic Syndrome, obesity, abdominal obesity, high FBG and high Blood Pressure (BP) compared to workers in nonindustrial environment. Mean BMI of gas employees was 26.47±3.9 kg/m^2.	Possible internal and external causes including air and chemical pollutants, exposed to noise and heat, and lifestyle habits particularly dietary intake, physical activity and sleep patterns.

Table 3. Studies done to improve diet and obesity status in oil and gas workers

Author (year)	Study design (follow-up)	Population	Grouping	Main results
Talvi e*t al* (1999)	Prospective cohort (3 years)	Employees in oil refinery, **Finland**	**Group A** (n=365): received special counselling according to their needs based on previous health assessment in the areas of dietary habits, obesity, blood pressure and/or serum lipids from regular staff (occupational health nurse and physician). Workers also received personalized exercise plan made by external physical fitness instructor. **Group B** (n=433): Worker that participated in health assessment and received written results with printed health promotion (HP) material	The counselling effectively improved Group A's physical fitness, while there were no changes in Group B. Explanatory variables for physical activity were level of education, value tending of health and participation in the counselling. During a three-year follow-up there were changes of worker HP needs. However, the assessment of HP needs only occurred once in the beginning of the study. **Author conclusion:** The study has high participation rate and low drop-out rates, workers also show positive attitude toward health promotion, however the changes of behaviors were uncertain.
Viterbo *et al* (2019)	Retrospective cohort (9 years)	Male workers in oil industry, **Brazil**	**Intervention** (n=1736): Worker in Bahia that received interdisciplinary health promoting strategies during annual medical assessment aimed to improve workers self-care towards their health and control the development of non- communicable diseases. **Control** (n= 54211): workers in Brazil excluding those in Bahia	Intervention group showed significant decrease in number of smokers, periodontal disease, absence days and increase in number of physically active workers. Small improvement in obesity status and hyperglycemia. However, there were no changes in blood pressure and coronary risks. **Author conclusion:** Interdisciplinary health promotion based on population needs associated with improvement of health and productivity.
Hassani *et al* (2020)	Randomized clinical trial (3 months)	Male employees with dyslipidemia in petrochemical company, **Iran**	**Intervention** (n=48): workers received routine medical care and five education session delivered by registered nutritionist covered three main topics (1) cardiovascular diseases (CVD), obesity and weight management (2) healthy diet and physical activity (3) conducted for family member about their roles to support workers health. **Control** (n=43): workers received routine medical care	The education brings improvement in fasting blood sugar and homocysteine, significant decrease in body weight and BMI (but not in body fat percentage) and positive effects in the nutritional knowledge and dietary intakes. After the interventions, there was significant declines on education groups unhealthy food consumption, such as sweet and pastries, soft drinks, and sugars. **Author conclusion:** Worksite nutrition education session was beneficial to improve knowledge and control the CVD risk factors.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ORIGINAL PAPER

Energy target achievement and its determinants in critically ill COVID-19 patients in Indonesia

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Abstract

Introduction. Achievement of energy target in critically ill Covid-19 patients in Intensive Care Unit (ICU) is challenging. This study was aimed to depict the possibility of achieving energy target and its determinants in critically ill Covid-19 patients.

Methods. A cross sectional study was conducted in ICU of dr. Kariadi Hospital Semarang, Indonesia. Secondary data were obtained from Covid-19 patients who were in ICU for minimum 3 days, from March to December 2020. Data collected included age, sex, Body Mass Index (BMI), comorbidities, Modified Nutrition Risk in Critically Ill (mNUTRIC) score, energy intake, route of nutrition delivery (enteral or combination of enteral and parenteral nutrition), lactate status, ICU length of stay (LOS), duration of mechanical ventilator and mortality. Risk Prevalence calculations were conducted to measure risks. Variables with significant associations and p< 0.25 were included in multiple logistic regression.

Results. A total of 188 subjects were included in the analysis. Most patients were male (62.8%) and obese (61.8%). As much as 56.9% patients were able to achieve energy target of 20 kcal/kgBW on day 3 of ICU stay. Those with low risk mNUTRIC score and nutrition delivery was through enteral and parenteral route were more likely to achieve target energy of 20 kcal/kgBW in the first 3 days in the ICU.

Conclusions. Achieving energy target of 20 kcal on day 3 of ICU stay for critically ill Covid-19 patients is feasible. Low mNutric score and nutrition delivery through enteral and parenteral route were two determinants for the achievement.

Keywords energy target in ICU, mNutric score, early nutrition in ICU, Covid-19

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Introduction

Achievement of energy target during the first week of ICU stay is mandatory for better outcome. Several factors determine the achievement, putting unstable hemodynamic and gastrointestinal intolerance as pitfalls in reaching energy target. Factors associated with hemodynamic such as vasopressor dose, lactate level, the use of mechanical ventilator may affect energy intake. Other factors such as age, comorbidities may also contribute to failure of energy intake achievement. Nutritional screening tool for ICU patients, Nutric score, often shows association with ICU outcome.

Feeding patients with vasopressor is possible. Previous study reported in critically ill patients with vasopressor, enteral feeding can be started when the dose is low-medium or decreased by time.[1] High lactate level indicates the presence of splanchnic hypoperfusion and thus feeding intolerance.[2] The use of mechanical ventilator indicates perfusion problems and may lead to disruption of feeding.[3]

Route of nutrition administration determine the success of energy target achievement. In non-intubated critically ill Covid-19 patients, semi solid oral diet may be administered. Oral Nutrition Supplement (ONS) was advised for those who cannot obtain energy target due to shortness of breath. Patients with High Flow Nasal Canule (HFNC) need to be assessed and monitored closely for fulfillment of energy and nutrients target from oral intake. Tube feeding or ONS can be initiated for patients with HFNC when chewing foods caused dyspnea. Early enteral nutrition is also recommended for patients who proceed to mechanical ventilation. When all measures have been conducted and energy intake remains inadequate, early parenteral nutrition is acceptable for any critically ill covid-19 patients.[4]

The amount of enteral nutrition administered for critically ill covid-19 patients is of interest. Energy need in the ICU is suggested to be determined by using indirect calorimetry. In hospitals where indirect calorimetry is unavailable, prediction equation may be used. During early period, ESPEN recommended energy supply to start with 20 kcal/kg BW/day, increased to 50-70% in the following day and reached 80-100% predictive energy at fourth day of ICU stay.[4] A recent study measured REE in 22 intubated covid-19 patients reported that median REE of patients were 19 kcal/kg actual BW in first week of ICU stay. These numbers were slightly lower in obese patients either using actual or adjusted body weight measurement. [5] Another expert recommended a steeply increased energy prescription from 10 kcal/kgBW on the first day, 15 kcal/kgBW on the second day and 20 kcal/kgBW on the third day.[6]

Regardless the increasing number of available guidelines for ICU Covid-19 patients, there have been limited studies which depicted application of nutrition therapy for these patients. This study was aimed to measure risk factors for energy target achievement in critically ill Covid-19 patients in Indonesia.

Methods

Study design and subjects

A cross sectional study was conducted in the ICU dedicated for Covid-19 patients in dr. Kariadi General Hospital, Semarang, Indonesia. Inclusion criteria were all confirmed Covid-19 patients who were in ICU for 3 days or more from March to December 2020. Exclusion criteria were patients with unstable hemodynamic or massive upper gastrointestinal bleeding.

Data collection and definitions

Data collected secondarily from e-medical record. Data obtained included characteristics of subjects such as age, sex, BMI, ICU length of stay (LOS) and mortality. Data for age and sex were obtained from patients' ID card. BMI (Quetelet index) of patients was calculated using formula Weight(kg)/height^2(m^2). ICU LOS was calculated from ICU admission until patients died or were allowed to be transferred to ward. Mortality was recorded as whether a patient transferred alive or died at the end of ICU stay. Other data collected for analysis were energy intake, route of intake, comorbidities, mNUTRIC score, dosage of vasopressor, the use of mechanical ventilator, lactate level.

Dependent variable was the achievement of energy target which was defined as whether a patient

achieved energy intake of 20 kcal on day 3 of ICU stay. This target based on a guideline for energy requirements of critically ill Covid-19 patient during early period in the ICU.[6]

Independent variables included route of intake, comorbidities, mNUTRIC score, dosage of vasopressor, the use of mechanical ventilator and lactate level. Route of intake was divided into enteral nutrition only and combination of enteral and parenteral nutrition. Comorbidities was defined as the presence of minimal 1 comorbidity at the time of admission, either reported by family or from previous medical record. mNUTRIC scores were calculated during the first 48 hours of ICU admission. Dosage of vasopressor was the maximum dose used during the period of ICU stay. It was categorized high when norepinephrine dose was more than 0.3mcg/kgBW or combination with other vasopressors such as dobutamine and vasopressin. Vasopressor dose was categorized as low if only norepinephrine was used and with dose 0.3mcg/kgBW or lower. [1] Use of mechanical ventilator was recorded as the number of days a patient was on mechanical ventilator during ICU stay. Lactate level that was measured in the first 3 day was used as variable in this study. It was categorized as more or less than 4 mg/L.

Statistical analysis

Data analysis was performed in SPSS 11 program. Nominal data were presented as frequencies while numeric data were presented as mean and standard deviation (SD) or median and interquartile range (IQR). Risk Prevalence was calculated for each independent variable. Further analyzed using multiple logistic regression to seek significant risk factors. Ethical Clearance has been obtained from Health Research Ethics Committee of RSUP dr.Kariadi Semarang no.531/EC/KEPK-RSDK/2020. Informed consent was not obtained as this was a retrospective study using secondary data from e-medical record.

Results

A total number of 188 eligible subjects out of 191 patients who were admitted to ICU from March to December 2020 were included in the analysis. **Table 1** depicted characteristics of our subjects, which showed that more than 30% subjects were elderly. Our patients were mostly male (62,8%) and obese (61.8%). A small number of subjects were undernourished based on BMI. Type 2 Diabetes Mellitus and hypertension were the two most frequent comorbidities observed in our subjects, followed by cardiovascular/ cerebrovascular diseases and chronic kidney disease. A small proportion of subject were pregnant women with hypertension and pre-eclampsia/eclampsia. According to mNutric score which was calculated in the first 24 hour of ICU admission, only 15% of our patients were admitted to ICU with high nutritional risk. Most of our patients were reported to have short period of symptoms before hospital admission and thus, a relatively fair condition at the point of admission.

More than 50% subjects were on mechanical ventilator and the rest were using HFNC. Few subjects wore non-rebreathing mask for a short period of time before putting on HFNC or being intubated. Most patients required mechanical ventilator in the first 5 days in the ICU, with the median of mechanical ventilator day length was 5 days (IQR 3 - 9). The longest duration of mechanical ventilator was 29 days. Median of ICU LOS was 8 days (IQR 4 - 11) with the maximum stay was 46 days. The mortality rate was as high as 53.7%, mostly those with mechanical ventilator (85.4%), elderly (60%) and undernourished based on BMI (100%).

In terms of energy target, more than 50% of subjects reached 20 kcal/kg BW/day during the first 3 days in the ICU. More than 80% of our subjects received enteral nutrition started on day 1 in the ICU and more that 90% received enteral nutrition during three days of ICU stay. About 60% of our subjects were prescribed supplemental parenteral nutrition in whom 50% of them received it during the first 3 days of their ICU stay.

Several factors associated with energy target achievement of 20 kcal on day 3 were observed and analyzed. Age, sex, the presence of comorbidities and dosage of vasopressor were not risk factors for achievement of energy target. Meanwhile, risk prevalence calculation suggested that patients who had low risk of malnutrition based on mNutric score, were not on mechanical ventilator, had lactate level

less than 4 mmol/L and had both enteral and parenteral nutrition as route of delivery were more likely to achieve energy target of 20 kcal on day 3 (**Table 2**).

Putting together, when a multiple logistic regression was performed, only mNUTRIC score group and route of nutrition administration became significant determinants (**Table 3**). Patients with low nutritional risk based on mNUTRIC score was 8.7 times more likely to achieved 20 kcal/kg BW at day 3. Similarly, patients receiving nutrition from both enteral and parenteral route, was 8.5 times more likely to reach 20 kcal/kgBW on day 3.

Discussion

Most of subjects were male and obese. This result is in accordance with other study in Indonesia which also observed a higher prevalence in these group of patients with Covid-19.[7] A meta-analysis of 75 worldwide studies reported that obese people have higher risks for being Covid-19 positive, hospitalization, ICU admission and mortality.[8] The prevalence of Covid-19 patients with BMI $\geq$ 30kg/m^2 in our study was lower compared to French studies which reported the range prevalence of 25% to 47%.[9, 10] Being obese put a person in higher susceptibility for some infectious disease such as influenza and nosocomial infection.[11] The link between obesity and Covid-19 infection may be explained through several mechanisms such as adipose inflammation, impaired immunity and comorbidities found in obese people such as hypertension and type 2 diabetes mellitus.[8]

Elderly patients comprised about one third of our subjects. This high proportion may be due to poor immunity states among older people. Higher prevalence of elderly with Covid-19 was also found in a study conducted in Indonesia's National General Hospital.[12] However, the prevalence of older people with Covid-19 in our study much higher compared to study conducted in Wuhan which reported the prevalence of 11.5%.[13]

Most prevalent comorbidities observed in our study were type 2 diabetes mellitus and hypertension. These findings were similar with study which were conducted in China[14] and Indonesia.[7] It suggested the role of ACE2 in the pathogenesis of Covid-19 infection.[15,16] These two comorbidities frequently occurs in obese people, suggesting metabolic dysfunction in these population.[8]

The prevalence of high mNUTRIC score was low in our study compared to other study findings. This may be due to different characteristics of study subjects across countries. Two studies in China reported thatqa mNUTRIC score was applicable to determine nutrition risk and mortality in critically ill Covid-19 patients.[17,18]

ICU LOS and VM length observed in our study were somewhat shorter compared to previous meta-analysis from 7 studies which reported duration of ICU stay and being ventilated of 7.8 and 10.1 days respectively.[19] These differences might be due to higher mortality in our study subjects in the ICU and those with MV compared to findings from the meta-analysis. Various mortality rates in critically ill Covid-19 have been widely published. Compared to our study, the ICU mortality rate of previous studies were similar, but, the proportion of deceased patients who were on mechanical ventilator in other studies were significantly lower.[20,21] Meanwhile, a meta-analysis from 28 studies from 7 countries found mortality rate of 28.3% and 43% of those who were in ICU and being in mechanical ventilator respectively. Mechanical ventilator usage was found to be the major predictor for mortality.[19]

Our study found that more than 80% of our patients tolerated small dose EN on day 1 in ICU (median 11.7 kcal/kg BW, IQR 8.4 – 15.1). A retrospective cohort study in critically ill Covid-19 patients reported that early enteral nutrition was feasible and safe for this group of patients during the first week of ICU stays.[22] Another retrospective study in critically ill Covid-19 patients receiving mechanical ventilator revealed that administration of EN in the first 24 hour of mechanical ventilation did no harm to the patients.[23] Our study also found that combining EN with PN made achievement of energy target of day 3 in ICU is possible. This was in concordance with a meta-analysis by Luo which reported that administration of combined PN and EN was reported to have no difference with EN only in terms of mortality, infection, nutrition related complication, ventilatory support or C-reactive protein (CRP).[24]

This study found that obtaining energy target of 20 kcal/kg BW in day 3 of ICU stay was possible. A

small retrospective study conducted in severe and critically ill Covid-19 patients in China reported that permissive under feeding is feasible in critically ill Covid-19 patients.[25] Interestingly, the LEEP Covid study reported that measured REE in critically ill Covid-19 patients were at the range of 15-20 kcal/kgBW during the first week, therefore, our study result was in line with LEEP Covid study.[5]

Bivariate analysis found that variables which significantly associated with energy target achievement of 20 kcal/kgBW were mNUTRIC score, the use of mechanical ventilator, lactate level and route of nutrition were. Risk prevalence for these variables indicated that in critically ill Covid-19 patients who had low mNutric score, were not on mechanical ventilator, had lactate level less than 4 mmol/L and received nutrition from both enteral and parenteral route were more likely reaching energy target of 20 kcal/kgBW on day 3. This may be explained that those patients were hemodynamically stable, less severe disease, and/or less complications, which may lead to disruption of nutrition delivery. Multiple logistic regression revealed that only mNUTRIC score group and route of nutrition administration became significant predictors. The plausible explanation for this finding was that low nutrition risk based on mNutric score indicated patients were in less severe ARDS and hemodynamically stable which made the delivery of nutrition was possible. The previous retrospective study in critically ill Covid-19 patients on mechanical ventilator also found that main reason for interruptions of enteral nutrition during the first week were hemodynamic instability and GI intolerance.[22] When an enteral route was used without any supplemental PN, it seemed that disruption of enteral feeding due to gastrointestinal intolerance/bleeding, unstable hemodynamic and fasting related procedure led to failure of energy target achievement at day 3. Adding supplemental parenteral nutrition seems feasible and safe for our subjects. A systematic review and meta-analysis comparing EN and combined EN with supplemental PN revealed that the later increasing energy intake without increasing ICU mortality and length of stay.[26]

Wrapping up, most of our subjects are male and obese, with two third of them are elderly. The ICU mortality rate is quite high. Our study confirms that achieving energy target of 20 kcal/kgBW during the first 3 days of ICU stay for critically ill Covid 19 patients is possible. Two determinants for the achievement of energy target are mNUTRIC score and the route of nutrition delivery. Further study confirming other factors such as renal and liver functions which may influence the achievement energy target may be needed.

Table 1. Characteristics of subjects

Characteristics	Mean ± SD	n (%)
Age (years old)	53.7±12.67	
≥ 65		62 (33.0)
< 65		126 (67.0)
Sex		
Male		118 (62.8)
Female		70 (37.2)
Nutritional status (BMI, Asia Pacific Criteria)		
Underweight (<18.5 kg/m^2)		4 (2.1)
Normoweight (18.5 – 22.9 kg/m^2)		37 (19.6)
Overweight (23.0 – 24.9 kg/m^2)		31 (16.5)
Obese Grade I (25.0 – 29.9 kg/m^2)		84 (44.7)
Obese Grade II (30.0 – 34.9 kg/m^2)		24 (12.8)
Obese Grade III/Morbid Obese (> 35 kg/m^2)		8 (4.3)
Comorbidities (excluding obesity)		
DM without or with complication		66 (37.5)
Hypertension		61 (34.7)
Cardiovascular/cerebrovascular disease		35 (19.9)
Chronic kidney disease		26 (14.8)
No reported or observed comorbidities		60 (31.8)
mNUTRIC Score		
High risk		18 (15.5)
Low risk		98 (84.5)
Patients on VM		106 (56.4)
VM length (days)	6,8 ± 5.46	
ICU LOS (days)	8.8 ± 6.83	
ICU discharge status		
Deceased		101 (53.7)
Alive		87 (46.3)
Achieved 20 kcal/kg BW at day 3		
Yes		107 (56.9)
No		81 (43.1)
Proportion of subjects received EN for the first 3 days in ICU		178 (96.7)
Proportion of subject received PN for the first 3 days in ICU		60 (51.7)

Table 2. Risk factors for achievement of energy target

Achievement of 20 kcal at day 3		No	Yes	RP (95% CI)
		n (%)	n(%)	
Age (year)	≥65	12 (16.2)	22 (21.6)	0.74 (0.33-1.53)
	< 65	62 (83.8)	80 (78.4)	
Sex	Male	49 (59.8)	70 (64.8)	0.93 (0.51-1.74)
	Female	33 (40.2)	38 (35.2)	
Comorbidity	Yes	57 (69.5)	70 (64.8)	1.06 (0.56-2.02)
	No	25 (30.5)	38 (35.2)	
Vasopressor	High	8 (22.2)	6 (26.1)	0.71 (0.21-2.46)
	Low-medium	28 (77.8)	17(73.9)	
m-NUTRIC score	High risk	13 (28.9)	5 (7.0)	5.03 (1.63-15.54)
	Low risk	32 (71.7)	66 (93.0)	
Mechanical Ventilator	Yes	66 (61.1)	42 (38.9)	6.70 (3.27-13.74)
	No	16 (19.5)	66 (61.1)	
Lactate level	> 4	20 (48.8)	11 (22.4)	3.18 (1.26-8.09)
	≤ 4	21 (51.2)	38 (77.6)	
Route	EN	55 (77.5)	62 (62.0)	2.11 (1.06-4.19)
	EN+PN	16 (22.5)	38 (38.0)	

EN: enteral nutrition; PN: parenteral nutrition; RP: risk prevalence

Table 3. Multiple logistic regression models for variables with p<0.05

	B	p	Risk (95%CI)
m-NUTRIC score	2.162	0.013*	8.7 (1.19-32.08)
Mechanical ventilator	0.872	0.271	2.4(0.47-10.6)
Lactate group	0.979	0.168	2.7 (0.70-11.65)
Nutrition route	2.140	0.005*	8.5 (2.15-30.23)

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Effects of enteral glutamine supplementation on intestinal permeability in acute pancreatitis: A literature review

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Abstract

Background. Glutamine has been shown to improve the gut mucosal barrier. However, the evidence for benefit of enteral glutamine on intestinal permeability in acute pancreatitis (AP) is limited.

Objective. To identify the effect of enteral glutamine supplementation on intestinal permeability in patients with AP.

Method. A systematic search was conducted by extracting evidence from published studies on enteral glutamine supplementation in three databases (PubMed, Cochrane Central Register of Controlled Trials, and SciElo) relevant to AP from 1 January 2010 till 31 December 2020. Outcomes assessed were intestinal permeability, infectious complication, hospital length of stay, and mortality rate.

Results. A total of 6 studies found by search, in which 2 human RCTs with 7 days duration of intervention with 1b-1c quality based on Criteria by Center of Evidence-Based Medicine, University of Oxford. Both studies showed the benefit of early enteral glutamine supplementation on intestinal permeability in patients with AP.

Conclusions. Enteral glutamine supplementation has been shown to improve the gut mucosal barrier in AP. Despite its significant improvement in intestinal permeability, glutamine supplementation did not display a consistently positive effect on clinical outcomes.

Keywords glutamine, enteral, acute pancreatitis, intestinal permeability

Abbreviations

AP: acute pancreatitis
EN: enteral nutrition
LMR: lactulose mannitol ratio
LOS: length of stay
SAP: severe acute pancreatitis
TPN: total parenteral nutrition

Introduction

Acute pancreatitis (AP) is one of the most common causes of hospitalization for a gastrointestinal condition in the United States, with a global incidence ranging from 5–30 cases per 100,000 population per year.[1] In the Eastern countries, especially Asia, the most common cause of AP is biliary disease (49–54%) followed by alcohol abuse (20%).[2] AP is an acute, non-bacterial inflammation of the pancreas, in which auto digestion of activated pancreatic enzymes occurs and results in edema, vascular damage, bleeding, and necrosis of the pancreas.[3] Approximately 20% of patients develop severe acute pancreatitis (SAP) with a substantial mortality rate of 20–40% in the presence of

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pancreatic necrosis.[4] In SAP, inflammatory response causes disruption of the intestinal barrier and translocation of gram-negative bacteria which can be responsible for infection of the necrotic pancreas, systemic inflammatory response (SIRS), sepsis, and multi organ dysfunction syndrome (MODS). Hence, the main goals of treatment in SAP is to maintain the integrity of the gut barrier since the early phase focusing attention on the role of gut as the first course for SAP systemic complications.[3,5]

Originally, patients with SAP were made nil per os (NPO) to minimize stimulation of the pancreas and to reduce pain. Despite the NPO state, patients were given total parenteral nutrition (TPN).[6] Lack of enteral feeding in TPN results in gastrointestinal mucosal atrophy, bacterial overgrowth, increased intestinal permeability and translocation of bacteria, which contribute to poorer prognosis.[7] In contrary, meta-analysis by Petrov, et al.[8] showed that enteral nutrition (EN) results in significant risk reduction for morbidity and mortality in patients with predicted SAP. Moreover, systematic review by McClave, et al.[9] also suggested that patients with SAP should begin EN early as it allows a trophic action on the intestinal wall, which maintain the intestinal barrier and prevent the bacterial translocation and results in better outcome.[6] Recent meta-analysis by Zhou, et al.[10] showed beneficial effect of adding immune-enhanced formulas to the standard nutrition therapy in patients with AP either via the enteral or parenteral route. Glutamine, as one of the immunonutrition, which is also the major substrate for intestinal cells, have been investigated for its protective effects on intestinal mucosal integrity and modulation of inflammatory response.[11,12] Several meta-analysis have been performed assessing the effects of parenteral and enteral administration of glutamine compared with conventional methods.[10,13,14] Studies confirm the improvements in serum albumin, C-reactive protein (CRP),[13,14] incidence of infection and mortality rate.[10,13,14] To our knowledge, there are no review yet discussing the effects of enteral administration of glutamine on intestinal integrity. This review will investigate the role of enteral glutamine supplementation on intestinal integrity in acute pancreatitis, along with mortality and morbidity in terms of infectious complication and hospital length of stay (LOS).

Clinical question

A 30-year-old woman was admitted to the hospital with 24h severe epigastric pain and intractable vomiting. Two days before admission, the patient began to have fever, headache, and nausea. The pain was worsened with eating. Her past medical history was otherwise negative, and she had no allergies. She denied alcohol intake or tobacco use. She has a two-time history of cesarean section, which was last two years ago. Examination revealed a woman with 38.5˚C fever and epigastric abdominal pain during superficial palpation, with no peritonitis signs. There were non-palpable masses and bowel sounds were normal. Abdominal ultrasonography showed a contracted gallbladder without lithiasis with normal biliary tree, hypoechoic extrapancreatic inflammation and pancreatic parenchymal inhomogeneity, with small amount of fluid localized peri-hepatic and in rectouterine pouch. Laboratory investigations showed leucocytosis, elevated serum lipase (3212 U/L) and amylase (278 U/L), and elevated IgM/IgG EndoCab. The patient was diagnosed with acute pancreatitis and immediately placed on a nasogastric tube and started to be given EN within 24 hours. The physician in charge would provide early enteral nutrition and investigate whether enteral glutamine has a role to improve intestinal permeability and subsequently reduce morbidity and mortality rate in patients with AP.

Methods

Three electronic bibliographic databases (Pubmed, Cochrane Central Register of Controlled Trials, and SciElo) were systematically searched by author E.A.S. All randomized controlled trials (RCTs) of enteral glutamine supplementation in acute pancreatitis between January 1, 2010 and December 31, 2020 were included in this review. Any included study had to assess intestinal integrity as an outcome and had to be a human trial in adults. We used the search terms 'glutamine' AND ('enteral' OR ‘oral’) AND ('pancreatitis' OR ‘acute pancreatitis’) AND (‘intestinal permeability’ OR ‘gut permeability’) to identify relevant studies (**Table 1**). Publications in non-English languages, unpublished studies, online proceeding, and non-full text paper were not included.

Titles and abstracts were screened by author E.A.S to identify relevant studies. Full-text articles of potentially eligible studies that met the selection criteria were obtained. The inclusion criteria for this review were RCT, participants aged at least 18 years old, single glutamine intervention, enteral administered intervention, and intestinal permeability as main outcome. Non-RCT, participants aged under 18 years old, and review articles were excluded. Any discrepancy was discussed with the senior author D.S.

All data from the eligible studies were extracted into tabular form. Extracted data included information on the first author, the country where the trial was held, the study population and sample size, intervention and comparison groups, the duration of intervention, the outcomes measured and their time of assessment, and the results of the clinical and/or laboratory parameter outcomes. The quality of the studies was assessed by two authors (E.A.S., D.S.) using guideline for RCT based on Criteria by Center of Evidence-Based Medicine, University of Oxford and the summary is provided in Table 2. Outcome measurements included intestinal integrity, incidence of infectious complication, hospital LOS, and mortality rate.

Results

The study selection process is summarized in Figure 1. The initial systematic search identified 6 citations of which 2 potentially eligible articles[15,16] was critically appraised. We excluded 4 study for duplications and non-human study. One record from PubMed excluded was a non-human study and three records from Cochrane were excluded for duplication. Details of the included studies are presented in Table 3 and Table 4. Two studies included in this review were RCTs of enteral glutamine supplementation in acute pancreatitis for 7 days which investigated intestinal permeability as an outcome.[15,16] Biomarkers used to assess intestinal permeability were different in both studies. Other outcomes included in this review were incidence of infectious complication, hospital LOS, and mortality rate.

Discussion

Study by Arutla M, et al.[15] showed significant reduction of polyethylene-glycol (PEG) in the intervention group after 7 days of supplementation. PEG, as well as sugars, or 51chromium-labelled ethylenediamine tetra-acetic acid (51CrEDTA) are probes used for examining intestinal permeability. Intestinal permeability analysis is based on the appearance of orally administered probes in the circulation and/or urine after permeation of the intestinal epithelium. Each probe has its specific advantages and disadvantages and requires a specific method of detection. PEG is one of the commonly used option for permeability analysis which is based on the use of PEG probes. PEG has few advantages over the use of 51CrEDTA and sugars for permeability analysis, such as it does not require radioactivity, it is not metabolized by enzymes or degraded by bacteria within the human gastrointestinal tract, and it is analyzed using less expensive and time-consuming method than other probes.[17] High levels of PEG found in the circulation indicates increased intestinal permeability. Significant reduction of PEG after enteral glutamine supplementation in AP demonstrate the beneficial effect of glutamine on intestinal permeability.

Glutamine is essential for the growth, survival, and physiological health of actively dividing cells such as enterocytes, fibroblasts, and lymphocytes. Gastrointestinal mucosal integrity is quickly restored and maintained by cell proliferation, migration, and differentiation. Enteral feeding appears to be the primary stimulus for the regulation of proliferative response in the intestinal tract, which is accomplished mainly by the glutamine. Gut mucosa is the major site of glutamine metabolism in which glutamine is a major source of energy for proliferation and differentiation of intestinal epithelial cells. Under conditions of severe inflammation, the physiological level of glutamine is inadequate to balance the damage and needs to be replaced.[18] Not only act as fuel for enterocyte, glutamine also modulates the inflammatory response and oxidative reactions, in which ultimately maintain the tight junction of intestinal cells.[19]

It has been identified that glutamine administration influences intestinal permeability.

However, which route is the most appropriate in providing glutamine supplementation to benefit gut integrity is still debatable. Enteral and parenteral glutamine supplementations have different metabolic pathways. A pilot study by Uranjek, et al.[20] investigating the effect of the route of glutamine supplementation on intestinal permeability in 81 intensive care unit (ICU) patients. The study showed no significant difference in lactulose mannitol ratio (LMR) between enteral glutamine compared with parenteral route.

Ligthart-Melis, et al.[21] demonstrated their study in 16 patients undergoing upper gastrointestinal surgery to receive an IV or EN infusion of L-[2-(15)N]glutamine. The study revealed that arterial [(15)N] glutamine was significantly lower during EN reflecting intestinal metabolism preferably takes up enterally administered glutamine compared with intravenously provided glutamine. This suggests that the route of administration of glutamine supplementation is influenced by the underlying condition.

The second study included in this review was study by Singh, et al.[16] which evaluating the effect of oral glutamine supplementation on gut permeability and endotoxemia (surrogate end point) in patients with SAP. The study discovered there was no significant difference in LMR between intervention and control group after intervention. However, there was significant increase in IgM antiendotoxin antibodies in intervention group.

Similar to study by Sharma, et al.[22] investigating the intestinal permeability and anti-endotoxin antibodies immunoglobulin in SAP compared to healthy controls. The study showed that the intestinal permeability (LMR) at day 1 and day 7 of admission was no different when compared with controls. In the natural course of AP, intestinal permeability has been found to increase gradually within the first 72 hours and normalize slowly from the second week to one and a half months.[23-25]

Singh, et al.[16] also demonstrated insignificant changes in LMR after glutamine supplementation in the intervention group as well as control group, possibly because of the maintained gut mucosal barrier of patients that were fed enterally. The IgM endotoxin antibody titer is an indirect marker for endotoxemia. The study found a significant increase in IgM endotoxin antibody in the group receiving glutamine after 7 days of intervention suggesting the decreased of endotoxemia. Compared to other studies with non-conclusive results, Pearce, et al.[26] conducted a study on 31 AP patients given enteral feed containing glutamine, arginine, and omega-3 fatty acid compared to isonitrogenous & isocaloric enteral feed for 3 days. There was significant difference in increment of IgG antiendotoxin antibody in control group compared to intervention group, however this effect was not seen in the IgM antiendotoxin antibodies and the explanation for this effect is not entirely clear.

Even though there was significant increase in intestinal permeability with enteral glutamine administration, both studies did not show a consistent clinical improvement as evidenced by equal infectious complications, hospital stay, or mortality in both groups. In line with meta-analysis investigating clinical benefit of immunonutrition over standard enteral formulas in patients with acute pancreatitis. There is no evidence that enteral nutrition supplemented with glutamine, arginine and/or omega-3 fatty acids has beneficial effect on infectious complications, hospital LOS, and mortality rate in acute pancreatitis compared to standard EN.[8]

Both included studies reported significant improvement in intestinal permeability. These studies were conducted in the same country. India, like any other developing countries, is concerned with spectrum of enteropathies, characterized by small intestinal inflammation, reduced absorptive capacity, and increased intestinal permeability.[27] This condition commonly affect people in developing countries as Menzies, et al.[28] speculated that in many tropical countries, especially where there is widespread poverty and poor sanitation, may be exposed to repeated gastrointestinal infection leading to a chronic reversible impairment of intestinal function.

Studies included in this review demonstrated beneficial effects of enteral glutamine supplementation on intestinal permeability in acute pancreatitis. However, this beneficial effect did not in accordance with any clinical improvements, for instance incidence of infectious complications, hospital LOS, and mortality rate. Despite significant improvement in intestinal permeability, both studies were underpowered consequently the results

obtained with enteral glutamine cannot be advocated for routine administration in patients with AP. An adequately powered larger study with longer duration of supplementation is required to substantiate the evidence.

Conclusion

The goal of nutritional support in AP is to reduce inflammation and maintain intestinal permeability. Enteral glutamine supplementation has been shown to improve gut mucosal barrier in AP. Despite its significant improvement in intestinal permeability, glutamine supplementation did not display a consistent positive effect on clinical outcome.

What is Already Known
Acute pancreatitis (AP) is associated with altered gut mucosal barrier.
Glutamine supplementation have been shown to improve gut mucosal barrier in AP.

What This Study Adds
Enteral glutamine supplementation improves intestinal permeability in AP patients

What are the future clinical and research implications of the study findings?
Investigators need to evaluate the effects of long-term enteral glutamine supplementation in a large multicenter RCTs of patients with AP.

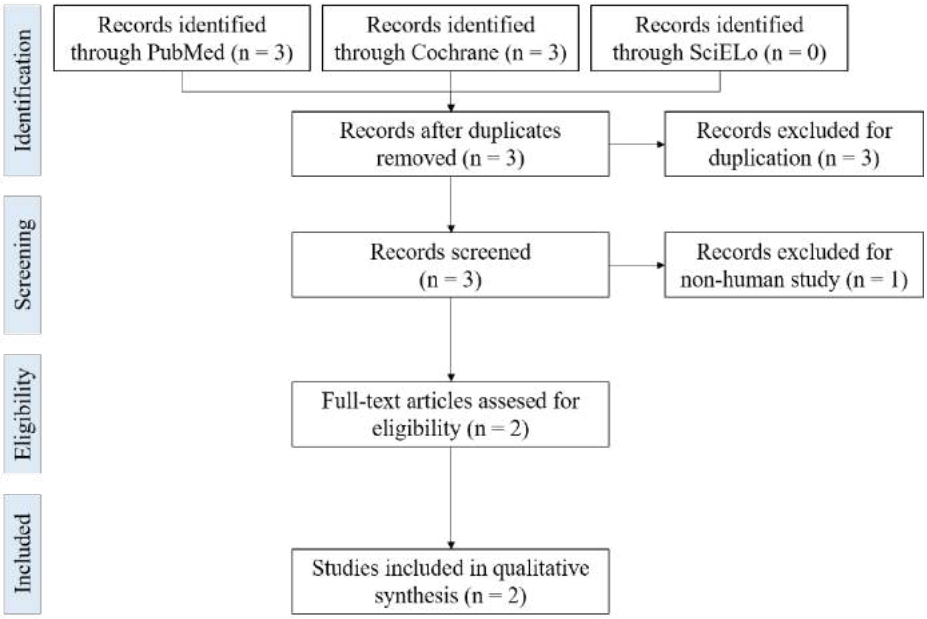

Figure 1. PRISMA flow chart depicting the article selection process for the review

Table 1. Terminology used in three databases

Database	Terminology	Hits	Result
PubMed	(((((glutamine[Title/Abstract]) OR (glutamine[MeSH Terms])) AND ((((enteral[Title/Abstract]) OR (enteral[MeSH Terms]) OR (oral[Title/Abstract]) OR (oral[MeSH Terms]))))) AND ((((pancreatitis[Title/Abstract]) OR (pancreatitis[MeSH Terms]) OR (acute pancreatitis[Title/Abstract]) OR (acute pancreatitis[MeSH Terms])))) AND ((((intestinal permeability[Title/Abstract]) OR (intestinal permeability[MeSH Terms]) OR (gut permeability[Title/Abstract]) OR (gut permeability[MeSH Terms])))) Filter: published in January 1st, 2010 – December 31st, 2020	3	2
Cochrane Central Register of Controlled Trials	(glutamine):ti,ab,kw AND ("Enteral"):ti,ab,kw AND (pancreatitis):ti,ab,kw AND ("intestinal permeability"):ti,ab,kw Filter: published in the last 10 years	3	0
SciElo	(glutamine) AND (enteral) AND (pancreatitis) AND (intestinal permeability) Filter: published in the last 10 years	0	0

Table 2. Critical appraisal of the RCT study based on criteria by Center of Evidence-Based Medicine, University of Oxford

Parameters	Questions	Arutla M, et al.[15]	Singh N, et al.[16]
Validity	Was the assignment of patient to treatments randomized?	Yes	Yes
	Was the randomization list concealed?	No	Yes
	Were the groups similar at the start of the trial?	Yes	Yes
	Aside from the allocated treatment, were groups treated equally?	No	Yes
	Were all patients who entered the trial accounted for?	Yes	Yes
	Were they analyzed in the group to which they were randomized?	Yes	Yes
	Were measures objective or were the patients and clinicians kept "blind" to which treatment was being received?	No	Yes
Importance	How large was the treatment effect?	Polyethylene glycol reduction in intervention group (7.61 ± 4.5), $P = 0.02$	IgM antiendotoxin Ab increment in intervention group ($P = 0.0164$)
	How precise was the estimate of the treatment effect?	Precise, the 95% CI of the results are narrow. Poly-ethylene glycol reduction in intervention group (7.61 ± 4.5), $P = 0.02$	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?	Precise, the 95% CI of the results are narrow. The study has the same characteristic as case scenario	The study has the same characteristic as case scenario
	Is the treatment feasible in my setting?	No	No
	Will the potential benefit of treatment outweigh the potential harms of treatment for my patient?	Yes	Yes
Level of evidence of this study based on Oxford CEBM		1c	1b

Table 3. Characteristic of the included studies assessing the effect of enteral glutamine supplementation on intestinal permeability in acute pancreatitis

Included studies	Participants (age at enrollment)	Sample size	Intervention	Control	Feeding start	Duration of intervention	Glutamine dosage
Arutla M, et al.[15] 2019 (India)	Patients aged 18-60 years old with AP with ≤ 72 hours of the onset of abdominal pain + APACHE II score ≥ 8 or SOFA score ≥ 2 or SIRS > 2 for 48 h or BUN rise > 5 mg/dL over 48 h from admission	n: 31 I: 18 C: 22	Standard nutrition + enteral glutamine	Standard nutrition	≤ 48 hours of admission	7 days	0.57 g/kg body weight per day
Singh N, et al.[16] 2014 (India)	Consecutive patients aged 18-80 years old with acute pancreatitis admitted to the ward	n: 80 I: 41 C: 39	10 g glutamine (KABIMMUNE) twice a day	10 g whey protein twice a day	≤ 7 days of the onset of symptom	7 days	20 g/day

AP, acute pancreatitis; APACHE, acute physiology and chronic health evaluation; BUN, blood urea nitrogen; C, control group; I, intervention group; SIRS, systemic inflammatory response syndrome; SOFA, sequential organ failure assessment

Table 4. Summary of clinical outcomes of included studies

Included studies	Number of patients	Intestinal permeability	Complication of infection	Length of stay	Mortality
Arutla M, et al.[15] 2019 (India)	I: 18 C: 22	There was significant PEG reduction in I group. Group I Day 1 (n 18/18): 39.91 ± 11.9 Day 7 (n 18/18): 32.30 ± 7.4 ***P* = 0.02** Group C Day 1 (n 22/22): 48.73 ± 12.6 Day 7 (n 22/22): 45.25 ± 7.9 *P* = 0.32	There was no difference in complication of infection (development of infected necrosis) between I and C group. I: 5/18 C: 6/22 *P* = 0.53	There was no difference in duration of hospital stay between I and C group. I: 15.58 ± 10.3 days C: 15.63 ± 18.8 days *P* = 0.99	There was no difference in in-hospital mortality between I and C group. I: 1/18 C: 1/22 *P* = 0.43
Singh N, et al.[16] 2014 (India)	I: 41 C: 39	There was no significant difference in LMR between I and C group after intervention. Group I Day 7 (n 29/41): 0.15 (0.02-2) Group C Day 7 (n 28/39): 0.14 (0.01-5) *P* = 0.8732 There was no significant increase in IgG antiendotoxin antibody in both I and C group. Group I Day 0 (n 39/41): 72 (4-1600) Day 7 (n 36/41): 86 (4-1600) *P* = 0.1667 Group C Day 0 (n 35/39): 74 (4-1760) Day 7 (n 29/39): 100 (2-1640) *P* = 0.7293 There was significant increase in IgM antiendotoxin antibody in I group. Group I Day 0 (n 41/41): 33 (4-175) Day 7 (n 37/41): 40 (8-350) ***P* = 0.0164** Group C Day 0 (n 38/39): 45 (2-180) Day 7 (n 32/39): 56 (7-350) *P* = 0.1552	There was no difference in complication of infection between I and C group. I: 21/41 C: 19/39 *P* = 1.000	There was no difference in duration of hospital stay between I and C group. I: 12 (1-101) days C: 11 (2-36) days *P* = 0.236	There was no difference in in-hospital mortality between I and C group. I: 5/41 C: 6/39 *P* = 0.753

AP, acute pancreatitis; C, control group; I, intervention group; LMR, lactulose mannitol ratio; PEG, polyethylene glycol

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Effect of intermittent fasting on fat mass and fat free mass among obese adult: A literature review

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Abstract

Introduction Obesity is a serious hurdle facing by the world nowadays. Even though so many efforts have been done, yet the prevalence is keep rising. Intermittent fasting is seen as an effective and optimal approach for improving nutrition status without undesirable side effect.
Objective to identify the effect of intermittent fasting on fat mass and fat free mass among obese adult.
Methods: a literature exploration was conducted from January to October 2020 by searching the relevant studies from several databases.
Results: many human clinical trials recommended that IF affects beneficial on body composition and body weight. Consuming calorie only in a certain time frame per day for 4-12 months put the body into a fast metabolism which influence the reduction of fat mass from 0.03–16.4% intervention and increasing of fat free mass for around 0.64 to 0.86%.
Conclusion: intermittent fasting may reduce fat mass and increase fat free mass in obese adult through the reduction of energy intake (fasting) and the benefit to adipose tissue, liver, pancreas, skeletal muscle, and the brain.

Keywords body composition, intermittent fasting, obesity, weight loss

Introduction

Obesity is an increasingly clinical problem and serious socio-economic issue faced by the world today.[1] It is a result of a positive energy balance accumulation from day to day and develops over many years which usually accompanied by wide range of health disadvantages.[2,3] Worldwide data from 1975 shows that obesity has about tripled at 2018, and more than 1.9 billion adults aged above eighteen are overweight; of these, over 650 million are obese.[4] Data from Indonesia basic health survey (*Riskesdas*) 2018 find that the percentage rise by 11.3% only for eleven years (2007–2018). [5]

Fasting in terms of nutritional aspect define in varies scope; moderate reduction of calorie intake (600-800 kcal), stricter reduction of energy intake (200-400 kcal), and zero-calorie fasting.[10] Intermittent fasting (IF) is considered as an energy deficit protocol that leads to lipid profile improve by energy deficit and/ or body weight reduction.[11] IF practice exists in several protocol; complete fasting every other day, 70% energy restriction every other day, consuming only 500-700 kcal for two consecutive days per week, and restricting food intake to a 6-8 hour time period daily.[12] Common form of IF include fasting up to 14 hours once or

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twice a week with ad libitum food intake for the remaining days, which is also known as periodic prolonged fasting (PF) or intermittent calorie restriction (ICR), without any requirement of water restriction. Fasting and CR are considered as an optimal intervention for improving health and lifespan without the undesirable side effect.[13,14]

Dietary habit is an important role in developing obese condition, even though the cause of obesity is complicated.[15] Thus, this study aimed to elaborate the effect of IF to fat mass and fat free mass among obese adult.

Methods

This study was designed as a literature review study to analyze the axisting data on the impact of IF on fat mass and fat free mass. Literature exploration was conducted from January to October 2020 by searching the relevant studies from PubMed, Scopus, ProQuest and Google Scholar using a combination of keyword "intermittent fasting", "obesity", "body composition", and "weight loss" as registered in the U.S. National Library of Medicine's MesH.

The result included in this study obtained from articles screened by title and abstract from cohort prospective study, meta-analysis, and systematic review which have fat mass or fat free mass status as the outcome. Study from animal subject was excluded from the review.

The first search recovered 46 results by using keyword 'intermittent fasting' and 'body composition'. Of these, there were 12 articles explained the impact of intermittent fasting on fat mass and fat free mass. Total of the final studies included in this review was 8 articles, because we exclude the article without the exact number or percentage of FM or FFM. Detail article's extraction was depicted in **Figure 1**.

Results

Many human study trials recommend that IF gives beneficial effects on weight, body composition, cardiovascular biomarkers, and aging.[13] Briefly, IF regiments influent metabolic regulation via effects on circadian biology, the gastrointestinal microbiota, and modifiable lifestyle behaviours. IF regiments that limit food intake during the fasting time may leverage circadian biology to improve metabolic health.[16] Consuming calorie only in a certain time frame per day (8 hours, and 10 hours window) puts the body into fast metabolism, and avoiding muscle catabolism during the remaining fasting hours.[12] There are many types of IF.[17] General explanation is provided in the **Table 1**.

Study review done by Mattson et al., 2016 conclude that from several IF study done in human subjects, numerous physiological indicators of health are improve due to IF, such as reduce level of insulin and leptin which parallel increases insulin and leptin sensitivity, reduce body fat, elevated ketone level, reduce resting heart rate and blood pressure, and increase heart rate variability (resulting from increased parasympathetic tone), reduce inflammation, increase resistance of the brain and heart to stress (e.g., reduced tissue damage and improved functional outcome in models of stroke and myocardial infraction), and resistance to diabetes.[18] Many clinical trial studies on human also depict that IF gives a result of weight loss, improvement in some metabolic biomarkers, reduce oxidative stress, reduce anger, confusion, and depression (**Table 2**).

Discussion

Obesity is a complex disease that involves interaction between environmental and genetic factors. Someone's genes define opportunities for their health and susceptibility to disease, while environmental factors determine which susceptible individuals will develop illness.[20]

Control of food intake does not depend on one signal changes, but it is determined by the integration of many inputs that provide body's energy status information.[21] Factors that influence food intake are shown in the **Figure 2**.

The excessive fat is predominantly stored in adipose tissue. Adipose tissue has key function in the secretion of factors, including cytokines, angiogenic factors, immune-related factors, prostaglandins, angiotensinogen, and proteins involved in the regulation of energy balance and carbohydrate metabolism (e.g. resistin, adiponectin).[22] In obesity, the increasing adiposity

with greater adipocyte size and number, leading to a higher leptin concentration, but without reduced food intake (leptin resistance).[1]

Multiple, high integrated and redundant pathway criss-crosses into and out of the arcuate nucleus; indicate that complex system involved in feeding and satiety process. Neuropeptide Y (NPY), one of the most potent appetite stimulators, leads to increase food intake that will promoting weight gain. Leptin is also important for body weight regulation. The amount of leptin in the blood is an excellent indicator of the triglyceride total amount stored in adipose tissue; the larger the fat store, the more leptin released to the blood. Leptin suppresses appetite, thus decreasing food consumption and promoting weight loss by inhibiting output of appetite-stimulating NPY stimulated by ghrelin. PYY_{3-36} is a counterpart of ghrelin which will rise during meals and signal of satiety.[21]

Energy balance can be modified either at the level of food intake or energy expenditure. In part of food intake, leptin controls food intake by the activation of hypothalamic receptors.

Adipose tissue secretes leptin in states of food deprivation (fasting), exercise, sympathetic nervous system (SNS), stimulation, exercise, and cold exposure. Leptin will be inhibited by obesity states, glucocorticoids, glucose and insulin. Leptin will reach hypothalamus and inhibit the secretion of NPY that normally reduce energy expenditure, enhance appetite and stimulate the synthesis and storage of fat. Obesity and insulin resistance negatively regulate adiponectin secretion from adipose tissue, whereas weight reduction increase its secretion.[21]

Plasma leptin in obese subject is usually normal for their fat mass, signing that leptin deficiency is not the primary cause of common obesity. However, there is also study show the linkage for involvement of leptin –or at least leptin gene locus- in the complex determinism of obesity and its related phenotypes in early onset of obesity.[24]

Usually, obesity, insulin resistance, diabetes, dyslipidemia, and fatty liver have a tendency to occur in the same individual as a manifestation of metabolic syndrome. Furthermore, metabolic dysfunction can arise from lipotoxicity caused by the excessive lipid intake and cannot be stored anymore in someone's adipose tissue. Lipid storage capacity that will manifest in individuals body weight from adipose tissue depends on genetic and environmental factors. Lipids are controlled tightly by homeostatic system, and it will become spatial and dynamic complex at multiple levels.[25] Metabolic profile is significantly associated with obesity and its metabolic co-morbidities. The physiological regulation of lipid membrane composition in obesity can be explained by seeing the Figure 4 below.

Lipid membranes adapt as adipocytes expand in size. Given that adaptation seems to involve a relative increase in precursors of pro inflammatory mediators, adaptation might increase vulnerability to inflammation.[25]

Studies recommend that changes in composition and metabolic function of gut microbiota in obese person may enable an 'obese microbiota to harvest more energy from the diet compare to 'lean microbiota', thus will influence net energy absorption, expenditure, and storage. Moreover, microbiota changes due to obesity-related manipulation can alter gut permeability and bacteria translocation to promote systemic inflamation.[16]

Dysfunctional adipose tissue lipid metabolism causes an increasing of circulating free fatty acids which will initiate inflammatory signalling in the population of infiltrating cells. This dysfunctional lipid metabolism accompanies obesity and affect impair insulin signaling.[26]

In term of environmental factors, there are many aspects that can influence individual's BMI. Body weight perception is a strong determinant for nutritional habit and weight management. Some researcher argue that some level of body dissatisfaction may be beneficial for average or above-average weight individuals, as it may lead to a healthy weight management behaviour like changes in diet such as increasing of vegetable and fruit consumption, increase physical activity, or have intention to weight control practice. Study done by Lian at 2009 conclude that students who overestimate their weight status were more likely to try to lose weight, while the revers happened to the students who underestimated their weight status.[27]

A study done by Langellier, 2015 conclude that frequency of fast food consumption is substantively greater among communities in urban and large urban area compare to rural area, and it will increase

dramatically with SES and educational attainment. Moreover, total food expenditure follow a very similar pattern.[28] Food which prepared away from home (e.g. eating at restaurant, vending machines, fast food outlet, or other place providing ready-to-eat food) is important to be documented, because foods prepared away from home tend to has larger portion sizes compare to homemade meals and to be higher in total energy and also energy density but lower in micronutrient density.[28,29]

Correlation between socio-economic status and body composition is still varies among studies globally. Many researches concluded that higher socio-economic status is associated with reduced risk of obesity, while the reverse is also shown to be true in several studies. Dietary shifting into poorer food choice can be caused by the increase of wealth e.g. bigger portion sizes and a more frequent intake of fast food. Yet, the higher economic status can also be the reason to more healthy diet because they can afford the price and they have enough knowledge on it.[28,30]

Sedentary lifestyle also has been shown to be a major contributing factor in increasing of obesity rate. Study done in the South African adults suggest that lack of exercise alone can account for 15% of obesity in that area.[30] In term of intermittent fasting, study from Bhutani et al.[15] found that only subject who did fasting and exercise group experienced decreased in fat mass, while those who are in the fasting or exercise alone are not.[31] Physical activity affects weight directly through energy expenditure, increase sensitivity for satiety signal and increase inhibitory control of the drive to eat may be involved.

Conclusion

In conclusion, some studies showed that doing an intermittent fasting for 6 to 28 months may reduce fat mass (around 0.03–16.4%) and increase fat free mass for about 0.64 to 0.86% in obese adult through the reduction of energy intake (fasting) and the benefit to adipose tissue, and skeletal muscle.

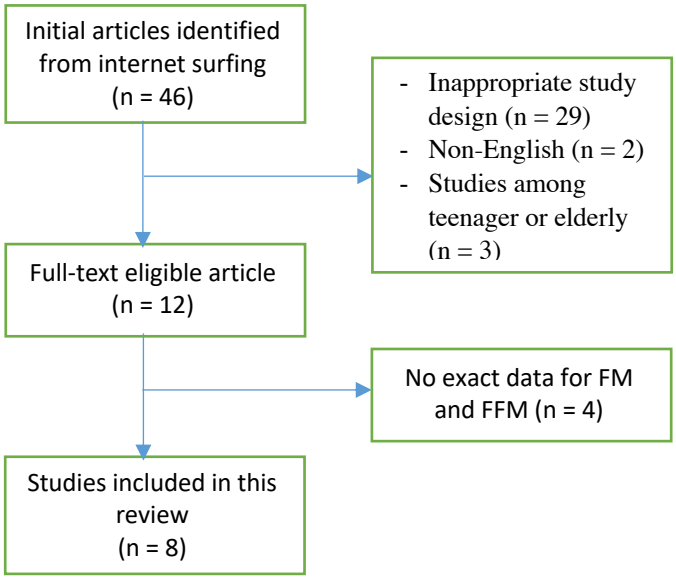

Figure 1. Flow of the study selection

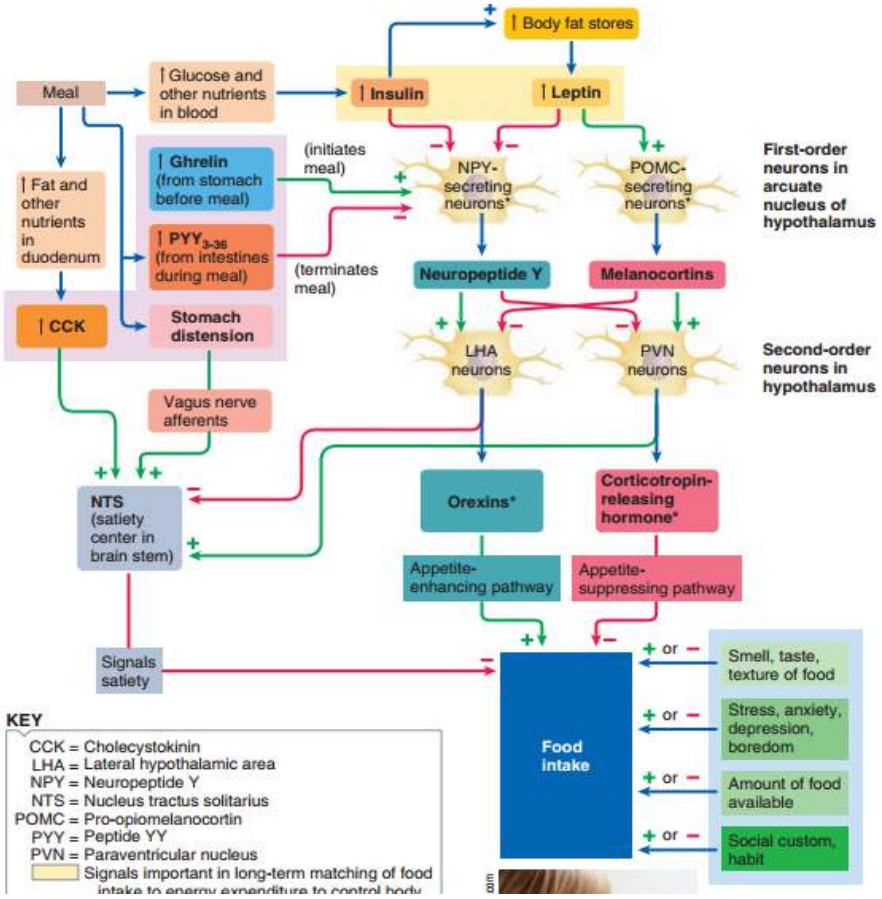

Figure 2. Factors that influence food intake
Figure explanation: CCK: Cholecystokinin, LHA: Lateral hypothalamic area, NPY: Neuropeptide Y, NTS: Nucleus tractus solitaries, POMC: Pro-opiomelanocortin, PYY: Peptide YY, PVN: Paraventricular nucleus.
*reference number [21]

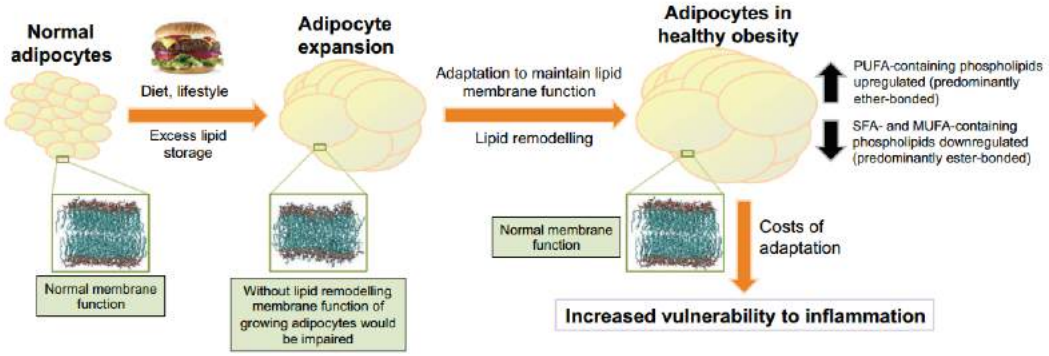

Figure 3. Model of physiological regulation of lipid membrane in obesity
*reference number[25]

Table 1. Type of intermittent fasting

IF Type	Description	Metabolic States Involved
Alternate day fasting	Alternating feast (ad libitum intake) and fast days (≤ 25% of energy needs)	Fed, post-absorptive, fasting (short duration, likely <36 hours between meals)
Modified fasting regiment	Allow for the consumption of 20-25% of energy needs on scheduled fasting days. This regiment is the basis for 5:2 diet	Fed, fasting (2 non-consecutive days a week, and ad libitum eating the other 5 days
Time-restriction fasting	Allows individual to consume ad libitum energy intake within specific windows, which include fasting period on routine basis. Ramadhan is the most common form of time-restriction feeding	Fed, post-absorptive (maximum duration between meals is usually < 16 hours)
Religious fasting	A wide variety of fasting regiments are undertaken for religious or spiritual purposes	Depend on the religious types of fasting
Periodic fasting	Fasting for up to 24 hours once or twice a week with ad lib intake on the remaining days	Fed, post-absorptive, fasting (up to 48 hours between meals depending on whether fast days are consecutive)

*reference number[13,16]

Table 2. Clinical trial studies result on IF regiments

Author	Year	Country	Intervention IF Regiment	Outcome
Harvie	2011	UK	25% energy restriction 2d/wk or 7d/wk on people with BMI 24-40 within 6 months	Comparable ↓ (leptin, free androgen index, total and LDL cholesterol, TG, BP)
Eshghinia	2013	Iran	25-30% energy needs (3d/wk) on overweight and obese population within 6 weeks	↓ BW, NS ↓ for (LDL, HDL, and TG)
Teng	2013	Malaysia	300-500 Cal/d deficit (2d/wk) as muslim sunnah fasting (≈13h) on obese people within 3 months	↓ (BW, %fat, energy intake, fat intake, BP, LDL, and total cholesterol)
Hussin	2013	Malaysia	300-500 Cal/d reduction from baseline + 2d/wk of muslim sunnah fasting + counselling on people with BMI 23-29.9 within 3 months	↓ (anger, tension, confusion, BW, BMI, and body fat), NS changes in mean depression scores
Catenacci	2016	USA	- Intervention: 0% energy needs on fast day, ad lib feast day - Control: 400 Cal/d deficit On people with BMI ≥ 30 within 8 weeks	NS ↓ for BW in both group, intervention group regained more FFM, control group regained more FM
Trepanowski	2017	USA	- 1st group: 25% energy needs on fast days + dietary counselling - 2nd group: 75% daily needs + dietary counselling - Control: 100% need daily On people with BMI 25-39.9 within 28 weeks	↓ BW (6% in 1st group, 5.3% in 2nd group), ↑ FFM and ↓ leptin in 1st and 2nd group (NS), no changes in circulating of adiponectin in any group

Table explanation: BMI: body mass index, BP: blood pressure, BW: body weight, FM: fat mass, FFM: fat free mass, HDL: high density lipoprotein, IF: intermittent fasting, LDL: low density lipoprotein, NS: not significant, TG: triglyceride, *reference number[13,16]

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

The effect of dietary fiber on insulin resistance in obesity: A literature review

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Abstract

Introduction Obesity has become a significant public health problem in developing countries such as Indonesia. According to WHO, 13% of adults aged 18 years and over were obese in 2016. In Indonesia, 21.8% of adults were obese. In obesity, the body's resistance to insulin will develop. Some studies showed a probable link between dietary fiber and insulin resistance. This research aims to investigate the role of the dietary fiber on insulin resistance in obesity.

Methods: This study is a literature study to determine the effect of dietary fiber on insulin resistance in obesity with sources from scientific publications 10 years back. The databases were PubMed and Google Scholar. The search term used was using the explode function for subgroup terms with operators ("and," or) for "dietary fiber", "obesity", "insulin resistance". Hand-searching was used to identify further potential eligible studies. There were no language restrictions, however only publications with full texts available were included. Total 138 publications titles and abstract were screened for their relevance to this literature review.

Results: A total of 25 publications were finally included. There are cross-sectional studies, randomized clinical trial, cohort studies, and article review. Some studies showed that dietary fiber had an effect on improve insulin resistance, but other studies did not find this effect.

Conclusion: The studies of dietary fiber effect on insulin resistance have inconsistent results. In the future, further studies are required for better understanding about the effect of dietary fiber on insulin resistance in obesity

Keywords dietary fiber, insulin resistance, obesity

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Introduction

Obesity has become a significant public health problem in developing countries such as Indonesia. Worldwide, obesity has nearly tripled since 1975. According to WHO, 13% of adults aged 18 years and over were obese in 2016.[1] In Indonesia, 21.8% of adults were obese.[2] Obesity is an excessive accumulation of fat due to an imbalance in food intake and expenditure and can cause various health problems. Obesity is always associated with the level of fat or adipose tissue and chronic inflammation. In obesity, the body's resistance to insulin will develop. The development of insulin resistance is characterized by a reducing ability to take up glucose in fat and muscle. This disorder is a factor that underlies type 2 diabetes mellitus. The incidence of obesity can be influenced by various factors such as genetic, dietary pattern, and physical activity.[3]

Insulin resistance is a state of reduced sensitivity or tissue response to insulin so that glucose cannot enter and be used by cells. The impact of insulin resistance was type 2 diabetes and other health problems like obesity, hypertension, dyslipidemia, and metabolic syndrome. Assessment of insulin resistance was significant and aimed to prevent the further impact of insulin resistance.[4]

Various factors influence insulin resistance like eating habits, high fat and high carbohydrate diet, alcohol, and specific micronutrient deficiency.[5] Besides that, lack of physical activity, stress, and lack of sleep are also contributing factors.[6] Some studies showed a probable link between dietary fiber and insulin resistance. This study aimed to investigate the role of dietary fiber on insulin resistance in obesity. Several studies described the effect of dietary fiber and insulin resistance in various subjects with different results, but this article focused on the effect of dietary fiber on insulin resistance in obesity. This study also discussed information based on the most recent studies in the last 10 years.

Methods

This study is a literature review research that looked for theoretical references relevant to the cases or problems found. According to Creswell[7] stated that literature reviews are summaries of articles from journals, books, and other documents that describe theories and information both past and present and organize literature into the topics and the manuscripts needed. The type of data used by the author in this study is data obtained from literature studies. A literature study is a method used to collect data or sources related to the topic raised in a study. Data analyzed by the descriptive analysis method. The methods of descriptive analysis by describing the facts then followed by analyzing the facts, not merely a description, but also providing sufficient understanding and explanation.[7]

This study is a literature study to determine the effect of dietary fiber on insulin resistance in obesity with sources from scientific publications 10 years back. The databases were PubMed and Google Scholar. The search term used was using the explode function for subgroup terms with operators (“and,” or) for “dietary fiber”, obesity”, “insulin resistance”. Hand-searching was used to identify further potential eligible studies. There were no language restrictions, however only publications with full texts available were included. Total 138 publications 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, 25 publications were finally included. There are cross-sectional studies, cohort studies, randomized clinical trial, and article review. Some studies showed that dietary fiber had an effect on insulin resistance, but other studies did not find this effect. Some studies described several factors associated with insulin resistance.

Discussion

Insulin resistance in obesity

Obesity-related insulin resistance is a complex disorder involving multiple pathway mechanisms.[8] Although obesity is not always associated with insulin resistance, most people with insulin resistance are obese or overweight. Obesity is a fundamental risk factor for initiation and development of insulin resistance.[9] Advances in molecular biology research have made better breakthroughs in finding much more to do with insulin resistance than just ten years ago. One mechanism for the signaling defects in obesity may be the increased expression and activity of several protein tyrosine phosphatases (PTPs), which dephosphorylate and thus terminate signaling propagated through tyrosyl phosphorylation. Some data indicated that at least three PTPs, including PTP1B, leukocyte antigen-related phosphatase (LAR), and src-homology-phosphatase 2 increased expression and / or activity in muscle and adipose tissue of obese humans and rodents. PTP1B and LAR showed to dephosphorylate the insulin receptor and IRS-1 in vitro. Mice in which PTP1B have increased insulin sensitivity and resistance to diet-induced obesity, at least in part, due to increased energy expenditure and suggests a regulatory role for PTP1B not only in insulin action but also in energy homeostasis. Interestingly, the insulin sensitivity is present in muscle and liver but not in adipocytes. There was a causal relationship between insulin sensitivity and leanness/energy expenditure or whether regulated by independent signaling pathways is a key question.[8]

Several mechanisms of which obesity causes insulin resistance are excess caloric intake (as commonly caused by a high-fat diet), adipose tissue dysfunction, oxidative stress, and inflammation at the tissue and systemic levels.[8,9,10] Oxidative stress results from an imbalance of production of reactive oxygen species (ROS) and antioxidant defenses. Excess ROS will increase the inflammatory factors which directly interfere with insulin signaling in its target tissue.[9]

Obesity causes a chronic low-grade inflammation. During this process, immune cells infiltrate metabolic organs, especially WAT (white adipose tissue) and the liver, where they secrete pro-inflammatory cytokines which act locally and systemically after being released into the blood circulation. Pro-inflammatory cytokine levels in obesity is not as high as when infection occurred, however increases 2-3 times compared to homeostatic conditions. The most widely recognized pro-inflammatory cytokines in obesity are TNFα and IL-6. IL-7, CCL-2, etc also contribute in it. All of these inflammatory cytokines inhibit insulin signaling in different pathways.[11] Hyperinsulinemia occurs in obesity and may be the cause of insulin resistance. Although it is commonly thought that hyperinsulinemia is resulted from insulin resistance, several studies suggest that high insulin level may lead to insulin resistance. Hyperinsulinemia in obesity is derived from overproduction of insulin or decreased clearance of insulin (**Figure 1**). Leptin resistance that occurs in obesity, may contribute to insulin overproduction in beta cells. Leptin inhibit insulin production in beta cell. Insulin clearance is carried out by the liver and kidneys. If there is malfunctioning of these two organs, then insulin clearance will decrease.[8]
Another mechanism for insulin resistance in obesity is based on genetic level. Increased global DNA methylation in obesity is positively correlated with insulin resistance. In obese people, there is an increased expression of the DNMT3a gene, which causes DNA methylation, either globally or locally, such as the main promoters of insulin pathway genes (INSR, SLC2A4).[12]

Effect of dietary fiber on insulin resistance

Fiber is a class of carbohydrates that cannot be digested by human digestive enzymes. Fiber categorizes in the group of complex carbohydrates and non-starch polysaccharides. The components of fibers classified into chemical properties like the ability of water solubility (soluble or insoluble fiber), the ability of fermented colonic microflora (fermentable vs non-fermentable fibers), or the viscosity (viscous vs non-viscous fibers). [13]

The fermentation bacteria of fiber in the large intestine produces short-chain fatty acids (SCFA), namely acetate, propionate, and butyrate. SCFAs play a significant role in the maintenance of health and disease progression. The highest levels of SCFA

are found in the proximal colon, where they are either used locally by enterocytes or transported across the intestinal epithelium into the bloodstream. Two main SCFA signaling mechanisms identified as the inhibition of histone deacetylases (HDACs) and activation of G-protein-coupled receptors (GPCRs). Because HDAC regulates gene expression, HDAC inhibition has multiple consequences.[14]

SCFAs in the gut activate G-protein-coupled (GPR) receptors, such as GPR41 (i.e., free fatty acid receptor 3; FFAR3) and GPR43 (i.e., free fatty acid receptor 2; FFAR2). These receptors are present in ileum and colon enteroendocrine L-cells, adipocytes, and immune cells. Both GPR41 and GPR43 on intestinal epithelial L-cells trigger the secretion of intestinal hormones (GLP-1 and PYY). Leptin is also released from adipocytes when SCFA binds to GPR41. PYY, GLP1, and leptin can decrease appetite. GLP-1 increases insulin secretion from pancreatic β cells and reduces glucagon secretion from the pancreatic islets, which leads to lower glucose production from the liver and increased peripheral glucose uptake. GLP1 can suppress appetite and food intake through the autonomic or central nervous system.[15]

SCFA will also stimulate PPARγ (Peroxisome Proliferator-Activated Receptor γ), where this activation will increase GLUT-4 in adipocytes.16 Activation of PPAR-γ causes the release of adiponectin from mature adipocytes, which stimulates AMP involved in regulating GLUT4 in muscles, stimulating increased acid oxidation fat in the mitochondria, as well as downregulation of gluconeogenesis in the liver, which will lead to increased insulin sensitivity in muscles and the liver.[15]

Other mechanism of fiber reduces postprandial hyperglycemia by increasing satiety which results in weight loss.[16] Soluble fiber slows gastric emptying and decreases absorption of macronutrients, causing a decrease in blood sugar and postprandial insulin levels because of the viscosity of the water-soluble fiber in the digestive tract. Different types of fiber have different effects on viscosity and absorption of nutrients. Guar gum is the most vicious type and has the best effect in lowering postprandial glucose.[17]

Insoluble fiber increases intestinal passage rate thereby decreasing absorption of nutrients, especially simple carbohydrates. This increased colonic transit which have a good impact on the gut microbiota which in turn increases the formation of SCFA.[18]

Several kinds of studies examining the relationship between dietary fiber and insulin resistance (**Table 1**). A cross-sectional study by Tucker et al[23] involving 6374 subjects aged 20 - 84 years, found that there is a significant relationship between HOMA IR and fiber intake in that group. There was also a negative and linear correlation between HOMA IR and fiber intake. It is explained that adults with high (Q4) fiber consumption significantly lower levels of insulin resistance (HOMA IR) than their counterparts (Q1-Q3). After controlling for differences in some demographic and lifestyle factors, and possible misreporting of energy intake, the inverse nutrients relationship between fiber intake and insulin resistance persisted.

Nevertheless, after adjusting for differences in abdominal obesity, there was no longer a relationship between fiber intake and insulin resistance. However, when participants divided into two groups based on whether or not they met the recommended fiber intake standard of 14 g per 1000 kcal, insulin resistance differences were substantial and adjusting for differences in abdominal obesity no longer eliminated the relationship. Findings of the present investigation highlight the role of abdominal obesity in the association between fiber intake and insulin resistance, and the value of consuming at least 14 g of fiber per 1000 kcal per day. Another study by Cuttler et al[23] also found similar results. The study involved subjects with PCOS and non-PCOS who then measured their fiber intake and HOMA IR. There was a significant relationship between HOMA IR and fiber intake, and there was a negative correlation between fiber intake and HOMA IR. An RCT study by Gower et al[21] also found similar results. This study involved 40 healthy female subjects aged 22 - 67 years, non-diabetic, and had a normal BMI - obese. The subjects divided into two groups, namely the insulin-sensitive group and the insulin-resistant group. Then given a resistant starch in the form of a snack with a dose of 15g / day and 30g / day for 4 weeks with a wash-out period of 4 weeks. At the end of the study, it was found that giving 30gr / day starch resistance could increase insulin sensitivity in the insulin-resistant group. Meanwhile, in the insulin-sensitive

group, the resistant starch did not affect insulin sensitivity.

In contrast to the results of the above studies, several studies obtained different results. Breneman et al[19] conducted a study of 264 healthy, non-smoking, and premenopausal women. The subjects were assessed for the fiber intake using a 7-day weighed food record, then divided into two groups, namely the high-fiber and low-fiber groups. The results of this study found that there was no significant difference from HOMA IR in the two subject groups. Another study by Ostrowska et al[20] also obtained similar results. This study involved 143 subjects and divided into two groups based on HOMA IR levels, namely the study group (HOMA IR> 2) and the control group (HOMA IR <2). The results showed that there was no significant difference in fiber consumption in the two groups. An RCT study by Roger et al[24] assessed the effect of giving a whole-grain diet on insulin sensitivity. The study involved 60 adult subjects aged 20 - 65 years, with stable weight, BMI 25–35 kg / m2, and/or increased waist circumference (≥94 cm for men and ≥80 cm for women). Subjects were given a whole grain diet and refined grain diet for 8 weeks with a wash-out period of 6 weeks. In the whole grain diet period, the mean fiber intake of the subjects increased and there was a significant difference with the mean fiber intake during the refined grain diet period. However, the administration of a whole grain diet did not alter insulin sensitivity but reduced body weight and systemic low-grade inflammation.

The study about fiber intake and insulin resistance showed different results. Many factors influence the differences in research results, for example, the age and gender of the subject. It is known that age and gender influence insulin resistance. Older age is associated with decreased insulin sensitivity due to an increase in adipocytes and decreased physical activity.[25] Another possible mechanism is that chronic inflammation tends to increase with age. Chronic inflammation impairs neutral lipid accumulation, adipose tissue function, mitochondrial function, and causes stress to the endoplasmic reticulum which results in insulin resistance.[26] Some studies only include female subjects, for example, the study of Brenneman, Cuttler, and Gower. There are differences in insulin sensitivity between men and women. The abundance of visceral and adipose tissue of the liver accompanied by low estrogen protective factors is associated with higher insulin resistance in men than in women. Estrogen is effective for increasing insulin sensitivity by a combination of many factors, such as directly affect insulin signaling in insulin sensitive tissue, releases of insulin from pancreatic beta cell, adipose tissue metabolism and energy expenditure, production of glucose from liver and regulates food intake from hypothalamus, and energy and metabolism.[27]

Other factors such as smoking status can influence the results of the study. Smoking is an independent risk factor for insulin resistance and type 2 diabetes. In the culture of muscle cell, nicotine exposure significantly increases phosphorylation of IRS-1ser636 and decreases insulin sensitivity. The two pathways known to stimulate phosphorylation of IRS-1ser636 (p44/42 mitogen-activated protein kinase [MAPK] and mammalian target of rapamycin [mTOR]) are both stimulated by nicotine.[28] Nicotine also causes oxidative stress which in turn increases the expression of TNFα thereby activating mTOR. Smoking reduces insulin mediated glucose uptake by 10% - 40% in men who smoke compared to men who do not smoke.[29]

Differences in the BMI and waist circumference of subjects in the study may also have influenced the results. BMI and waist circumference are associated with insulin resistance, where the mean HOMA IR results of subjects with normal nutritional status are lower than those with overnutrition and obesity.[30]

Another factor is the race differences of the previous studies. Genetics has an important role in the incidence of insulin resistance. Insulin resistance may occur in people with a family history of diabetes. Insulin resistance may also occur in certain ethnicities. In the US, black Americans and Pima Indians have a higher risk of insulin resistance than Caucasian Americans. In Asian countries, Indians and Chinese are also at high risk of developing insulin resistance.[8]

The assessment of the intake method also influences the results of the study. For example, Otruwska's study showed the assessment of intake used food recall. This method relies heavily on the subject's memory. It is easy to make mistakes when informing the food portions and affect the total

amount of assessed intake. Weighed food records conducted in Brenneman's study can avoid recall bias and errors in determining food portions.

Conclusion

Dietary fiber is a significant component of the diet. Fiber has many functions in the body, one of which is to increase insulin sensitivity. In obesity, where insulin resistance will occur, fiber is expected to improve insulin sensitivity. The studies of dietary fiber effect on insulin resistance have inconsistent results. Some studies showed that dietary fiber had an effect on lowering insulin resistance, but other studies did not find this effect. Several factors affected this difference, such as gender, sex, genetic, smoking status, and physical activity. In the future, further studies are required for better understanding about the effect of dietary fiber on insulin resistance in obesity.

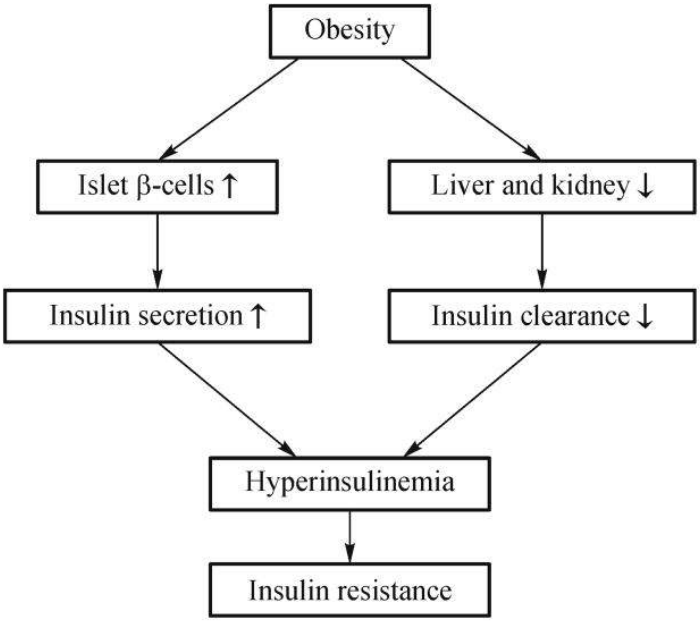

Figure 1. Hyperinsulinemia in obesity[8]

Table 1. Characteristics of the studies that examined dietary fiber and insulin resistance

Author	Study Design	Subjects	Results/ Conclusion
Brenneman CB, et al. 2012[19]	Cross-sectional study	264 healthy, non-smoking, premenopausal women	No significant differences in HOMA IR between groups with low and high total fiber intake.
Ostrowska L, et al. 2013[20]	Cross sectional study	143 subjects. Study group (HOMA IR>2)=76, Control group (HOMA IR<2)=67	No significant differences in the consumption of fiber between groups.
Gower BA, et al. 2016[21]	randomized, placebo-controlled, double-blind, cross-over study	40 healthy, non-diabetic women aged 22–67 years in the normal-weight to obese	Consumption of Resistant Starch at a dose of 30 g/d in the form of a snack food item was associated with improved insulin sensitivity in insulin resistant populations. It didn't affect insulin sensitivity in insulin sensitive populations.
Cutler DA, et al. 2018[22]	Cohort study	87 PCOS women, 50 non-PCOS women	There is significant differences in HOMA IR between groups, fiber intake was negatively correlated with HOMA-IR.
Tucker. 2018[23]	Cross-sectional study	6374 adults, 20–84 years	There is significant differences in HOMA IR between groups based on quartile of fiber intake, fiber intake was linearly and inversely related with HOMA-IR.
Roager HM, et al. 2019[24]	randomised cross-over trial, two 8-week dietary intervention periods comprising whole grain diet and refined grain diet, separated by a washout period of ≥6 weeks.	60 adults age 20–65 years old and weight stable with a body mass index of 25–35 kg/m^2 and/or increased waist circumference (≥94 cm for men and ≥80 cm for women).	Whole grain diet did not alter insulin sensitivity but reduced body weight and systemic low-grade inflammation.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Association between apolipoprotein B and dietary fibers

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Abstract

Introduction Global awareness to the importance of natural fibers in vegetables and fruits are still generally very low. Indonesian people consume less fibers, which has been associated with the development of heart disease. Heart disease has been known as the leading cause of morbidity and mortality. Apolipoprotein B (ApoB) is a component of atherogenic particles that can be used as a marker for an increased risk of cardiovascular disease. Researches on apoB profile and its relationship with fiber intake has provided inconsistent results. This is an article review of the current literatures on the relationship between dietary fiber and serum apoB levels.

Methods: This is an article review of the current literatures on the relationship between dietary fiber and apoB. We searched PubMed and Google Scholar using keyword "dietary fibers" and "ApoB" to capture meta-analyses, observational and experimental studies. A total of 97 publication and abstracts were screened for this review. After careful screening, nine studies were finally included.

Results: Two studies did not find associations between dietary fiber and serum apoB, while other seven found the association. Dietary fiber has been reported to be involved in the metabolism of serum cholesterol and blood pressure; hence, the deficiency of dietary fiber intake is believed to contribute to the epidemic of cardiovascular diseases. Several factors including nutritional status, dietary diet pattern, age, gender, physical activity, and smoking habits might influence the relationship between dietary fiber and serum apoB.

Conclusion: More studies are required in the future for better understanding on the effect of dietary fiber on the apoB; hence, the risk of cardiovascular diseases.

Keywords apolipoprotein B, fibers, cholesterol metabolism, heart disease, healthy promotion

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Introduction

Fruits and vegetables are considered in dietary guidance because of their high concentrations of dietary fiber.[1] According to the National Basic Health Research (Riskesdas) data in 2013, the national average proportion of low fruit and vegetable consumption prevalence for Indonesians aged 10 years and older was 93.5%. Similarly, the Riskesdas data showed the prevalence of 95.5% in 2018.[2] These data suggesting that public awareness and knowledge regarding the consumption of dietary fiber from vegetables and fruit is considerably very low and tend to get worse. According to data from the Ministry of Health, the Indonesian population consumes fiber 10.5 g/day generally.[3] This finding indicating that Indonesian met only half of the recommended daily fiber intake. Recommended fiber requirements based on the Nutrition Adequacy Rate (AKG) is 30–38 g/day. These values are also lower compared to the mean fiber intake in the UK and USA, which are 18 g/day and 16 g/day respectively.[4] Additionally, the data from the World Health Organization (WHO) shows that Indonesians consume fruit and vegetables only 34.55 kg per year,[5] which is less than half the Food Agriculture Organization (FAO) recommendation of 73 kg per capita per year.[6]

Many evidences have directed to the role of dietary fibers to prevent the development of several chronic diseases such as cancer, type 2 diabetes, obesity and cardiovascular.[7,8] In respect to the cardiovascular disease, dietary fiber has repeatedly been reported to be beneficial in reducing serum cholesterol and blood pressure; hence, the deficiency of dietary fiber intake is believed to contribute to the epidemic of cardiovascular disease.[9] In support, the results of a study indicated that consuming fiber 15-29 grams per day is sufficient to reduce mortality and the incidence of heart attacks and higher intakes of dietary fiber could provide even greater protection.[10]

Heart disease is a major health problem and cause approximately one-third of deaths globally.[11] WHO data showed that seventeen million people in the world are estimated die from heart disease in 2015, 75 % of which occur in developing countries.[12] Riskesdas data in 2018 shows that 1.5% Indonesians suffer from coronary heart disease.[13] Over 200 risk factors for heart disease have been identified, abnormal lipids profile is regarded as the most important risk factor.[14] Atherogenic dyslipidemia characterized by elevated levels of serum triglyceride (TG) levels and low-density lipoprotein cholesterol (LDL-C) with low levels of high-density lipoprotein cholesterol (HDL-C) plays a significant role in the development of heart disease.[15] Study by Sniderman *et al.*[16] highlighted the age-dependent association between apoB and the risk of cardiovascular events. ApoB have been proposed as a marker to quantitate the atherogenic damage, due to the fact that it is the component constituent of the atherogenic particles; hence, plasma apoB levels reflect the total numbers of atherogenic particles.[16] Study suggested that the apoB is a better candidate risk parameter than non-HDL cholesterol for identifying a subgroup of individuals with elevated cardiovascular risk.[17]

There are several factors that affect the circulating apoB levels. These factors are divided into groups, namely the nutritional and non-nutritional factors. The nutritional factors including nutritional status, dietary fibers, fat, and carbohydrates, while the non-nutritional factors are age, gender, physical activity, and smoking habits.[18] The dietary fiber can reduce levels of apoB through a distinct mechanism for each fiber source. Recently, study suggesting that the dietary fiber can reduce levels of apoB through gel formation which increases food transit time, delays gastric emptying, decreases nutrient absorption, and slows digestion.[19] Additionally, study showed that animals fed with fibers exhibited increased LDL-ApoB turnover, leading to the upregulation of hepatic LDL receptors and trigger faster catabolism and clearance.[19]

Decreasing apoB levels due to the dietary fibers can result in the reduced risk of cardiovascular disease. Research on the effect of soluble fiber on lipid profiles has been reported by several independent studies. One clinical trial by Ramos *et al*.[20] in 116 people with hypercholesterolemia showed that apoB levels in the group fed with fiber significantly lower after after 12 weeks. Another clinical trial in 28,984 Swedish individuals showed a significant correlation between dietary fiber intake and apolipoprotein B.[21] Unfortunately, research on the profile of apolipoprotein B and its relationship

with fiber intake so far has provided inconsistent results. In this manuscript, we provide a systematic literature review on the highly variable research results on the association between Apolipoprotein B and fiber intake to gain a comprehensive insight.

Methods

This article is a literature review using any meta-analyses, observational and experimental studies that are relevant to this article. According to Creswell and Poth, literature reviews are written summaries of articles from journals, books, and other documents that describe theories and information both past and present; organizing literature into the topics and documents needed.[22] The type of data used by the author in this study was searched from PubMed and Google Scholar using the explode function for subgroup terms with operators ("and,"or") for keyword "dietary fibers" and "Apolipoprotein B" to capture all meta-analyses, observational and experimental studies that included findings on the relation of dietary fibers and apoB. Hand-searching was used to identify further potential eligible studies. A total of 97 publication titles and abstracts were screened for this literature review. The inclusion criteria used in this study are categorized based on study design, specific interventions, participants, and outcome assessed. Study designs of evaluations included in the review was controlled trials with either a randomised crossover or parallel study design with an intervention period equal or greater than 14 days. The analysis was limited to primary sources of fibre for which there were more than 5 trials per type of fibre (i.e. for oat products, psyllium, pectin and guar gum). Specific interventions included in this review were water-soluble dietary fibers from a single source, including pectin, oat bran, guar gum, and psyllium. Participants included in this review were men or women who either healthy, hyperlipidemic, obese or diabetic. Outcomes assessed in this review were correlation between dietary fiber intake and apolipoprotein B. After careful screening, nine studies were finally included. The data obtained then analyzed by descriptive analysis method. The method of descriptive analysis is carried out by describing the facts which are then followed by analysis with sufficient understanding and explanation.

Results and Discussion

Dietary fibers

Definition and classification of fibers

Dietary fiber was originally defined as a non-digestable constituents of the cell wall of the plant.[23] Later on, dietary fiber was determined as any component of plant that resistant to hydrolysis by human digestive enzymes.[24] In 2000, American Association of Cereal Chemists (AACC) defined dietary fibre as the edible parts of plant or analogous carbohydrates that are resistant to digestion and absorption in the human small intestine with complete or partial fermentation in the large intestine. Dietary fiber includes cellulose, hemicellulose, lignin, pectins, gums, β- glucan, resistant starch, fructans, chitosan and chitin.

Fibers can be classified according to their type and solubility. Based on the type, fiber is divided into dietary fiber and functional fiber. Dietary fibers include cellulose, hemicellulose, pectin, lignin, gum, fructan and resistance starch; while functional fibers include cellulose, pectin, lignin, gum, fructan, β-glucan, and psyllium. Fiber can also be classified based on its solubility into soluble fiber and insoluble fiber. Soluble fibers include hemicellulose, pectin, gum, β-glucan, and psyllium; while insoluble fibers include lignin, cellulose, fructans, and polyols.[24]

Dietary fiber can be obtained from daily food ingredients such as vegetables, nuts, fruit, and cereals. The amount and composition of fibers vary between food. The fiber content of different food sources is listed in **Table 1** .[24]

Recommended daily intake for dietary fibers

Current dietary guidance recommends that Americans consume 14 g of fiber per 1,000 kcal. Recommendations for fiber intake for adults and children are shown in **Table 2**. However, most Americans only consume about 15 g of fiber per day.[25] Meanwhile, in Indonesia, recommended fiber requirements based on the Nutrition Adequacy Rate

(AKG) is 30–38 g/day depend on the age and gender of the individual. At 19-29 years of age, it is recommended that men consume 37 grams of fiber/per day while woman is 32 grams/day. At the age of 30-49, 36 grams per day are recommended for men while for woman is 30 grams per day. Regardless, the Indonesian population consumes fiber 10.5 g/day generally.[33]

Apolipoproteins

Structure of the apolipoproteins

The complete amino acid sequence of the ApoB100 consists of 4536 amino acids with a molecular weight of 550 kDa.[26] The mature ApoB100 is the 27 amino acids N-terminal truncated version of the pre-mature ApoB100 with the molecular mass of 513 kDa.[27] ApoB100 has a globular amino terminal domain, which reacts with microsomal triglyceride transfer proteins. The apoB gene is located on the short arm of chromosome 2. Study have identified one hundred twenty-three genetic variants in the apoB gene. The apoB100-3,500Arg-Gln affects its receptor binding and causes a disorder known as familial defective apolipoprotein B-100 (FDB).[28] ApoB100 is synthesized in hepatocytes and it could be degraded under certain conditions.[29] ApoB is an atherogenic component found in VLDL, IDL, and Lpa. Therefore, apoB represents the circulating atherogenic lipoprotein particles.

ApoB48 consists of 2152 amino acids with a molecular mass of 264 kDa. ApoB100 and apoB48 are produced from a single gene. ApoB48 is generated by cell-specific RNA editing of a CAA codon to a premature UAA termination codon and is identical to the N-terminal 48% of apoB100.[30] ApoB48 is synthesized by enterocytes, secreted in chylomicrons and stored in chylomicron remnant. Since one molecule of apoB48 is present in each chylomicron particle, it can be used as a marker for the chylomicrons.[31] Particles smaller than 70–80 nm can penetrate blood vessel walls. Therefore, chylomicron remains, but not nascent chylomicrons, are considered to be atherogenic. Chylomicron waste is enriched with ester cholesterol by exchange with HDL.[32]

Lipoprotein classes

Insoluble lipids are transported in a complex with proteins as lipoproteins by circulatory system. Lipoproteins have a central hydrophobic core of non-polar lipids, consisting of cholesterol esters and triglycerides that is surrounded by a hydrophilic membrane consisting of phospholipids, free cholesterol, and apolipoproteins. Plasma lipoproteins are divided into five classes chylomicrons, Very Low Density Lipoprotein (VLDL), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), and lipoprotein.[33] Apolipoproteins regulate and control lipoprotein metabolism and lipid transport by acting as ligands for lipoprotein receptors, guiding the formation of lipoproteins, and serving as activators or inhibitors of enzymes involved in the metabolism of lipoproteins.[34]

Lipoprotein metabolism

Lipoproteins are lipid protein particles that carry hydrophobic substances in a hydrophilic environment of the blood. Lipoproteins are classified based on their hydrated density, in an ascending order, into chylomicrons, VLDL, IDL, LDL and HDL.[35] Apolipoproteins or apoproteins are proteins that make up lipoproteins, which serve as receptor-binding and regulatory proteins. The cores of these particles contain hydrophobic molecules such as triglycerides (TG) and cholesteryl esters. The liver, intestines, spleen, brain and testes synthesize apolipoproteins and at their surface contain lipoproteins. There are 4 main types of lipoproteins, namely Apo A, B, C, and E. One or more apolipoproteins make up each lipoprotein including apo A is the main apolipoprotein constituent of High-density liporotein (HDL), while apo B100 is the main apolipoprotein in LDL and can also be found on VLDL. Lipoproteins have different sizes according to their lipid composition and apolipoprotein content. This characteristic changes as a result of the reaction of enzymes such as lipoprotein lipase (LPL), hepatic triglyceride lipase (HTGL), lecithin-cholesterol acyltransferase (LCAT) and cholesterol ester transfer protein (CETP).[36] Apolipoprotein functions to activate and regulate enzymes in lipoprotein metabolism, maintain the integrity of the lipoprotein complex structure, and become ligands for specific cell surface receptors. The formation and metabolism of lipoproteins is influenced by both the apolipoprotein

content and its conformation. Hepatocytes produce apoB100 and the small intestine produces apoB48 which is a glycoprotein of the apo B group.[37] Apolipoproteins control cellular intake of lipoproteins by binding with lipoprotein receptors. ApoB100 and apolipoprotein E (apoE) bind to the apoB/E (LDL) receptor. ApoE also binds to LDL receptor-related protein (LRP). Apolipoprotein A binds to the BI scavenger receptor.[35]

The exogenous lipoprotein pathway starts with the absorption of the dietary cholesterol and fatty acids in the intestine, and incorporation into chylomicrons. Chylomicrons enter the circulation and travel to peripheral sites. Chylomicrons are triglyceride-rich and normally catabolized within minutes by the endothelium-associated lipoprotein lipase (LPL), releasing free fatty acids (FFA), which are taken up and metabolized by the liver, muscle, and adipose tissues; and chylomicron remnants are formed. Chylomicron remnants are then taken up by the liver. *via* the low-density lipoprotein (LDL) receptor and the LDL receptor–related protein (LRP).[33,35,38]

The endogenous lipoprotein pathway begins in the liver with the assembly and secretion of triglyceride-rich VLDL particles, which transport triglycerides from the liver to peripheral tissues. The triglycerides carried in VLDL are hydrolysed by LPL in muscle and adipose to form intermediate-density lipoproteins (IDL) or VLDL remnants, which can be taken up by the liver or can be further hydrolyzed to LDL particles. LDL is converted to bile acids in the liver, then secreted into the intestines; while in non-hepatic tissues, LDL is used for the synthesis of hormones, cell membrane, or being stored. LDL is also taken up by macrophages.[35,38]

LDL transports cholesterol to hepatocytes and other peripheral tissues with the help of ApoB100 for the recognition and uptake of LDL by the LDL receptor. Meanwhile, the oxidized LDL (ox-LDL) is taken up by macrophages and vascular smooth muscle cells. These can lead to excess accumulation and the formation of foam cells, which is a major step in the plaque formation and development of atherosclerosis.[39] The small dense LDL cholesterol (sdLDL-c) is one of LDL subclass associated with raised TG and decreased HDL-c levels and more atherogenic than larger LDL particles.[40]

HDL plays a crucial role in reverse cholesterol transport, acting as a vehicle for cholesterol shuttle from peripheral cells to the liver for excretion and catabolism which occurs in three phases: extravascular, intravascular, and intrahepatic.[41] It also provides a reservoir of C apolipoproteins, which are required for the metabolism of chylomicrons and VLDL. Reverse cholesterol transport can be performed in three different routes: (1) HDL with multiple apoE is taken up by the liver mediated by LDL receptor, (2) accumulated cholesteryl esters from HDL is taken up by the liver *via* the scavenger receptor B1, (3) cholesteryl esters are transferred by the cholesteryl ester transfer protein (CETP) from HDL to triglyceride-rich lipoproteins.[42] Many experimental and epidemiologic studies have indicated the protective effect of HDL against atherogenesis indicates its function in reverse cholesterol transport. Disturbances in the metabolism of lipoproteins is a major contributor of the antiatherogenic properties of HDL; thus, determined as risk factor for coronary heart disease.[43]

Factors affecting apolipoprotein B

There are several factors that cause an increase in apo B including nutritional factors (nutritional status, dietary fibers, fat, and carbohydrates) and non-nutritional factors (age, gender, physical activity, and smoking habits).

1. Nutritional status

Obesity is one of the risks of cardiovascular disease due to its relationship with high triglycerides, LDL cholesterol, low HDL cholesterol, increased blood glucose, insulin resistance and hypertension. New findings regarding metabolic risk factors associated with fat and obesity are the presence of a small dense LDL phenotype, postprandial hyperlipidemia with atherogenic accumulation and excessive lipoproteins production containing apolipoprotein B. These lipid disorders are characteristic of metabolic syndrome and is associated with an inflammation which partly due to the adipose tissue itself. An important relationship between obesity, metabolic syndrome and dyslipidemia, is insulin resistance in peripheral tissues that leads to increased liver fatty acids from food sources,

intravascular lipolysis and from adipose tissue resistance to the antilipolytic effect of insulin.[44]

2. Diet pattern
Study in 28,984 Swedish individuals showed a significant correlation between dietary fiber intake and apolipoprotein B.[21] Another clinical trial by Ramos *et al.*[20] in 116 people with hypercholesterolemia showed that apoB levels in the group fed with fiber significantly lower after after 12 weeks. Additionally, study by Anggadiredja *et al.*[45] in 41 individuals with hypercholesterolemia showed that 4 weeks of fibers supplement treatment affects apolipoprotein B levels.

3. Age and gender
Research conducted by Anagnostis et al.[46] showed that advancing age is positively associated with increased levels of apolipoprotein B. Those study also explains that at the age of 50-55 years, men generally have a higher average apolipoprotein B than women.

4. Smoking habits
Smoking is one of the causes of heart attacks. Nicotine causes the secretion of catecholamines, cortisol, and growth hormone, which results in adenyl cyclase activation in the adipose tissue. Lipolysis will be initiated from triglycerides and fatty acids will be secreted into the plasma. Circulating fatty acids binds with albumin and results in increased synthesis of triglycerides and VLDL in the liver. Thus, results in increasing triglycerides and VLDL and decreasing HDL. Since apolipoprotein B is required to produce LDL and VLDL, high levels of LDL and VLDL is associated with high apolipoprotein B.[47]

5. Physical activity
Study revealed that months of aerobic exercise decreased apoB concentration in hypercholesterolemic men.[48] In contrast, another study by reported that aerobic exercise for 20 weeks did not affect the concentration of apoB. Others found no change in apoB concentrations during either long or short aerobic exercise. Some factors must result in these various outcomes such as age.[49]

Association between apolipoprotein B and dietary fibers

Dietary fiber has been studied by various researchers to provide evidences of its beneficial effect in lowering cholesterol levels. The increased risk of cardiovascular disease has a positive correlation with the improvement of LDL cholesterol levels.[50] Soluble fiber has a positive effect on apoB levels in respect of preventing cardiovascular disease. ApoB is the dominant lipoprotein component in LDL particles, which is also found in VLDL and IDL. ApoB have been proposed as a marker to quantitate the atherogenic damage, due to the fact that it is the component constituent of the atherogenic particles; hence, plasma apoB levels reflect the total numbers of atherogenic particles.[25,51] Research on the association of ApoB levels and dietary fibers intake shows controversial results (**Table 3**). This may be due to differences in the characteristics of the subject, especially in the source of food and metabolism in the body in various populations.

Two studies did not find associations between dietary fiber and serum apoB, while other seven found the association. Dietary fiber has been widely reported to be involved in the metabolism of serum cholesterol (both atherogenic and non-atherogenic) and blood pressure; hence, the deficiency of dietary fiber intake is believed to contribute to the epidemic of cardiovascular diseases. Several factors including nutritional status, dietary diet pattern, age, gender, physical activity, and smoking habits might influence the relationship between dietary fiber and serum apoB; thus, explaining the different results. The clinical utility of apoB is of the most value in populations such as those with obesity and type 2 diabetes in whom the risk of CVD is elevated.[58] Trapping of apoB particles drives the atherosclerotic process from beginning to end.[59] Cholesterol is a critical component of the apoB particles within the arterial wall. The mass of cholesterol within plasma does correlate positively with the number of apoB particles within plasma. But variance in the mass of cholesterol per apoB particle produces variance in the relation between cholesterol and apoB and therefore a difference in the relation of each to risk.[60] EAS and EFLM accept that cardiovascular risk relates more closely to apoB than to LDL-C/non-

HDL-C; therefore, the clinical utility of apoB exceeds LDLC/non-HDL-C.[61,62]

Unfortunately, there are still few studies that did not find associations between dietary fiber and serum apoB one of which is study by Ho *et al.*[53]. Interestingly study by Ho *et al.*[53] showed that konjac glucomannan did not appear to significantly affect the overall effect estimate for apoB, the reduction of 0.05 g/L is higher than that reported in the previous reported meta-analysis of oats (−0.03 g/L) and barley (−0.03 g/L) β-glucans by Ho *et al*.[55]. Therefore, more studies are required to better understand the role of konjac glucomannan and β-glucans on apoB, specifically the mechanism of which causing the results to be distinctive.

Conclusion

The results of the studies on the relationship between dietary fibers and serum apoB levels have been inconsistent; while some studies found the negative correlation between dietary fibers and serum apoB levels, others did not. Dietary fiber has been widely reported to be involved in the metabolism of serum cholesterol (both atherogenic and non-atherogenic) and blood pressure; hence, the deficiency of dietary fiber intake is believed to contribute to the epidemic of cardiovascular diseases. Several factors including nutritional status, dietary diet pattern, age, gender, physical activity, and smoking habits might influence the relationship between dietary fiber and serum apoB; thus, explaining the different results. More studies are required in the future for better understanding on the effect of dietary fiber on the level of serum apoB; hence, the risk of cardiovascular diseases.

Table 1. Dietary fiber content of various food sources[24]

Food Sources	Soluble Dietary Fiber (g/100 g)	Insoluble Dietary Fiber (g/100 g)	Total
Fruits (raw)			
Apple with skin	0.70	2.00	2.70
Banana	0.58	1.21	1.79
Grape	0.24	0.36	0.60
Mango	0.69	1.08	1.76
Orange	1.37	0.99	2.35
Pear with skin	0.92	2.25	3.16
Pineapple	0.04	1.42	1.46
Strawberry	0.60	1.70	2.30
Watermelon	0.13	0.27	0.40
Beans (cooked)			
Black beans			8.7
Red beans	1.36	5.77	7.13
Nuts			
Almonds			12.3
Peanuts			8.1
Vegetables (cooked)			
Broccoli	1.85	2.81	4.66
Carrot	1.58	2.29	3.87
Lettuce (raw)			1.3
Corn			2.0
Mushroom			2.4
Cooked potatoes with skin	0.61	1.70	2.31
Steamed potato, skinless	0.99	1.06	2.05
Grains and Products			
Rice (cooked)			
White			0.3

Food Sources	Soluble Dietary Fiber (g/100 g)	Insoluble Dietary Fiber (g/100 g)	Total
Red			1.8
Bread			
White			2.4
Wheat			6.8
Cereal (cold)			
All rice bran			29.3
Raisin skin			11.1
Corn flakes			2.5
Wheat biscuits			10.6

Table 2. Recommended fiber intake in Indonesia and the United States

Gender	Age (year)	Recommended fiber intake (gram)	
		Indonesia	United State
Man	19 – 29	37	38
	30-49	36	
	≥ 51		31
Woman	19 – 29	32	25
	30-50	30	
	≥ 51		21

Table 3. Characteristics of studies on the association between apoB and dietary fibers

Author	Study Design	Subjects	Results/Conclusion
Yulia *et al.* (2016)[52]	Double blind randomized clinical trial with parallel design	28 individuals with obese I (BMI of 25-29.9 kg/m^2), aged 30-50 years.	*Psyllium husk* fiber 8.4 g/day and low-calorie balanced diet 1200 kcal/day in obese I individuals did not reduce apo B level in 4 weeks
Ho *et al.* (2017)[53]	Meta-analysis study	12 publications (n = 370) were included. Six trials reported on apoB (n = 162).	**Results from 6 studies did not show any effect of konjac glucomannan, a viscous soluble fiber, on apoB**
Antoniazzi *et al.* (2019)[54]	Population-based observational study	190 individuals with heterozygous familial hypercholesterolemia	Inverse association was encountered between fibers with ApoB
Ho *et al.* (2016)[55]	Meta-analysis study	Fifty-eight trials (n 3974) retrieved from MEDLINE, Embase, CINAHL and Cochrane CENTRAL assessing the effect of oat β-glucan diets compared with controlled diets apoB.	**Oat β-glucan, a viscous, soluble fibre, has a lowering effect on apoB**
Rakvaag *et al.* (2019)[56]	Double-blind, randomized, controlled, parallel intervention study	73 subjects with abdominal obesity (abdominal circumference ≥80 cm for women or ≥94 cm for men) age ≥40 years.	Low-fiber cereal consumption for 12 weeks reduced fasting apolipoprotein B.

Author	Study Design	Subjects	Results/Conclusion
Frondelius *et al.* (2017)[21]	Population-based cohort	74,318 healthy individuals, men and women aged 44–74 years between 1991 and 1996	There was a significant correlation between dietary fiber intake and apolipoprotein B.
Ramos *et al.* (2011)[20]	Randomized, parallel-design study with blinded endpoints	Subjects with primary hypercholesterolemia (n= 116).	ApoB levels in the group fed with fiber significantly lower after after 12 weeks
Anggadiredja *et al.* (2020)[45]	Double-blind, randomized, parallel-group study	50 hypercholesterolemic participants (fasting LDL-c concentration of > 130 mg/dL), 18 years of age	Four weeks of fibers supplement treatment significantly affects apolipoprotein B levels.
Jovanovski *et al.* (2018)[57]	Meta-analysis study	28 trials (n = 1924) retrieved from Medline, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials	Supplementation of *Psyllium* fiber effectively improves apoB (95% CI: -0.08, -0.03 g/L; P < 0.0001)

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

The role of nutrition and pancreatic enzyme replacement therapy in children with cystic fibrosis

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Abstract

Background Cystic fibrosis (CF) is an inherited genetic disorder with high mortality and morbidity. CF is strongly correlated with malnutrition due to higher energy losses, pancreatic insufficiency, chronic inflammation, higher resting energy expenditure, and feeding problems. Malnutrition in CF patients associated with worse survival. Thus, appropriate and prompt nutritional intervention should be addressed to reduced malnutrition in CF patients.

Methods The literature search was performed on 9 August 2021 in four major databases such as MEDLINE, EBSCOhost, Cochrane Reviews, and Web of Sciences to find the role of nutrition and pancreatic enzyme replacement therapy in pediatrics population with cystic fibrosis.

Recent findings In recent decades, early nutritional management and pancreatic enzyme replacement therapy (PERT) have been shown to improve CF patient's outcomes. Nutrition should be given in higher calories compared to healthy individuals with close and regular nutritional status monitoring. High protein and fat diets are essential for CF patient's overall survival. Adequate level of micronutrients should be ensured to avoid morbidity caused by micronutrients deficiency. Regular pancreatic insufficiency screening should be done annually in order to start PERT early. Further research focusing on body composition, growth chart, protein intake, and PERT are needed to further improve the management of CF patient.

Conclusion Nutritional intervention and PERT play an important role in prolonging CF patient survival. Both treatments should be initiated early with nutritional status close monitoring and tailored to each individual. Collaboration with parents and children is critical to warrant that CF patients followed the dietary advice.

Keywords cystic fibrosis, nutritional therapy, pancreatic enzyme therapy

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Introduction

Cystic fibrosis (CF), also known as mucoviscidosis, is one of the most common lethal inherited autosomal recessive genetic disorders found in the Caucasian population. There are approximately 1 in every 3,000 – 4,000 Caucasians born with this disorder. Although CF is notably found in Caucasians, it could also occur in other ethnicities with lesser prevalence.[1]

Cystic fibrosis is caused by mutation in gene encoding the Cystic Fibrosis Transmembrane Conductance Regulator (CFTR) protein. Mutation leading to CFTR dysfunction mainly in regulating sodium and chloride transport system across numerous epithelial and other membrane cells. There are over one thousands of CFTR mutations of which give rise to its broad spectrum of phenotypes, ranging from single-organ pathology to classic CF.[2] CF can affect multiple organs such as liver, reproductive organs, intestine, and others, with considerable morbidity and mortality especially comes from its pathology in lungs and pancreas.[1]

In the lungs, the chloride ion channel dysfunction results in decreased airway surface liquid, causing dehydration, thickened mucus, and ciliary function impairment. This condition promotes microorganisms to infect and causing inflammation, hence damaging and obstruct the airway. This vicious cycle of infection, inflammation, and airway obstruction contributes to the significant mortality in CF patients. In pancreas, the mechanism of chloride absorption and bicarbonate secretion of pancreatic ductal epithelial cells play essential roles in fluid secretion and optimizing digestive enzyme's function. The CFTR mutation found in CF patients altered those mechanisms, causing pancreatic secretions to become lower in volume and pH with higher protein content, thus obstructing intra-pancreatic ducts and impairing the absorption process. This premise is further supported by the fact that around 15-20% of CF babies have meconium ileus shortly after born. Malabsorption leading to undernutrition also expected due to the exocrine pancreas and intestinal resorptive processes malfunction, generating other morbidities for CF patients.[3]

Numerous CF complications caused a lot of children did not surpass the first five years of life, with life expectancy approximately only six months when CF first introduced in 1938. Decades later, after the researcher's continuous effort to advance and develop CF therapies, there is a significant improvement in CF patients' survival with median survival age now beyond 30 years. One of the main pillar among other CF key treatment that could markedly increase patient's survival is nutritional management.[4]

Nutrition plays a vital role in CF prognosis; however, patient with CF usually presented with some degree of undernutrition due to malabsorption secondary to pancreatic insufficiency, higher energy intake, higher energy losses, and abnormal metabolic activity. Malnutrition in CF patients has been found to strongly correlated with poor pulmonary outcome, meanwhile good nutritional status is associated with prolonged survival and better lung function. Thus, close monitoring of nutritional status and early nutritional management is critical for CF patient's overall survival. This review aims to summarize the latest evidence and guideline regarding the role of nutritional intervention along with the use of pancreatic enzyme replacement therapy in CF management, especially in the pediatric population.

Methods

In order to summarize the role of nutritional intervention and pancreatic enzymes in CF, a database search has been performed using MEDLINE, EBSCOhost, Cochrane Reviews, and Web of Sciences on 9 August 2021. The search strategy was conducted by using keywords such as "pediatric", "infant", "children", "nutrition therapy", "diet therapy", "pancreatic enzyme replacement therapy", "PERT", "cystic fibrosis", and "mucoviscidosis". The inclusion criteria were English language journal articles, guidelines, review articles, systematic review, or meta-analysis with pediatric as a subject population. The exclusion criteria were literatures that have been published for more than 5 years. Exceptional will be made for aged articles providing information that could not be found in recent articles.

Results and Discussion

Nutritional status and cystic fibrosis

Cystic fibrosis patients often presented with malnutrition. European Cystic Fibrosis Society (ECFS) Patient Registry data showed that in 2010 about half of CF patients have some degree of malnutrition. The latest ECFS Patient Registry data showed that after the age of 2, children with CF have a lower average BMI compared with their non-CF same-age population.[5] Several underlying mechanisms for malnutrition such as increased resting energy expenditure (REE), malabsorption caused by pancreatic insufficiency, deficiency of fat-soluble vitamins, chronic inflammation, CF-related diabetes, decreased appetite (due to medications side effects), gastrointestinal problems (constipation, bacterial overgrowth, distal intestinal obstructive syndrome), and behavioral feeding problems. Malnutrition in CF leads to worse outcomes on account of worse lung function, immunological alteration, lower quality of life, stunted growth, and shorten life expectancy.[6] The risk of malnutrition further worsen by CF-related diabetes and other metabolic complications. In CF-related diabetes, patients have insulin deficiency that will lower insulin's anabolic activity. Other CF complication, CF-related liver disease, correlated with several nutritional deficiencies, especially calcium, essential fatty acids, and fat-soluble vitamins.[7]

For decades, effort has been made to decrease malnutrition in CF patients by using diet high in calorie and fat, fat-soluble vitamin supplementation, and pancreatic enzyme replacement therapy (PERT). Those efforts resulted in the improvement of CF patient's nutritional status. The median BMI percentiles of children with CF in 2002 is 43% meanwhile, in 2017 the median increased to 75.1%. The same improvement could also be seen in the number of children with a weight < 10^{th} of which the number decreased from 23.1% to 10.4%.[8]

The role of nutritional management in cystic fibrosis patient

Nutritional intervention should be started as early as possible by the time cystic fibrosis diagnosis is made, with the best outcome came from the detection in the first days of life through newborn screening.[9] A good nutritional status is strongly associated with a better outcome, lower incidence of CF-related diabetes, fewer days of hospitalization, and better lung function. Better lung function has been proved by the capability of Forced Expiratory Volume in one second (FEV1) to reach its highest potential at six years of age in those children who reached the 50^{th} percentile of weight for length/BMI earlier in life. After reached the higher FEV1, child with CF have been seen able to maintain good growth pattern for the rest of their early childhood.[10]

Given the importance of nutritional status, nutritional care should be started aggressively early in life, preferably in the first year of life and continued over the lifetime. The European Society for Clinical Nutrition and Metabolism-The European Society for Pediatric Gastroenterology Hepatology-and The European Cystic Fibrosis Society (ESPEN-ESPGHAN-ECFS) through their guideline recommends that CF patients nutritional status should be monitored frequently by measuring anthropometric status (weight, height, BMI) and body composition.[11] Body composition should also be measured due to the fact that around 14%-24% CF child with normal BMI has low fat-free mass (including muscle). Muscle composition correlated with better prognosis. Children with normal BMI do not necessarily have a better outcome if they have a low lean mass of muscle. One of the methods used in measuring body composition is using Bio-Electrical Impedance Analysis (BIA) with CF-specific equations, one of which was developed by Charatsi et al. BIA with CF-specific equations showed better accuracy in reflecting overall nutritional status than other examinations without validation to CF.[12] However, there is also other recommended body composition assessment such as dual-energy X-ray absorptiometry (DXA), air displacement plethysmography, handgrip strength, and double-labeled water measurement. There was still limitation in the usage of body composition such as the unavailability of consensus on the used equation, technique, and proper references. Hence, there was no consensus in the threshold for fat free mass and fat free mass index, warranting further studies.[13]

Besides muscle mass, bone mineral density (BMD) should also be assessed. Lean body mass and

bone mineral content are shown to better reveal nutritional deficits rather than low BMI and better predict lung function. Calella et al. found that lean body mass has significant correlation with FEV_1 and was a significant predictor for pulmonary function.[14] Lower values of fat free mass and bone mineral density are associated with worse lung function. BMD is evaluated by using DXA due to high rate of osteopenia and osteoporosis in CF patients. The European Cystic Fibrosis Bone Mineralization Guidelines recommend that DXA examination be performed every 1-5 years, starting from 8 to 10 years of age. For children with short height (the height is > one standard deviation lower than same-age healthy children), bone mineral density Z score should be adjusted for their statural age to avoid overestimation in children with short stature.[11]

The frequency of nutritional status measurement depends on the patient's age and their nutritional status at the time of their presentation. Infants (0-2 years old) with undernutrition should undergo nutritional status measurement every 1-2 weeks until they reached the 0 SD (50^{th} percentile) weight and length for healthy same-age population. After they reached the intended nutritional status, they could continue monitoring monthly for their first year of life and every three months after. Ideally, every malnourished or stunted children should be monitored more frequently.[11]

To ensure the success of nutritional intervention program, parents should be educated with this higher daily intake needs so they could provide the CF child with appropriate and balanced diets. Dietary counseling should also be given to the child to maintain healthy feeding and correct behavioral feeding problems commonly found in CF patient. A dietary review using 24-h recall or 3-5 days diet record will help in the qualitative and quantitative evaluation of nutritional intake. Thus, dietary review is recommended to be performed every 3 months especially for those with nutritional risk.[11]

Special consideration should be taken in CF-related diabetes (CFRD). CF patients with diabetes tend to have lower BMIs and height compared to those without diabetes. The nutritional decline commonly started 4 years before CFR diagnosis and was believed to be resulted from the catabolic effects of insulin insufficiency. In CFRD, good nutritional status should be achieved while maintaining the normal blood glucose levels. In general, patients with CFRD followed the same dietary recommendations with those without diabetes. However, there are several adjustments. In carbohydrate consumption, refined simple sugar particularly sugary beverages, juices and soda pop should be restricted. It is recommended to consume six servings of grains and 3-4 servings of dairy daily. In fats consumption, it is recommended to have food with higher omega-3 fatty acids content to lower inflammation which commonly seen in CFRD.[16]

For newly diagnosed infants, the energy intake should come from exclusive breastfeeding if possible. If exclusive breastfeeding is not possible, regular infant formula can be used. Evidence showed that breastfed infants had better lung functions and fewer infections, possibly because of better immune function and docosahexaenoic acid (DHA) content in breastmilk. Children with poor growth or malabsorption might get benefit from high energy or hydrolyzed formula. However, there are no enough evidence to support the usage of those formulas. Both breastfed or formula-fed infants should take additional sodium supplementation and be introduced to solid food at the same time with healthy infants.[11] The summary of energy and macronutrient recommendation can be seen in **Table 1.**

Recommendation for micronutrient intake

CF patients often have micronutrient imbalance due to intestinal malabsorption, chronic inflammation, and increased sweating. Extra attention especially should be put on salt, iron, calcium, and zinc content. Salt supplementation is needed in all CF patients. Breastmilk, standard formula, and baby foods have relatively low sodium content and do not provide adequate sodium. Sodium deficiency could impair infant growth; thus, sodium assessment and supplementation should be carried out in infants. The ESPEN-ESPGHAN-ECFS guideline recommends that breastfed infants are given 1-2 mmol/kgbodyweight/day sodium diluted in formula or water whenever sodium deficiency is discovered. However, this dosage can be increased by considering the presence of hot environmental conditions, diarrhea, vomiting, or other conditions that could make significant sodium losses. The

North American guidelines recommend that sodium supplementation in infants does not exceed 4 mmol/kg body weight/day. In older children, the body's sodium level could be assessed through sodium: creatinine ratio. Supplementation could be given by sodium chloride capsules administered several times a day.[11]

Malabsorption in CF patients leads to low level of fat-soluble vitamins, including vitamin D. Low level of vitamin D resulted in low calcium. Calcium level in CF patients should be assessed at least annually with special consideration in children with growth faltering or weight stagnation. Calcium supplementation should be given if calcium intake is deficient, according to the daily recommended calcium intake established by the European Food Safety Authority (EFSA) that is shown in the summary table below (**Table 2)**.[11]

Malabsorption also leads to iron deficiency in CF patients, resulted in iron deficiency anemia and poor outcome. Iron levels should be monitored annually. The ESPEN-ESPGHAN-ECFS guidelines recommend that iron deficiency be screened first through serum iron values. If the result is low, further laboratory work such as serum ferritin, transferrin saturation, and total iron-binding capacity should be done to differentiate between iron deficiency anemia or anemia of chronic inflammation. Iron supplementation could be given if the iron deficiency is proved.[11]

Zinc deficiency was correlated with growth faltering, eye problems, delayed sexual maturation, and anorexia in CF patients. Thus, zinc supplementation is recommended in CF child with aforementioned condition with the supplementation dosage 1 mg/kg/day (max 15 mg/day) in infants (0-2 years) and 15mg/day in older children (2-18 years). The supplementation is suggested to be given in 6 months.

CF children are commonly found with fat-soluble vitamin (vitamin A, D, E, K) deficiency with a prevalence 10-35%, resulted from pancreatic insufficiency. Low levels of vitamin A correlated with impaired lung function and poorer clinical status in CF patient. Low levels of vitamin D associated with reduced bone mineral density. Low levels of vitamin E resulted in the increase of oxidative damage and low level of vitamin K leads to increase susceptibility of significant bleeding and low bone mineral density. Numerous morbidities associated with fat-soluble vitamin give a rationale for fat-soluble vitamin plasma level evaluation annually. If there is a deficiency, supplementation should be given. It is better to consume the vitamins simultaneously with high-fat diets and pancreatic enzyme supplementation to increase absorption.[11]

Vitamin A level in serum should reach the normal range of serum retinol concentration. Supplementation can be started by giving low-dose retinol and gradually stepping up the dosage guided by the evaluation of serum values. Alternatively, in children age 6-8 years, supplementation can also be given in the form of daily provitamin beta carotene, with the dosage 1 mg/kg body weight/ day for 2 weeks and with 10mg/day as maintenance dose thereafter. If the normal values have been achieved, the frequency of retinol serum level concentration could be lowered to once in a year. The sign of vitamin A toxicity should also be evaluated regularly.[17]

For vitamin D, there is a variety of recommended plasma levels between studies. The US Cystic Fibrosis Foundation recommends the minimal threshold for 25-hydroxy vitamin D (25(OH)D) concentration in serum is 30ng/mL, meanwhile The European Cystic Fibrosis Bone Mineralization and the ESPEN-ESPGHAN-ECFS guidelines recommends the minimum value is 20ng/mL. The supplemental dose of vitamin D is still being debated; however, it is recommended to give 400 IU/day with maximum dose 1000IU/day in infants, and 800 IU.day with maximum dose 2000 IU and 4000 IU/day for children 1-10 years and >10 years, respectively. Vitamin D dosage should also be determined based on the initial serum concentration, sun exposure degree, and dietary intake. Similarly with vitamin A, vitamin D serum levels should also be monitored annually.[11]

Regular vitamin E (α-tocopherol) supplementation in CF patients is also recommended especially for patient with serum α-tocopherol:cholesterol ratio less than 5.4 mg/g. The vitamin E supplement should be given in order to achieve the recommended serum α-tocopherol concentration for CF patient. Lastly, another fat-soluble vitamin that should be given to CF patient is Vitamin K_1. Until now, there is no consensus in the most effective dosing for vitamin K_1. However, it is

believed that the best supplementation dosage are 0.3-1mg/day for infants and 1-10mg/day for older children and adults.[11]

The goal for nutritional status

The main goal for CF patient is to reach the same growth with their healthy same-age population when at the same time also have a high lean body (muscle) mass. Indicators that are used for defining adequate nutritional status differs from age to age. In infants (0-2 years), the nutritional status is said to be sufficient when patient weight for length (WFL) reached $\geq 50^{th}$ percentile of their age-matched healthy population. Meanwhile in older children (2-18 years), the indicator is $\geq 50^{th}$ percentile of BMI. Ideally, growth chart adapted from patient own ethnicity or nationality will be better to evaluate the nutritional status. If there are no adapted growth chart version, international growth chart (GC) 2006 by World Health Organization (WHO) and Centers for Disease Control and Prevention (CDC) 2000. Originally, WHO 2006 GC is commonly used in infant aged 0-2 years meanwhile CDC 2000 in older children aged 2-18 years. However, in the CF population, there were discrepancy between those two GCs in certain ages. Zhang et al. reported that 29% children aged 2 years with WFL $\geq 50^{th}$ percentile on WHO GC were $< 50^{th}$ percentile on CDC GC. Besides, in BMI GC, 50^{th} percentile on CDC GC was equal with 70^{th} percentile and 67^{th} percentile on WHO GC. This discrepancy resulted on inaccurate nutritional target and clinical outcomes prediction. Machogu et al. in his study found that patients with WFL $\geq 50^{th}$ percentile on both charts had a significant higher FEV_1 compared to WFL $\geq 50^{th}$ percentile on single chart alone. This finding resulted in the release of Cystic Fibrosis Foundation guideline with WFL target $\geq 75^{th}$ percentile on WHO GC for children aged 12-24 months. Further studies comparing long term outcomes in CF patients using WHO, CDC, or national GC are needed.[13]

CF children that already reached their desired nutritional status can be given preventive nutritional counseling in order to maintain their good nutrition. If the children experienced weight stagnation, weight faltering, or failure to thrive, diet modification and oral nutritional supplementation should be given to promote adequate growth. For children with persistent undernutrition, another measure such as enteral tube feeding, should be considered.

Anthropometric measurement using BMI alone in older children is not enough to define adequate nutritional status. Body composition measurement should also be done to ensure that lean body (muscle) mass contributed for a significant portion in those measurement. High BMI with low lean body mass and high fat composition in the exact opposite, contributed for poor outcome.[15] Additionally, annual blood tests for nutritional review; such as iron status, blood count, electrolyte, plasma fat-soluble vitamin levels, serum liver function test; should also be performed to further evaluate CF patient nutritional status.[11] **Table 3** summarizes the goal of nutritional status in CF patients.

The role of pancreatic enzyme replacement therapy in cystic fibrosis patient

Pancreatic insufficiency is found in 85-90% of CF patients and strongly correlated with malnutrition. It is commonly developed in the first year of life. The CFTR mutation impaired the chloride and bicarbonate transport system in pancreatic epithelial causing pancreatic secretions became thickened with decreased pH, leading to pancreatic ductal obstruction. Pancreatic chronic obstruction resulted in the impairment of pancreatic exocrine enzyme digestive function and created fibrosis leading to pancreatic insufficiency. CF patient with pancreatic insufficiency could not digest and absorb fat diet or fat-soluble vitamin due to the dysfunction of exocrine pancreatic enzyme, hence, the infants with pancreatic insufficiency commonly have lower weight and length z-score compared to their healthy counterparts. The children passed 80% of their diet fat contents in their stool due to lipase deficiency.[18] The pancreatic insufficiency should always be screened in every CF patient by the time of diagnosis and should be repeated annually. CF patient should also be questioned about gastrointestinal symptoms during clinical follow-up. Pancreatic insufficiency ought to be suspected if patient clinically has diarrhea without any other possibility or known to have 2 CFTR mutation that associated with pancreatic insufficiency.[11] Several methods to

diagnose pancreatic insufficiency such as fecal pancreatic elastase-1 examination and coefficient of fat absorption. If the results are abnormal, the PERT should be initiated as early as possible. The abnormal results defined by low fecal pancreatic elastase-1 (<100µg/g stool).[18]

Nowadays, PERT has becoming one of the main treatment for CF patients due to its ability in improving life expectancy and nutritional status of CF patients (**Table 4**).[19] ECFS Registry Data collected from 38 countries showed that in 2018, approximately 83% patient with CF has already used PERT.[5] The dosage for PERT determined by the lipid content in patient diet and the lipase needed for the diet. For infants up to 12 months, it is recommended to give 2000-4000 U lipase/120mL breastmilk or formula and 2000 U lipase/gram of fat in diet if infants already consume solids. For children 1-4 years, it is recommended to take 2000-4000 U lipase/gram dietary fat with maximum dosage 10.000/U lipase/kg per day. In children > 4 years, it is suggested to take PERT with starting dose 500 U lipase/kg/meal with maximal dosage 10.000 U/lipase/kg per day. PERT usually given in the form of enteric-coated tablets or microsphere.[11] However the dosing of PERT was still much debated. The usage of lipase units/kg body weight/meal as a denominator only used body weight to decide PERT dosage and could result in over or under supplementation based on the nutrient intake. Meanwhile, the usage of lipase units/g fat does not implicate other macronutrients.[13] Besides, there was no correlation found between PERT dose and BMI. Gelfond et al in his studies found that the higher PERT dosing do not give a better clinical benefit compared to lower dosing regimen.[20]

Other important assessment in cystic fibrosis children

CF correlated with numerous complications. Other examinations are performed in order to detect those complications in early stage. The measurement of pulmonary function by using forced expiratory volume in 1s ($FEV_{1)}$ should be performed every 3 months to detect the decline of lung function. FEV_1 can also be used to evaluate the improvement after nutritional intervention. CF also could lead to liver disease; thus, the liver function should also be monitored annually by physical examination, enzyme assays, and ultrasound. Liver disease should be suspected if CF patient presented with hepatomegaly, persistent abnormal liver function test (3 months consecutive above upper normal limits aspartate transaminase, alanine transaminase, and gamma-glutamyl transpeptidase), and abnormal ultrasonography. The blood glucose test is suggested to be conducted annually in order to detect CF-related diabetes.[11]

Conclusion

Nutritional intervention and PERT play an essential role in CF management and contribute to better survival. Given its importance, nutritional intervention and PERT should be initiated as early as possible by the time the CF diagnosis is made. The nutritional intervention consists of giving a higher daily energy intake than healthy individuals (with special consideration to higher protein and fat diet composition), micronutrient supplementation, and fat-soluble vitamins supplementation. The nutritional status should be monitored regularly by measuring the anthropometric status. In addition, other assessments that could also reflect nutritional status should also be performed regularly, such as body composition, bone mineral density, numerous serum biomarkers, and electrolyte concentration. Collaboration with parents and children also important. Parents and children should be educated on the importance of following dietary nutrition advice and regularly checking their condition. Besides nutritional intervention, PERT should be initiated early when pancreatic insufficiency is suspected in follow-up visit. Early administration of PERT correlated with better outcomes.

Even though a comprehensive guideline in managing CF patient nutrition was already available, there are some potential fields to be explored in order to further improving holistic CF management. Research aims to determine the consensus in body composition measurement (in regard to its technique, equation, fat free mass and fat free mass index threshold) and growth chart; further investigation in recommended protein intake and protein sources that could easily digested by CF patient; and accurate PERT intakes, are needed.

Table 1. The summary of energy and macronutrient recommendation in CF patient[11,16]

Topic	Age	Recommendation
Recommended Daily Energy Intake	All ages	110-200% calories of their recommended dietary allowance for similar-age healthy population
Dietary Composition	All ages	35%-40% fat, 40-45% from carbohydrates, and 20% protein
Education	Infants and younger child	Parents should be educated about child's higher daily energy intake needs so they could provide the CF child with appropriate and balanced composition of diets
	Older child	Dietary counseling should be given to maintain healthy feeding and correct behavioral feeding problems
Dietary Review	All ages	Dietary review should be assessed every 3 months by using 24-h recall or 3-5 day diet record in order to evaluate qualitative and quantitative nutritional intake and whether patient/parents have already adhered to nutritional advices.
CFRD	All ages	Carbohydrate: limit refined simple sugar, six servings of grains, and 3-4 servings of dairy Fats: consume food with higher omega-3 fatty acids content
Breastfeeding	Infants (0-2 years)	Exclusive feeding if possible, formula feeding if not possible, with additional sodium supplementation. Solid foods should be started at the same age with healthy population.

Table 2. The summary of micronutrient recommendation in CF patient[11]

Micronutrient	Age	Evaluation	Recommendation
Sodium	Infants (0-2 years)	Sodium:creatinine ratio	1-2 mmol/kg body weight/day sodium diluted in formula or water. Can be increased up to 4 mmol/kg body weight/day (in the present of hot environmental conditions, diarrhea, vomiting)
	Older children		Sodium chloride capsules administered several times a day
Calcium	0-6 months	Calcium intake should be assessed annually. More frequent assessment can be performed if there is a growth faltering	200 mg daily
	7-11 months		280 mg daily
	1-3 years		450 mg daily
	4-10 years		800 mg daily
	11-17 years		1150 mg daily
	18-25 years		1000 mg daily
Iron	All ages	Annually using serum iron. If the SI is abnormal, performed serum ferritin, transferrin saturation, and total iron binding capacity test.	Give iron supplementation only after resolving other possible etiology (example: inflammation) and the iron deficiency still persists
Zinc	Infants (0-2 years) with zinc deficiency risk	Identify infants or child with zinc deficiency risk: growth faltering, eye problems, delayed sexual maturation, and anorexia	1mg/kg/ day (maximum 15 mg/day) for 6 months
	Child > 2 years with zinc deficiency risk		15 mg/day for 6 months
Fat-Soluble Vitamins			
Vitamin A	All ages	Annually, and 3-6 months after the change in dosage.	Vitamin A supplementation should be given if patient do not reach their normal range of serum retinol concentration. The supplementation that could be given:

		Evaluate sign of toxicity	• Retinol (low-dose, gradually increase the dosage guided by the retinol serum values)
	children age 6-8 years		Alternative to retinol, daily provitamin beta carotene 1 mg/kg body weight/ day for 2 weeks and 10mg/day as maintenance dose thereafter
Vitamin D	Infants	Annually, and 3-6 months after the change in dosage. The minimum target is serum-25 (OH) D 20ngmL	400 IU/day (maximum 1000 IU/day)
	Children 1-10 years		800 IU/day (maximum 2000 IU/day)
	Children > 10years		800 IU/day (maximum 4000 IU/day)
Vitamin E	Infants (< 12 months)	Annually, and 3-6 months after the change in dosage. The target is serum α-tocopherol :cholesterol ratio > 5.4 mg/g	50 IU/day
	> 1 years		100-400 IU/day
Vitamin K	Infants		0.3-1 mg/day
	Older children		1-10mg/day

Table 3. The nutritional status goal in CF patient[11]

Age	Measurement	Target	Evaluation
Infants (0-2 years)	Weight-and-length	≥ 50th percentile of their age-matched healthy population	• Every 1-2 weeks if the weight-and-length/BMI do not reach 50th percentile • Every 1 months in the first year of life • Every 3 months > 1 years of life
Older children (2-18 years)	BMI	≥ 50th percentile of their age-matched healthy population	
Other Assessment			
Children 8-10 years	Bone mineral density (BMD)	Matched with standard BMD z score of same age and sex healthy individuals	Every 1-5 years depends on the presence of risk factors using DXA
All age	Body composition	High lean body muscle mass	Evaluation using BIA with CF-specific equations, DXA, air displacement plethysmography, hand grip strength, and double labelled water measurement

Table 4. The recommended PERT dosages[11]

Age	Dosage
Infants (0-12 months)	2000-4000 U lipase/120mL breastmilk or formula and 2000 U lipase/gram of fat in diet if infants already consume solids
Child (1-4 years) Child (> 4 years)	2000-4000 U lipase/gram dietary fat with maximum dosage 10.000/ u lipase/kg per day starting dose 500 U lipase/kg/meal with maximal dosage • 10.000 U/lipase/kg per day, or • 1000-2500 U lipase/kg per meal, or • 2000-4000 U lipase/gram dietary fat

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

A diagnostic test for malnutrition in adults: mid-upper arm circumference towards body mass index: A literature review

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Abstract

Body mass index is commonly used for detecting malnutrition. At certain conditions, body mass index cannot be measured, so mid-upper arm circumference can be an alternative measurement for detecting malnutrition. Several studies have proposed the cut-off point of mid-upper arm circumference in adults along with its sensitivity, specificity, and area under the ROC curve (AUC). This article aims to describe the diagnostic test for malnutrition using the upper arm circumference in adults and summarize the results of the related studies.

Keywords BMI, diagnostic test, malnutrition, MUAC

Introduction

Nutritional status is defined as a body condition that is the result of a balance of intake, absorption, use of nutrients that can affect physiological and pathological conditions.[1] If for any reason, such as insufficient intake, increased demand for nutrients, or a disorder in the absorption/use of nutrients, there is a negative balance, then undernutrition/malnutrition develops.[2] Malnutrition is assessed based on an assessment of food intake, laboratory tests, anthropometric measurements, and clinical observation. Anthropometric measurements involve measuring physical dimensions and body composition, the results can be vary depending on age, sex, race, and nutritional status. This measurement is often used to assess energy and protein imbalances, as well as to assess the degree of malnutrition, but cannot explain a specific nutrient deficiency.[3] Some anthropometric measurement methods used to assess nutritional status are body mass index (BMI) and mid-upper arm circumference (MUAC). In certain conditions, it can be difficult to perform height and weight measurements to calculate BMI.[4] Mid-upper arm circumference can be an alternative measurement for undernutrition screening. To date, there was no valid cut-off point for mid-upper arm circumference in adults as in children. This article aims to describe the diagnostic test for malnutrition using the mid-upper arm circumference in adults and summarize the results of the related studies.

Body mass index

Body mass index was first described by Adolph Quetelet in 1835, so it is also called the Quetelet index.[5] BMI is defined as body weight in kilograms divided by the square of height in meters.[3,5] It is a commonly used measurement for assessing nutritional status quickly, easily, and non-invasively.[3]

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The body mass index has some limitations, it cannot differentiate between body weight due to fat mass or fat-free mass. BMI values can be high due to excess fat mass, muscle mass (for example in athletes), or edema.[1,3] In certain circumstances, BMI is difficult to assess, for example, if the patient is unable to stand or conditions that affect height measurements such as kyphosis, compression fractures vertebral due to osteoporosis, or scoliosis.[6] The World Health Organization (WHO) established the BMI cut-off value for assessing nutritional status by relating it to morbidity and mortality. BMI <18.5 kg/m^2 is categorized as undernutrition/malnutrition.

Mid-upper arm circumference

The measurement of the MUAC is made at the midpoint between the acromion and olecranon. MUAC is consist of subcutaneous fat and muscle, so any changes in MUAC can represent changes in muscle mass, subcutaneous fat mass, or both. In malnourished patients who tend to have low subcutaneous fat, changes in MUAC are more representative of changes in muscle mass. Measuring MUAC is easy, fast, and only uses a simple tool (measuring tape).[3] MUAC measurement can be performed in patients who cannot stand because it can be taken in a lying position. There was no significant difference between measurements of upper arm circumference in standing and lying positions (p-value = 0.855).[7]

In the measurement in a standing position, the subject stands with feet together and arms bent 90 degrees at the elbows with palms facing up. The examiner stands behind the subject and looks for the acromion process of the scapula. Then the examiner holds the end of the measuring tape at the acromion and pulls it up to the olecranon. After that, the examiner holds the measuring tape in that position and marks the midpoint between the acromion and olecranon. Subjects were asked to straighten their hands then the measuring tape was looped on the marked point and measured in the nearest millimeter.[8] For more details see **Figure 1**.

Several studies have been conducted to assess the usefulness of measuring the MUAC.[9–12] McMillan et al.[9] assessed the influence of several variables (BMI, weight loss, skinfold thickness, MUAC, albumin, C-reactive protein, and cancer type and stage) on Karnofsky performance status in 148 advanced gastrointestinal cancer patients. From multiple regression analyzes, only MUAC and $\log_{10}$ C-reactive protein (R^2 = 0.462, P <0.0001) in men and only MUAC and weight loss in women (R^2 = 0.485, P <0.01) as an independent predictor of Karnofsky performance status.[9]

MUAC is inversely related to the risk of all-cause mortality.[10,11] Higher MUAC with normal BMI has a low risk of mortality.[10] Whereas low MUAC has a statistically significant relationship with increased risk of mortality in the elderly that is stronger than with low BMI and calf circumference.[12]

A diagnostic test for malnutrition

Assessing the validity of screening tools is one of the goals of diagnostic tests. Besides, diagnostic tests also aim to establish a diagnosis of disease, for patient treatment, and epidemiological studies. The basic principle of a diagnostic test is to find a new diagnostic test that has several advantages over the previous diagnostic test. Some of them are that the diagnostic value is not much different, it is not invasive, easier to use, and cheaper.[13]

The validity of an instrument with a nominal scale can be assessed by comparing it with the best available diagnostic tool (gold standard). BMI is used as the gold standard in this diagnostic test. MUAC meets the basic principle of a diagnostic test because MUAC does not require expensive equipment, easy to perform, and not invasive. MUAC can be used to assess nutritional status if MUAC has high sensitivity (a slight possibility for false negative) and fair specificity.[13] Information obtained from the diagnostic test of MUAC towards BMI is presented in **Table 1**.

Receiver operating characteristic (ROC) curve of MUAC towards BMI

The receiver operating characteristic (ROC) curve is a graph that presents the bargaining between sensitivity and specificity to determine the cut-off point of MUAC towards BMI.[13] The Y coordinate is the sensitivity against the false positive (1-specificity) value as the X coordinate. The cut-off point of MUAC is determined based on the highest

sensitivity and specificity or the highest Youden's index (sensitivity + specificity – 1).[15]

Diagnostic test performance can be assessed by calculating the area under the ROC curve (AUC). An AUC values range from 0 to 1, the closer to number 1 the better the diagnostic test. An AUC value equal to 1 represents a perfect diagnostic test, which is very accurate in distinguishing between malnutrition or not.[15,16] The categories used to summarize accuracy of AUC in ROC analysis were as follows: AUC of 0.9–1 (excellent), 0.8–0.9 (good), 0.7–0.8 (fair), 0.6–0.7 (poor) and 0.5–0.6 (fail). A test with an AUC ≥0.85 is generally considered as an accurate test.[17]

Research about MUAC cut-off point for detecting malnutrition

Various studies have shown a significant correlation between MUAC and BMI, it is known that individuals with low MUAC are likely to have a low BMI.[4,6,18–23] Research conducted by Brito et al.[8] on 1373 inpatients at a hospital in Spain, showed that there was a correlation between BMI and MUAC with $r = 0.78$ ($p < 0.001$). The cut-off point value for detecting malnutrition obtained from this study was 22.5 cm for both men and women. This study also obtained a regression equation to find BMI, that is 0.042 + 0.873 x MUAC (cm) ($R^2 = 0.609$). Tuck and Henessy[19] also developed a regression equation to determine the BMI from MUAC. For males: BMI = 1.01 x upper arm circumference - 4.7 ($R^2 = 0.76$) and for women: BMI = 1.10 x upper arm circumference - 6.7 ($R^2 = 0.76$).[19] This equation has been validated in the study of Barosa et al.[24]

Food and Nutrition Technical Assistance III Project (FANTA) conducted a meta-analysis regarding the sensitivity and specificity of various cut-off points for MUAC in adults (men and women who were not pregnant) to identify malnutrition measured by BMI <18.5 kg/m^2. This study suggested that MUAC in the range of ≤23.0 to ≤25.5 cm can be used as an indicator of low BMI (BMI <18.5 kg/m^2), with acceptable sensitivity and specificity values. The cut-off point of MUAC ≤24.0 cm was chosen for reasons of optimal sensitivity and specificity.[4]

Several proposed cut-off points of MUAC for detecting malnutrition along with its sensitivity, specificity, and AUC was summarized in **Table 2**. The cut-off point of MUAC may be varied due to differences in body composition among different races, especially the distribution of body fat, which may be not adequately captured by measures of overall adiposities (BMI) when compared to MUAC, which measures regional adiposity. The higher cut-off point might be more accurate in Asian populations that have a higher proportion of body fat than other races (e.g., Caucasians and Africans).[25] Overall, the sensitivity, specificity, and AUC of MUAC towards BMI is good enough, so MUAC can be used for detecting malnutrition.

Conclusion

Since the sensitivity, specificity, and AUC of MUAC is good, it can be an alternative measurement for detecting malnutrition in adults, particularly in a community setting or low-resource setting. It can also be used in a hospital setting when BMI cannot be measured. There was no valid cut-off point of MUAC that can be used in all population. populations. Further research needs to validate this cut-off point.

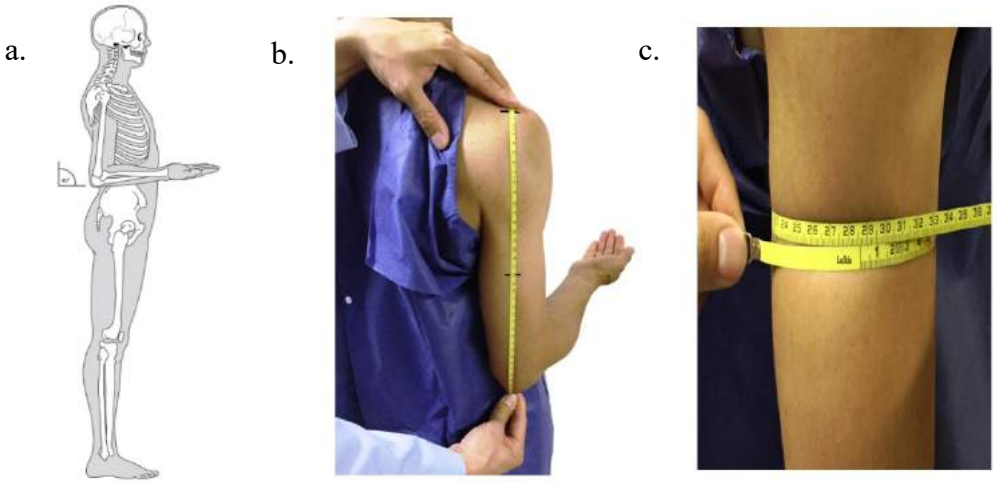

Figure 1. MUAC measurement in a standing position
a. Standing position of the subject b. Position the tape correctly and mark the midpoint of the upper arm. c. Measure the circumference of the mid-upper arm
Source: reference number 8

Table 1. 2x2 table for MUAC and BMI

		Malnutrition (measured by BMI)		Total
		BMI < 18.5 kg/m^2	BMI ≥ 18.5 kg/m^2	
MUAC	< cut-off point	True positive (a)	False positive (b)	a+b
	≥ cut-off point	False negative (c)	True negative (d)	c+d
	Total	a+c	b+d	a+b+c+d

From the table above can be assessed sensitivity, specificity, positive predictive value, and negative predictive value:
a. Sensitivity = a / (a + c).
b. Specificity = d / (b + d).
c. Positive predictive value = a / (a + b).
d. Negative predictive value = d / (c + d).[4,14]

Table 2. The cut-off point of MUAC from various studies for detecting malnutrition

Researcher	Subject	Total subject	MUAC cut-off point (cm)	Sen	Sp	AUC
Brito et al.[6]	Inpatient, Spain	1373 subjects	22.5	67.7	94.5	0.92
van Tonder et al.[18]	Inpatient, South Africa	86 males	23.7	86.4	78.6	0.88
		80 females	23.5	93.1	100	0.98
Goswami et al.[20]	Elderly, India	267 males	25.7	80.2	78.6	0.85
		259 females	24.3	79	79	0.86
Das et al.[22]	Adults slum dwellers, India	467 males	22.7	85.71	74.8	0.85
		488 females	21.9	91.67	79.89	0.93
Sultana et al.[21]	Inpatient, Bangladesh	260 males	25.1	92.6	79.4	0.814
		390 females	23.9	92.6	76.6	0.882
Thorup et al.[23]	Urban public hospitals, Nepal	302 subjects	24.5	92.86	82.48	0.94
FANTA-III[4]	A meta-analysis from 17 studies with various population	-	24	81.9	85.6	-

Sen: sensitivity; Sp: specificity; AUC: area under the ROC curve

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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LITERATURE REVIEW

Probiotics administration as a prevention for postoperative infectious complications in colorectal cancer patients: A literature review

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Abstract

Background Colorectal cancer is the third leading cause of death from cancer in adults in the United States, with increasing prevalence in other countries. Radical resection is the gold standard of treatment in most cases of colorectal cancer, with a high rate of postoperative complications. Perioperative probiotics can improve the immune response and the postoperative intestinal microbiota environment. Although several studies have shown the benefits of probiotics in preventing postoperative complications of infection, the administration of perioperative probiotics in colorectal cancer patients is still controversial.

Objective. The purpose of this critical appraisal is to know the effectiveness of administering probiotics to prevent infectious complications in colorectal cancer patients.

Methods. Literature research using Pubmed, Cochrane, and EBSCOhost was carried out and 2 articles were obtained in the form of meta-analysis using STATA v11 and Revman v5.2 that was critically examined using the FAITH method. A comprehensive search for all studies was done to find all relevant studies using both MeSH terms and text words. The article should describe the assessment of quality and criteria used in method section, also provide information on the quality of individual studies in result section to minimize bias. The result section should state whether heterogeneity exists and mention possible reasons.

Results. Based on 2 meta-analyses that have been critically examined, which each consisting of 13 and 7 studies, giving probiotics can reduce the overall infection rate after colorectal cancer surgery. One meta-analysis showed an odds ratio (OR) of 0.51 (95% CI: 0.38 – 0.68, p = 0.00). Probiotics, such as *Lactobacillus acidophilus* and *Bifidobacterium longum* can also reduce the incidence of surgical site infections (OR = 0.59, 95% CI 0.39 – 0.88, p = 0.01) and pneumonia (OR = 0.56, 95% CI 0.32 – 0.98, p = 0.04). Probiotics did not provide statistically significant benefits in preventing urinary tract infections, leakage of anastomosis, and duration of postoperative pyrexia compared to the control group. Seven articles analyzed in the second meta-analysis showed probiotics to be useful in preventing postoperative infections with OR 0.5388 (95% CI, 0.4058-0.7154, P <0.0001).

Conclusions. Combination of more than one strain of probiotics such as *Lactobacillus* and *Bifidobacterium* is promising for the prevention of infections in patients undergoing colorectal cancer surgery.

Keywords colorectal cancer, probiotics, lactobacillus, postoperative infection

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Introduction

Cancer is one of the major health problems throughout the world and is the second leading cause of death in the United States. Colorectal cancer is the third leading cause of death from cancer in adults in the United States.[1] In China, colorectal cancer ranks fifth for cancer deaths.[2] In Indonesia, based on the 2018 Basic Health Research, the prevalence of cancer increased compared to 2013 from 14 to 18 per 10,000 lives with the highest prevalence at the age of 55-64 years.[3]

Radical resection is the gold standard of treatment in most cases of colorectal cancer, although patients with colorectal cancer who undergo surgery often experience complications of postoperative infections. Postoperative infections can cause negative impact on long-term prognosis because they increase the morbidity and mortality of patients. Postoperative morbidity in colorectal cancer reaches 15-23.2%.[4-6] Postoperative infections in colorectal cancer patients occur due to intestinal dysbiosis caused by perioperative stress, inflammatory responses and intestinal mucosal atrophy due to perioperative fasting and ischemia of the intestinal tract which induces translocation of intestinal microbiota into the intestinal mesenteric lymph glands to other organs.[7-9]

Prevention of postoperative infections including restoration of normal intestinal microbiota and prevention of bacterial translocation must be undertaken to minimize postoperative complications.[10] Probiotics are beneficial microorganisms in regulating homeostasis of microbiota, immunity and maintaining intestinal mucosal barrier. Administration of oral probiotics, such as *Lactobacillus* and *Bifidobacterium* is reported to be able to reach the colon and rectum in an active form to form colonies in the intestinal mucosa.[11,12] The use of preoperative combination of several probiotics, such as *Lactobacillus* and *Bifidobacterium* can enhance the immune response and improve the postoperative intestinal microbiota environment. Although several studies have shown the benefits of probiotics in preventing postoperative complications of infection, the administration of perioperative probiotics in colorectal cancer patients is still controversial. Synbiotics are essentially a synergistic combination of probiotics and prebiotics. Research by Anderson, et al.[13] concluded that the administration of synbiotics against the protection of the intestinal mucosal barrier did not produce meaningful results. Another research conducted by Consoli, et al.[14] showed that administration of *Saccharomyces boulardii* can reduce levels of IL-23 and IL-10 and inhibit T-cell activation, strengthen the intestinal barrier, and inhibit proinflammatory cytokine production. Research done by Gianotti, et al.[15] showed that administration of *Lactobacillus johnsonii* (La) and *Bifidobacterium longum* (BB536) in colorectal cancer patients before surgery was able to reduce the number of intestinal pathogenic bacteria and modulate local immune responses.

Research on the benefits of probiotics includes specific strains and doses that are adequate for cancer patients has not yet achieved conclusive results. Based on the literature, combination of more than one probiotic such as *Lactobacillus* and *Bifidobacterium* can improve the intestinal microbiota environment, the immune system and prevent complications, especially postoperative infections. For this reason, a literature study and critical study are needed to assess the benefits of probiotics in colorectal cancer patients in preventing complications of postoperative infections.

Clinical scenario

A male patient aged 51 years came to the hospital with complaints of lower left abdominal pain arising and subsiding in the last 9 months. The patient also complained of difficulty defecating, small round hard, blackish-colored feces. CT scan results showed the patient had a tumor in the large intestine. The patient lost 15 kilograms in 1 year. Patient claimed to often consume grilled foods from a young age and rarely consume vegetables and fruits. The patient's blood pressure 120/80 mmHg, the pulse rate 84 times/minute, the respiratory rate 20 times/minute, the temperature 36^0C.

The conjunctiva anemic, the abdomen flat with normal bowel sounds. The patient's body weight 59 kg, his body height 169cm, and body mass index 20.6 kg/m^2. Laboratory tests showed that Hb was 7.4 g/dL, hematocrit 23%, leukocytes 2,900/μL, platelets 645,000/μL. The results of a large bowel

biopsy showed a sigmoid colon adenocarcinoma. From the surgical department, the patient is planned to have a colon resection and colostomy. Therefore, a critical study will be conducted on the effectivity of administering probiotics to reduce complications of postoperative infections.

Clinical question

P: Adult colorectal cancer patient
I: Patients receiving perioperative probiotics supplementation
C: Patients who have not received perioperative probiotic supplementation
O: Postoperative infectious complication

Methods

The literature search was done on 3 databases (PubMed, Cochrane, and EBSCOhost) using advanced search on December 22, 2019.
Critical review is carried out using the FAITH method (Find, Appraise, Include, Total Up, Heterogeneity).[16]

Eligibility criteria

Article selection was based on the inclusion and exclusion criteria, which addressed the clinical question. The inclusion criteria were: 1) colorectal cancer patients over 18 years old; 2) patients got perioperative probiotics; 3) the study design used was a Randomized Controlled Trial, Cohort, or Case-control. The exclusion criteria were: 1) research in the form of reviews, comments, conference abstracts, letters, sections in a book or non-clinical study; 2) research that did not include the dose of probiotics used; 3) provision of probiotics used in combination with prebiotics or as synbiotics; 4) research that was not done in humans; 5) research that did not mention the odds ratio (OR) or the difference in the standard mean difference (SMD); 6) research that did not include probiotic strain.

Critical appraisal of Ouyang et al. [17]

This meta-analysis uses Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) as a guide. The method section describes the search strategy by taking relevant studies from the Pubmed, Embase, Cochrane, and CNKI databases, but does not include data collection from relevant and unpublished studies. One of the weaknesses of this meta-analysis is that it only includes English and Chinese studies so that it is possible to lose important data in other language studies. Thirteen studies have been assessed as having complete, unbiased, and not selective data in their reporting. Twelve studies were also carried out by blinding. The study included in this meta-analysis has a low risk of bias involving 12 articles which are RCT design studies and 1 study which is a controlled clinical trial. The types of probiotics involved in this study varied greatly in terms of species, dosage, and duration of administration. The type of probiotics used are *B. longum, B. bifidum, B. mesentericus, L. bulgaricus, L. acidophilus, L. plantarum, S. thermophilus, E. faecalis, C. butyricum, S. boulardii* either given alone or in combination with a dose range of $10^6 – 10^{11}$ CFU/day. Probiotics were given 2-4 times per day with a range of administration varies from 8 days before to 14 days postoperatively. The results of the meta-analysis study are presented in the form of a summary table and Forest plot. Heterogeneity tests have been carried out and no heterogeneity was observed among studies on the effects of preventing probiotics on postoperative infection rates ($p = 0.60$, $I^2 < 0.01$). Forest plots evaluate the preventive effects of probiotics on overall postoperative infections. Data from 13 studies were collected to calculate pooled OR. The analysis model showed a pooled OR for overall infection was 0.51 with 95% CI 0.38 to 0.68. This meta-analysis concludes that the use of probiotics can prevent infections in patients undergoing CRC surgery and improve surgical recovery.

Critical appraisal of Calaca et al.[18]

This meta-analysis uses Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as a guide. The research was taken from 5 databases namely Pubmed, Science Direct, Scielo, Scopus, and LILACS systematically from 2005 to 2016. The search was not limited to English-language studies, but also involved studies published in Spanish and Portuguese. The studies included in this meta-analysis are studies published

in leading journals, in the form of seven RCTs published from 2010 to 2016 and sample sizes ranging from 20 to 161 (average 90.1). The results of the meta-analysis study are presented in the form of a summary table and forest plot. Seven articles were analyzed to assess the effect of probiotics on infectious complications with $I^2 = 14.3\%$ (DF = 25, p = 0.2338) in the infection group. The type of probiotics used are *B. longum, B. bifidum, L. johnsonii, L. acidophilus, L. plantarum, E. faecalis, C. butyricum* either given alone or in combination with a dose range of $10^7 – 10^{11}$ CFU/day. Probiotics were given 2-4 times per day with a range of administration varies from 7 days before to 12 days postoperatively. Overall, the assessment of heterogeneity in this systematic review shows low heterogeneity. Two studies showed positive effect on probiotics for infectious complications with OR = 0.5388 (95% CI, 0.4058 – 0.7154, p <0.0001). This systematic reviews and meta-analysis show that the combination of more than one microorganism such as *Lactobacillus* and *Bifidobacterium* is promising for the prevention of infections.

Discussion

Complications of postoperative infections, including surgical site infections, urinary tract infections, sepsis and pneumonia resulted in increased length of stay and morbidity in patients. The two meta-analyses obtained from literature research and critical study are systematic reviews that are well-prepared and meet critical reviews using the FAITH method. Both of meta-analyses, shown that combination of probiotics, such as *Lactobacillus* and *Bifidobacterium* play an important role in preventing infections after colorectal cancer surgery including overall infections, surgical site infections, and pneumonia.

From the two systematic reviews conducted, it was found that four studies were similarly involved in both of meta-analyses. The probiotics used in these studies were *E. faecalis, C. butyricum, B. mesentericus, B. bifidum,* and *L. plantarum*.[17] The meta-analysis conducted by Calaca, et al.[17] involved 7 studies and was published in 2017. One of the studies in the meta-analysis conducted by Calaca et al[17] was RCT research conducted by Liu et al.[19] Research by Liu, et al.[19] shows that administration of perioperative *Lactobacillus plantarum, Lactobacillus acidophilus, Bifidobacterium longum* can reduce the inflammatory response and decrease the length of stay in patients following colorectal cancer surgery. Microbial dysbiosis due to stress and inflammatory responses after colorectal cancer surgery improves with the administration of *Lactobacillus plantarum, Lactobacillus acidophilus, Bifidobacterium longum*.

Analysis using the Forest plot found that the benefits of probiotics in preventing surgical site infections were only found in one out of 4 studies, so the results of the analysis were not statistically significant (OR 0.6538, 95% CI 0.3951 – 1.0817).[8] The results of the analysis of the effectivity of the administration of probiotics to the detection of bacteria in the blood taken from 4 articles gave significant results with OR 0.4069 (95% CI, 0.2662 – 0.6222, P <0.0001). Seven articles analyzed to assess the benefits of probiotics in preventing postoperative infections gave significant results with OR 0.5388 (95% CI, 0.4058-0.7154, P <0.0001).

A meta-analysis carried out by Ouyang, et al.[17] involving 13 studies showed that the preventive effect of probiotics (*B. longum, B. bifidum, B. mesentericus, L. bulgaricus, L. acidophilus, L. plantarum, S. thermophilus, E. faecalis, C. butyricum, S. boulardii)* on anastomotic leakage and urinary tract infections did not show significant results, possibly because collection of more updated researches may lead to the main differences this meta-analysis compared to previous meta-analysis. An evaluation using the Forrest plot showed that probiotics (*B. longum, B. bifidum, B. mesentericus, L. bulgaricus, L. acidophilus, L. plantarum, S. thermophilus, E. faecalis, C. butyricum, S. boulardii)* had an overall preventive effect on postoperative infections (OR 0.51, 95% CI 0.38 – 0.68). Preventive effects of probiotics on surgical site infections in 9 studies showed significant results with OR 0.59 (95% CI 0.39 – 0.88) as well as against pneumonia prevention (OR 0.52 with 95% CI 0.32 – 0.98).[17]

There are several weaknesses to be noted in this meta-analysis. First, this study only took data from published research without taking data from other unpublished studies and therefore could result in loss of data in other relevant studies. Secondly, this study only analyze the individual effects of

probiotics without involving research with prebiotics or as synbiotics that might affect the results of the analysis even though the role of prebiotics or synbiotics in the prevention of postoperative infections is also still not conclusive. Third, some important data such as serum antibody concentration and inflammatory factors are only available in a number of studies so no in-depth analysis is performed. Fourth, the probiotics strain and doses in several studies collected were not consistent with each other. Several studies that combined probiotics with other treatment should be excluded so that they might not induce confounding factor in this meta-analysis.[17]

Conclusion

Combination of more than one strain of probiotics such as *Lactobacillus* and *Bifidobacterium* is promising for the prevention of infections in patients undergoing colorectal cancer surgery which provides benefits in post-surgical recovery and decreases the length of treatment. The dose that can be given ranges from $10^6 – 10^{11}$ CFU/day with the frequency of administration 2-4 times per day and range of administration varies from 8 days before to 14 days postoperatively. The administration of probiotics must still be adjusted to the patient's condition and the therapy given. Further research is needed to determine the best type of probiotic strain along with the optimal dosage and duration of administration to prevent complications of postoperative infections in colorectal cancer patients.

Table 1. Terminology

Database	Terminology	Hits
PubMed	Search ((prevent[Title/Abstract] OR treat[Title/Abstract]) AND (probiotics[Title/Abstract] OR probiotics[MeSH Terms] OR lactobacillus[MeSH Terms] OR lactobacillus[Title/Abstract])) AND ((colon cancer[Title/Abstract] OR rectal cancer[Title/Abstract]) OR colorectal cancer[Title/Abstract])	71
Cochrane	ID Search #1 (prevent):ti,ab,kw OR (treat):ti,ab,kw (Word variations have been searched) #2 (lactobacillus):ti,ab,kw OR (probiotics):ti,ab,kw (Word variations have been searched) #3 (colon cancer):ti,ab,kw OR (rectal cancer):ti,ab,kw OR (colorectal cancer):ti,ab,kw (Word variations have been searched) #4 #1 AND #2 AND #3	71
EBSCOhost	Search Alert: ("probiotics” OR “lactobacillus”) AND ("treat" OR "prevent") AND ("colon cancer" OR "rectal cancer" OR “colorectal cancer”) Research Article	50

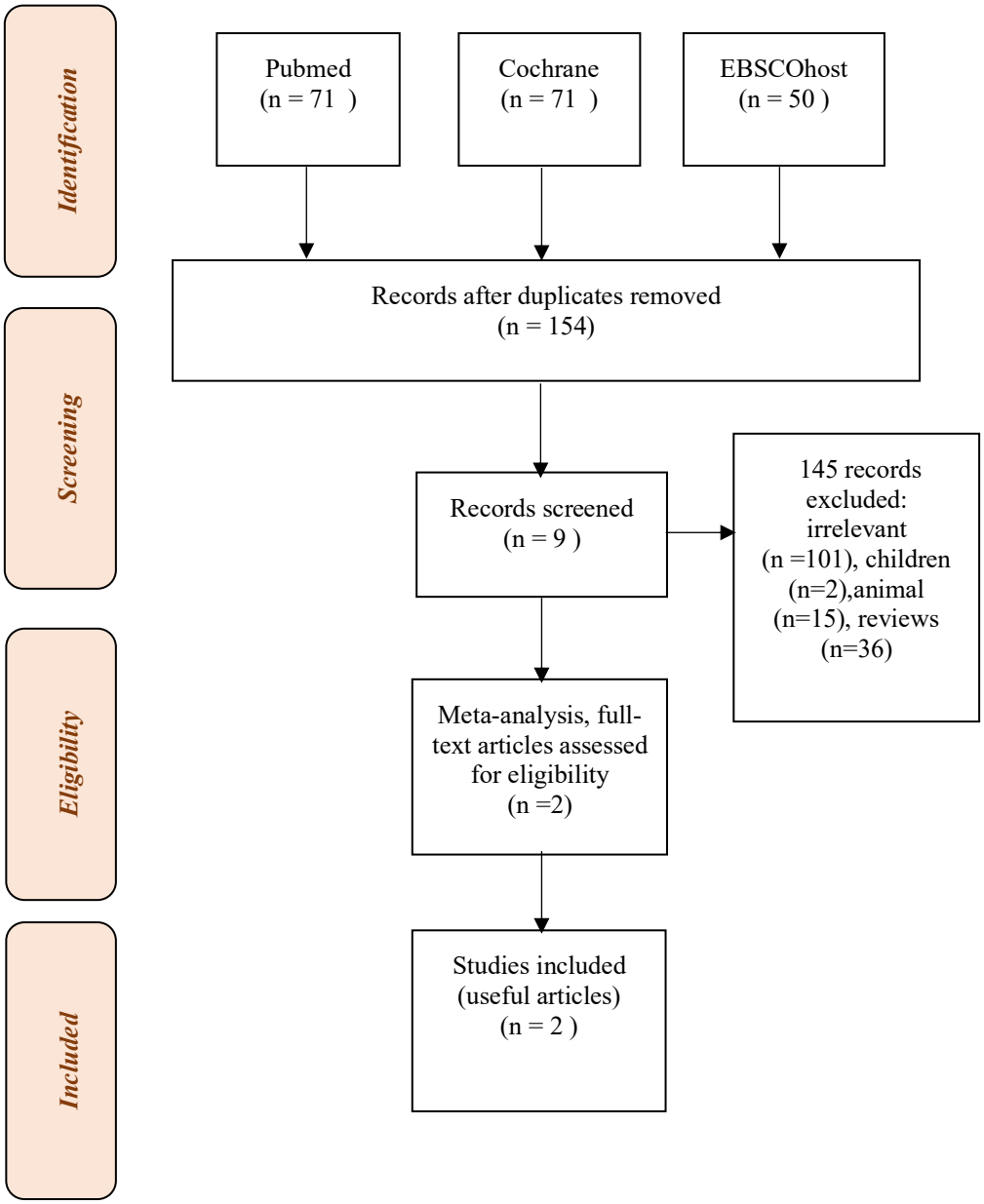

Figure 1. PRISMA Flowchart

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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