



Editorial

Nutrition for elderly individuals during the Covid 19 pandemic

Clinical Nutrition : Nutrition and Metabolism

Original Paper

- Effect of vitamin D supplementation to prevent acute respiratory tract infection: an evidence-based case report
 - Effect of carnitine on patients with heart failure: an evidence-based case report
- Correlation between intensive phase treatment of antituberculosis drugs with nutritional status of patients with tuberculosis in Kupang city
 - Efficacy of branched-chain amino acid to increase muscle strength in chronic heart failure patients: an evidence-based case report
- The effect of omega 3 fatty acid supplementation on HbA1c serum in geriatric patients with type 2 diabetes mellitus: an evidence-based case report
 - Correlation between serum vitamin C level and COPD assessment test score in chronic obstructive pulmonary disease patients

Community Nutrition: Nutrition Through Life Cycle

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- Comparison of short-term memory between stunting and non-stunting children in urban and rural elementary school students in Kupang 2019

Food and Nutrition/ Functional Food

Original Paper

- Effect of *Moringa oleifera* leaf powder supplementation on weight gain of toddler in the working area of Naibonat health center, Kupang regency
 - Effect of isoflavone consumptions on the recurrence and survival rate among breast cancer patients: an evidence-based case report

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Nutrition for elderly individuals during the COVID-19 pandemic

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Introduction

As Japan has been facing an increasingly aged society ahead of the rest of the world, much interest has been focused on interventions for treating frailty and sarcopenia to extend healthy life expectancy in recent years. The COVID-19 pandemic has led to a crisis in healthcare systems all over the world. It has had a huge impact on not only public health but also the global economy. Due to the lack of effective vaccination and pharmacological antiviral intervention, pandemic control is dependent on public health measures. These measures have basically aimed to decrease social activities and face-to-face communication, including the restriction of public gatherings and compulsory stay-at-home policies.¹ Even though these strategies are effective in controlling the pandemic, social and economic influences have obviously affected vulnerable groups of people, including elderly individuals. Therefore, it is important to enhance the effectiveness of pandemic control measures while

minimizing secondary negative consequences. This article aimed to describe the importance of maintaining good nutritional and mental health for elderly individuals during the COVID-19 pandemic, with a particular focus on frailty management.

Elderly individuals are vulnerable during in the COVID-19 pandemic

Several studies support an age gradient in the severity and mortality of COVID-19.²⁻⁸ It is known that human immunity is supported by nutritional status. In this regard, the immune strength of malnourished and sarcopenic individuals against bacterial and viral infections is lower. In general, elderly individuals tend to have multiple comorbidities, altered body composition (such as sarcopenia), decreased swallowing and ingesting ability, and decreased cognitive function. Moreover, they are disadvantaged socioeconomically. In fact, the rates of severe disease were significantly different depending on the age group.⁹ Furthermore, mortality was also higher in the older age groups, and comorbidities, such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease, and cancer, were associated with an increased risk of death.² In this regard, maintaining good nutritional status as well as preventing infection is important for elderly individuals.

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Nutrition, physical activity, and socialization are important factors for frailty management to enhance physical and mental resilience. However, these three factors are disturbed now because current public health measures can exert unintended adverse secondary effects through a wide range of downstream societal consequences.³ The restriction of social activities induces physical frailty, or sarcopenia. Physical distancing increases social isolation and loneliness, leading to depression, cognitive decline, and exacerbations of chronic diseases.¹⁰⁻¹² A report published by the Japan Day-service Welfare Association showed that seniors' activities of daily living (ADL) had deteriorated due to reduced operation of healthcare and social services for elderly individuals.¹³ In general, aging is the primary cause of sarcopenia and older adults lose muscle mass as they age. Rates of sarcopenia have accelerated rapidly with restrictions in social activities. Sarcopenic change results in not only decreased ADL but also blood flow stagnation, glucose tolerance, and immune weakness. Taken together, from a nutritional intervention perspective during this COVID-19 pandemic, nutritional care for enhancing immunity to reduce the infection rate and severity and preventing the progression of frailty is important for elderly individuals.

Nutritional care for elderly individuals during the COVID-19 pandemic

Having a well-balanced diet three times a day regularly is essential for our health. It has been reported that malnutrition can be an independent prognostic factor for influenza infection.^{14,15} The latest food uptake standard issued by the Japan Ministry of Health, Welfare and Labor in 2020 recommended energy intake from protein be increased to 15-20% for those over 65 years old when considering the nutritional management of sarcopenia. The recommended daily protein intake is 1.2-1.5 g/kg body weight. As elderly individuals are generally resistant to muscle anabolism, they need to consume good-quality proteins containing branched-chain amino acids (BCAAs). BCAAs play an important role in muscle synthesis to repress protein degradation and activate protein synthesis. BCAAs are also reported to have roles in gut health, immune function, and insulin sensitivity.¹⁶⁻¹⁸ Tuna,

bonito, poultry, beef, egg, beans, and milk are all rich in BCAAs. Recently, among BCAAs, leucine and β -hydroxy- β -methylbutyrate (HMB, its metabolite) have attracted attention for the effective synthesis of muscle proteins [19]. Vitamins and trace elements tend to run short when a balanced diet is destroyed, and their deficiency hinders immune function. It has been reported that vitamin D deficiency is related to the development of infectious diseases, such as influenza infection, human immunodeficiency virus infection, and hepatitis C virus hepatitis.^{20,21} We presume that intake of a sufficient amount of vitamin D plays a role in preventing COVID-19 infection, since vitamin D deficiency is common among elderly individuals.^{22,23} Vitamin A may also play a role in protecting from infection and is considered to be important among pediatric infectious diseases.²⁴ Other vitamins, such as E, B6, B12, selenium, and zinc, are also related to immune function, and zinc deficiency has been shown to increase susceptibility to various pathogens.²⁵

Probiotics are beneficial in promoting a healthy gut and immune system.²⁶ Probiotics can be found in cultured dairy products and fermented products. Vitamin D is naturally found in fatty fish, such as salmon and tuna, and in small amounts in dairy products, egg yolks, and mushrooms. Vitamin A can be found in many fruits and vegetables, such as carrots, sweet potatoes, tomatoes, broccoli, spinach, mango, and peppers.

Adding seafood, fruits, vegetables, dairy products, and beans into the diets of elderly individuals will ensure adequate intake of these immune-boosting minerals.

In addition to the nutritional care described above, in order to avoid losing appetite, routine exercise is important for elderly individuals. In terms of frailty management, enriching the lives of elderly individuals with proper exercise and social relationships should be taken into consideration. Incorporating information and communications technology and social networking services may play a role in these achievements as communication tools and should be promoted positively among older adults during the COVID-19 pandemic.

Conclusion

The COVID-19 pandemic has led to the declaration of a state of emergency for the first time in Japan. We have been seized with fear under the strict restriction of our daily lives for pandemic control. I have summarized the requisite nutritional care to preserve the physical resilience of elderly individuals, which also aims to manage frailty. Elderly individuals should be encouraged to have a healthy and active lifestyle during this pandemic.

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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Effect of vitamin D supplementation to prevent acute respiratory tract infection: an evidence-based case report

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Abstract

Background: One of the frequent health problems that regularly occurs in Indonesia, as a tropical country is an acute respiratory tract infection, including influenza. Since immunological benefit of vitamin D already proven, hypothetically, vitamin D can be used as protective agent to prevent influenza or other respiratory tract infections.

Objectives: This evidence-based case report was focused on the evaluation of protective ability of vitamin D supplementation to prevent influenza or other acute respiratory tract infections.

Methods: Literature searching was conducted on PubMed data base and Cochrane Library using the related keyword combinations.

Results: Two randomized-clinical trials (RCTs) and a meta-analysis study were fulfilled the eligibility criteria. Vitamin D supplementation did not reduce the incidence of influenza but reduce the incidence of non-influenza infection. High-dose vitamin D supplementation had no effect on the reduction of acute respiratory tract infection incidence. The meta-analysis concluded that vitamin D supplementation reduced the risk for acute respiratory tract infection and the stronger effects occurred on low-levels of vitamin D serum.

Conclusions: Vitamin D supplementation may prevent acute respiratory tract infections, especially in subjects with low-levels of vitamin D serum.

Keywords vitamin D, acute respiratory infection

Introduction

Acute respiratory tract infection was occurred on 46% of population/years. Influenza were prevalent in a third of them. This health problem can affect people in all age-groups.¹ As a tropical country, Indonesia has a greater risk for infectious disease, including acute respiratory tract infection. Fourteen percent of all severe acute respiratory tract infection

is caused by influenza. The incidence is highest in childhood population.²

Various micronutrients are proposed to be protective role to prevent influenza or other acute respiratory tract infection, including vitamin D. Vitamin D has various beneficial effect on immune responses. Several immune cells have receptor, hence be able to respond vitamin D. Vitamin D acts in autocrine or paracrine processes in B and T cells. It also enhanced the activities of macrophage and dendritic cells. Hypothetically, vitamin D supplementation can be used to prevent influenza or other acute respiratory tract infections.^{3,4}

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Clinical Illustration

A 30- years old woman came with her son age 5- years old as patient of clinical nutrition outpatient department in General Hospital. She tells her physicians that some of her son's close friends in school had suffered from cough, rhinorrhea, and fever since a week ago. He routinely contacts with them during the school time. The mother worried that her son would be infected by his friends. She has vitamin D tablets in her house, so she was wondering could vitamin D supplementation prevent the disease ?

Clinical questions

Could vitamin D supplementation prevent influenza or other acute respiratory tract infections among children ?

P : Children

I : Vitamin D supplementation

C: Placebo

O: Prevent influenza or acute respiratory tract infection incidence

Methods

Article searching was conducted on PubMed database and the Cochrane Library on April 7, 2020. The key words combination on Table 1 were used within the searching process. English systematic review, meta-analysis, clinical trial or observational study in the last five years: 1 January 2014 — 31 December 2019 publication were included. The study with other specific medical conditions (such as pregnant, cancer, bowel disease) were not included. An animal study and non-relevance article were also excluded. Critical appraisal was conducted using critical appraisal tools for clinical trials and systematic review that published by The Center of Evidence-Based Medicine (CEBM)

Results

According to literature searching, with mentioned strategy, we obtained the literatures as presented number in Table 1 based on each key words combination. After duplicates removed, a total of 13 articles were recorded. Four of them were excluded

due to other specific condition including pregnancy (2 studies), asthma (1 study), and bowel disease (1 study). The other six studies were excluded since not relevant topics. Finally, we obtained two randomized clinical trials and one-meta analysis.

From two tables above we can see that vitamin D can protect against respiratory non influenza infection better than respiratory influenza infection. We needed 93 patients treated with vitamin D to prevent 1 patient infected with influenza contrasted with non influenza patients which only need 17 patients treated to get the same results.

Discussion

Vitamin D expands the number of antimicrobial peptide cathelicidine in respiratory epithelium, which has been shown to reduce the severity of the disease and the replication of influenza virus in vitro.⁸ However we found a different result, vitamin D can protect someone from non-influenza respiratory infection rather than influenza itself, this findings need further research. A combination of the aims of these clinical trials could answer two dissected-clinical questions. After the necessity of vitamin D supplementation to prevent influenza or acute respiratory tract infection, we also could know which dose to be used for it. The two included clinical trials showed an almost concordant conclusion. Loeb et al⁵ reported that vitamin D supplementation did not reduce the incidence of influenza, but significantly reduced non-influenza viral infection. On the other hand, Aglipay et al⁶ concluded the high-dose vitamin D supplementation did not reduce the incidence of viral respiratory tract infection, not specifically caused by influenza. The later also showed that compared to standard-dose vitamin D supplementation, the high-dose one had no difference in the median time to the first laboratory-confirmed infection and the number of laboratory-confirmed infections.

As a strength of these two clinical trials, the outcomes were confirmed validly and accurately. The cause of infections was diagnosed using polymerases chain reaction (RT-PCR). Both clinical trials also described the distribution of infection causes. The two clinical trials had a similar limitation. Loeb et al⁵ had subjects with high-baseline vitamin D levels among the two groups.

Meanwhile, Aglipay et al⁶ started the study early of the winter. Probably, it implicates the lack of effect of high-dose vitamin D supplementation due to high-baseline vitamin D serum level at the end of the summer was relatively high. Another limitation, due to restricted by ethical consideration, the clinical trial conducted by Aglipay did not compare the intervention group to placebo.

The meta-analysis study confirmed the effect of vitamin D supplementation to reduce the incidence of acute respiratory tract infection. Vitamin D supplementation is a protective factor for all-cause of acute respiratory tract infection based on the adjusted odds ratio of 0.88. The meta-analysis also concluded that the protective effects of vitamin D supplementation were stronger in patients with low baseline vitamin D serum levels (< 25 nmol/L).⁷

The clinical trials and meta-analysis also had two similar limitations. First, they did not analyze the potential confounders such as baseline nutritional status and record of dietary patterns. Some studies revealed underweight, overweight, and obesity as independent risk factors for influenza.^{9,10} Second, three included studies also did not analyzed the level of patient adherence on each study.

Conclusion

According to two clinical trials and one meta-analysis, vitamin D supplementation neither reduce nor prevent influenza. However, high-dose of vitamin D supplementation may protect non-influenza respiratory tract infection in patients with low-vitamin D serum levels.

Table 1. Keyword and the numbers of included-articles

Database	Terminology	Number of article(s)	
		Hits	Included
Pubmed	“vitamin D supplementation” AND “influenza” AND “prevention”	6	2
Pubmed	“vitamin D supplementation” AND “influenza-like illness” AND “prevention”	0	0
Pubmed	“vitamin D supplementation” AND “acute respiratory tract infection” AND “prevention”	1	1
Cochrane	“vitamin D supplementation” AND “influenza” AND “prevention”	13	2
Cochrane	“vitamin D supplementation” AND “influenza-like illness” AND “prevention”	0	0
Cochrane	“vitamin D supplementation” AND “acute respiratory tract infection” AND “prevention”	0	0

Table 2. Characteristics of each study

	Loeb et al. ⁵	Aglipay et al. ⁶	Martineau et al. ⁷
Study Design (Levels of evidence)	RCT (1B)	RCT (1B)	SR/MA (1A)
Objective of the study	To investigate the ability vitamin D supplementation to reduce influenza and other upper viral respiratory tract infections.	To investigate whether high-dose vs standard-dose vitamin D supplementation could prevent the wintertime upper respiratory tract infections in young children.	To assess the overall effect of vitamin D supplementation on risk of acute respiratory tract infection.
Patients (subjects)	Children and adolescents aged 3-17 years in Thanh Liem District of Vietnam.	Young children aged 1-5 years in Toronto, Canada.	Broad range of age in total analysis.
Intervention and Comparison	Vitamin D (14.000 IU/week) versus placebo during 8 months.	High dose (2000 IU) versus standard dose (400 IU) supplementation of vitamin D during 4-8 months	Vitamin D supplementation (400 IU-30.000 IU) versus placebo.
Number of Subjects (or study for meta-analysis)	650 vs. 650 subjects	349 vs. 354 subjects	25 RCT studies with 11.321 total of subjects.
Outcomes	<ul style="list-style-type: none"> The incidence of influenza between supplemented subjects was not different to placebo (7.7% vs 6.6%, <i>Hazard ratio</i>. [HR]: 1.18, 95% CI: 0.79-1.78). Vitamin D supplemented subjects had a lower incidence of non-influenza respiratory tract infection (22.5% vs 28.5%, HR 0.76, 95% CI: 0.61-0.94) 	<ul style="list-style-type: none"> There was no difference in the number of laboratory-confirmed infections among the groups. (RR, 0.97; 95% CI, 0.80-1.16). There was no difference in the median time to the first laboratory-confirmed infection: 3.95 vs 3.29 months. Vitamin D did not reduce the occurrence of non-influenza respiratory tract infection (RR: 1.01; 95% CI 0.83 to 1.23). 	<ul style="list-style-type: none"> Vitamin D supplementation can reduce the risk of acute respiratory tract infection. (adjusted odds ratio: 0.88, 95% CI 0.81-0.96). Protective effects of vitamin D supplementation were stronger in patient with low baseline vitamin D serum level (< 25 nmol/L).

Table 2. Characteristics of each study (continued)

	Loeb et al.⁵	Aglipay et al.⁶	Martineau et al.⁷
Limitation	At the baseline, vitamin D serum level of the subjects were not significantly different but they had high level vitamin D serum level. It makes the different of occurrence were not significantly different.	The study conducted at the early winter. The basal vitamin D serum was high due to peak level of vitamin D serum was occurred in the end of summer.	The dose-related effect were not accounted. The outcomes measurement in each study quietly different.
Conclusion	The incidence of influenza were not reduced by vitamin D supplementation. However, vitamin D reduced moderately non-influenza viral infection.	Compared to standard dose, high-dose of vitamin D supplementation did reduced viral respiratory tract infection.	Vitamin D supplementation can prevent the overall acute respiratory tract infection.

Table 3. Validity Assessment for RCTS by Loeb et al and Aglipay et al

Are the results of this single preventive therapeutic trial valid?		
Question	Loeb et al	Aglipay et al
Was the assignment of patient to treatment randomised? And was the randomisation list concealed?	Yes, patients were randomly assigned to either the experimental or placebo control group. Yes, the list was concealed, they use external research organization to ensure randomization and concealment purpose.	Yes, patients were randomly assigned to either the high dose or standard dose group. Yes, the list was concealed.
Were all patents who entered the trial accounted for at its conclusion? And were they analysed in the group to which they were randomised ?	This study used intention to treat analysis.	This study used intention to treat analysis.
Were patients and clinicians kept blind to which treatment was being received ?	Yes	Yes
Aside from the experimental treatment, were the groups treated equally?	Yes	Yes
Were the groups similar at the start of the trial?	Yes, we can check in the baseline characteristics table.	Yes, we can check in the baseline characteristics table.

Validity

Table 4. Validity assessment of meta-analysis by Martineau et al

Are the results of this systematic review of therapy valid?	
Question	Martineau et al
Is it a systematic review of randomised trials of the treatment you're interested in?	Yes.
Does it include a methods section that describes: finding and including all the relevant trials?	Yes, it is explained in the Methods subsection "study identification and selection, and data collection process". They included trials from any languages. They performed systematic search in major databases, but did not search unpublished material using handsearching method.
Assessing their individual validity?	Yes, quality of included studies were assessed using the Cochrane Collaboration risk of bias tool and five GRADE considerations (study limitations, consistency of effect, imprecision, indirectness, and publication bias).
Were the results consistent from study to study?	Yes, vitamin D supplementation can reduce the risk of acute respiratory tract infection. (adjusted odds ratio: 0.88, 95% CI 0.81-0.96).

Importance

Table 4. Comparison of vitamin D and placebo on influenza infection

Influenza infection	Intervention	
	Vit D	Placebo
Yes	50	43
No	600	607

Absolute Risk Reduction (ARR) = 1%

Number Needed to Treat (NNT) = 93

Table 5. Comparison of Vitamin D and Placebo on Influenza Infection

Non Influenza infection	Intervention	
	Vit D	Placebo
Yes	146	185
No	504	465

ARR = 6%

NNT = 17

Applicability

Table 6. Critical appraisal on the applicability

	Loeb et al. ⁵	Aglipay et al. ⁶	Martineau et al. ⁷
Resemblance of the study subjects with the case	Children and adolescents aged 3-17 years in Thanh Liem District of Vietnam. Resemblance is strong, since the case is Indonesian kid age 5	Young children aged 1-5 years old in Toronto, Canada. Moderate resemblance because different race	Low resemblance because, this is a systematic review which include age 6 months until 80 years old patients.
Agreement to the value and preference in the community	Very likely to agree since vitamin D is well known among Indonesian population.		
Feasibility of the therapy in the setting of daily clinical practice	Very feasible, vitamin D is easily found everywhere in the local drug store.		

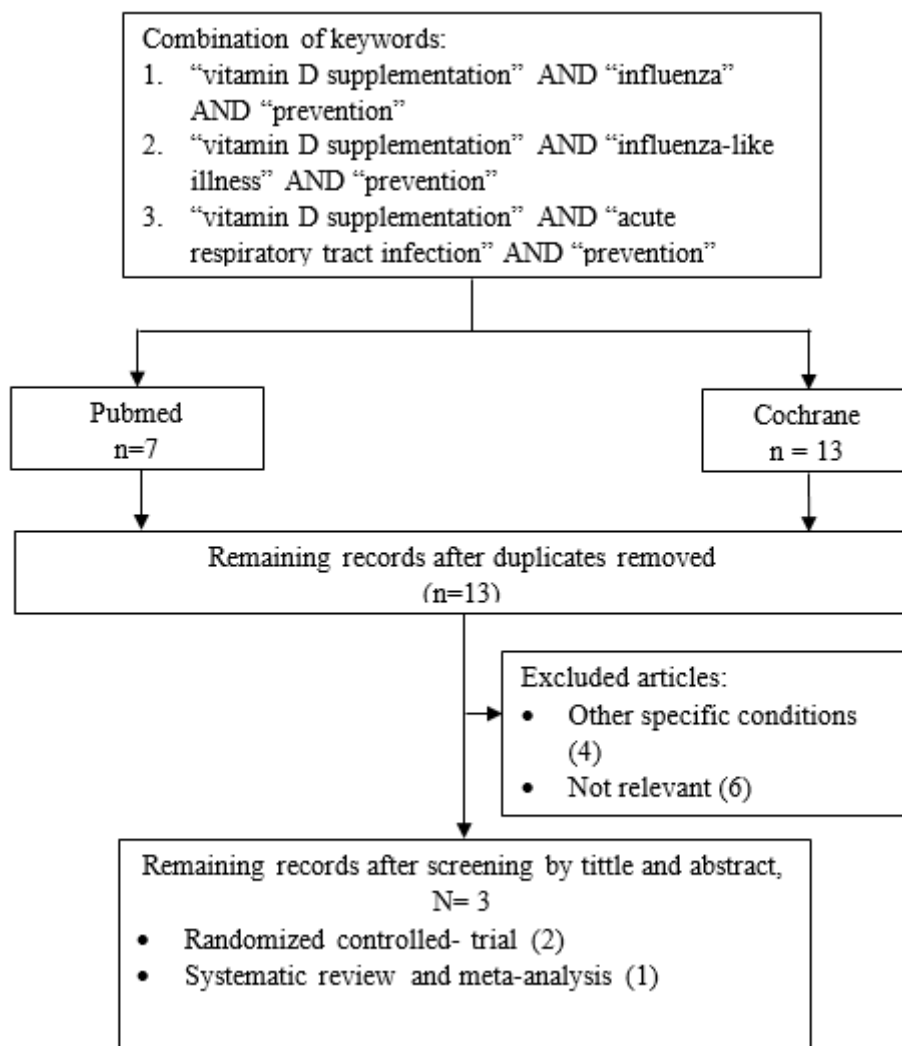


Figure 1. The PRISMA flowchart for the selection articles

Conflict of interest

The authors declare no conflict of interest regarding this study.

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Effect of carnitine on patients with heart failure: an evidence-based case report

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Abstract

Background: Heart disease is one of the leading causes of death in Indonesia. Nutritional management plays an important role in overcoming heart disease, both as prevention and treatment. Carnitine plays a role in fat metabolism and can reduce the formation of thrombosis, resulting in improved heart function and quality of life of patients.

Objectives: This study is aimed to identify the effect of carnitine in patients with heart failure.

Methods: Existing research findings and articles are selected based on inclusion and exclusion criteria in three databases, namely PubMed, Cochrane and Wiley. The outcome were functional capacity and heart function.

Results: One meta-analysis that address with the clinical questions was obtained, and based on that article, giving carnitine to patients with heart failure has effects on increasing functional capacity, heart function, BNP serum and NT-proBNP levels. However, no effects found on mortality. Furthermore, no significant side effects on carnitine was found.

Conclusions: Carnitine supplementation at a dose of 1 up to 6 g/day has a positive impact on functional capacity, heart function, BNP serum and NT-proBNP levels in patients with heart failure, alongside with minimal side effects.

Keywords carnitine, heart failure, outcome

Clinical scenario

Mr. S, age 50, was admitted to the emergency room with the chief complaint of shortness of breath for the last 3 days, which would arise suddenly and became worse when in a sleeping position. History of diabetes was denied, however he had a history of high blood pressure for the past one year and was not taking medications regularly. Physical examination

revealed cardiomegaly, normal heart sounds, no murmurs or gallops. Laboratory results: Hb 16 g/dL, leukocytes 6500/mm³, platelets 230,000/uL, LDL 243 mg/dL, triglycerides 267 mg/dL, uric acid 10 mg/dL, troponin I 0.29 ng/mL, BNP 312 pg/mL. Electrocardiography test showed an enlarged left ventricle. The patient's body weight was 65.7 kg, with a height of 160 cm, and a body mass index of 25.6 kg/m². The patient was hospitalized and received treatment from internists and clinical nutrition specialists. Patient was diagnosed with obesity grade 1,¹ heart failure class 4 according to the New York Heart Association (NYHA), dyslipidemia, and hyperuricemia. Patient was given oral carnitine supplementation when discharged from the hospital at a dose of 1.5 g/day for 3 months

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period, and showed an improvement in NYHA class. Patient did not show any side effects after carnitine supplementation.

Introduction

Heart failure is a global problem with 26 million people worldwide and with 670,000 new cases found in America. Heart failure is the most common cause for hospital admittance in the United States and Europe.² In Indonesia, heart failure prevalence is 5%, with mortality rate up to 20%.³

One of the nutrients that has been found having an essential role for patients with heart failure is carnitine, which is an amino acid derivative that plays a role in fat metabolism and mitochondrial defence. Several studies have shown that carnitine, especially in the form of propionyl-L-carnitine, can reduce the accumulation of coronary artery thrombosis and embolism. Some sources of carnitine are milk and milk products, and red meat.

The role of carnitine in fat metabolism is as the transporter of acyl co-A into the mitochondrial matrix, so that fat can undergo β -oxidation and become a source of energy, especially for heart muscle cells.⁴ Healthy adult usually consume carnitine at a dose of 2-5 mg/kgBW/day.⁵

Patients with heart failure often suffer from carnitine insufficiency due to reduced intake, malabsorption, and decreased muscle mass. Carnitine insufficiency results in reduced left ventricular diastolic function, reduced physical activity ability, and an increased risk of heart attack.⁷ However, carnitine has not yet been recommended as a routine therapy in patients with heart failure by the American College of Cardiology Foundation / American Heart Association (ACCF / AHA).⁸ Even so, giving carnitine can be a nutritional therapy for patients with heart failure that can help improve heart function and the quality of life of patients. Jing et al.⁹ carried out a research by administering carnitine intravenously twice a day for seven days, in the form of 1 g of L-carnitine dissolved in 100mL of normal saline in patients with heart failure. The assessment was carried out on the NYHA class of patients. The results showed a 60.9% improvement in the NYHA class of intervention group, compared to the 44.7% improvement in the NYHA class of placebo group. A meta-analysis study of the effects

of carnitine given orally in accordance with the needs of 3 g/day or more on mortality rate in patients with acute myocardial infarction did not show any significant impact.¹⁰

This evidence-based case report will discuss specifically about the effects of carnitine on patients with heart failure.

Clinical questions

P: Adult patients with heart failure

I: Carnitine

C: Without carnitine

O: Functional capacity and heart function

Clinical question: What is the effect of carnitine as a nutritional management on functional capacity and heart function in patients with heart failure?

Methods

Article Search Strategy

Existing research articles were generated from PubMed, Cochrane Library, and Wiley Online on December 12, 2019. Searching terminology is described in Table 1.

Article Selection Strategy

Eligibility Criteria

Screening is based on Mesh Term, an assessment of conformity with PICO, and with inclusion and exclusion criteria. The inclusion criteria were 1. Study subjects were adult patients (aged ≥ 18 years old), 2. Subjects diagnosed with heart failure with various stages 3. Clinical trials or meta-analysis with carnitine treatment 4. Journals published in the last 5 years 5. Tests clinically carried out in humans. Meanwhile, the exclusion criteria were 1. Journal is not written in English and 2. full text is not available.

Method of critical appraisal

All authors did the critical appraisal by using the method according to the Center of Evidence Based Medicine (www.cebm.net) for intervention studies that has been modified in Indonesian language.

Findings

Based on the results of the search from the database, and by assessing the inclusion and exclusion criteria, an article that is eligible to be included as a reference for critical review is used (Figure 1).

Selected articles are meta-analysis of clinical trials, with a total number of 1625 patients. The length of follow-up of the subject in the articles is from 7 days to 3 years. Carnitine given to patients with a dose of 1 to 6 g/day.

The articles obtained have a level of evidence 1, which is a meta-analysis of 17 clinical trials. Findings from articles used in this work illustrate that carnitine administration has a positive impact on functional capacity and heart function. The validity of the criteria can be seen in table 3. The relevance of the criteria can be seen in table 4.

There were no differences of mortality rate in patients with heart failure ($p=0.08$) and carnitine side effects ($p=0.83$), there was an increase in functional capacity marked by a decrease in NYHA class ($p<0.01$), decrease in BNP serum markers ($p=0.01$) and NT-proBNP ($p<0.01$), as well as increased cardiac function ($p<0.01$).

Discussion

Song X et al. conducted a meta-analysis study for the effects of carnitine supplementation on patients with heart failure with a search time limit until September 30, 2016. The study looked for randomized controlled literature from various databases, abstracts of scientific meetings, as well as manually from unpublished articles and studies. Based on the search, 17 appropriate journals were found, with a total of 1625 research subjects. Patients' age ranged between 43 and 78 years. Carnitine dosage given ranged from 1 to 6 g/day, and administered from 7 days to 3 years. Patients receiving carnitine were classified as NYHA class II-IV, with a LVEF of 27% to 52% before the intervention.

Outcomes from this study showed that carnitine had a positive impact on the functional capacity, which is characterized by a decrease in NYHA class.¹¹ The literature that has the greatest weight in the meta-analysis was the research conducted by Jing ZC et al. The study gave carnitine of 1 g intravenously, twice a day for seven days. The effectiveness of carnitine reached 60.7% compared

to the control group of 44.7% ($P=0.012$). The 6-minute walk test did not show significant difference between control and intervention ($P=0.14$).⁹ The study from Song X et al. also showed that carnitine had positive effect on serum-BNP ($P=0.01$) and NT-proBNP ($P=0.0003$). Both BNP and NT-proBNP can act as prognostic factors in patients with heart failure or in patients with asymptomatic left ventricular dysfunction.¹¹

The heart function also showed significant improvement. The heart functions assessed were LVEF ($P<0.00001$), SV ($P<0.00001$), CO ($P<0.00001$), E / A ratio ($P=0.0003$), LVESD ($P=0.002$), LVEDD ($P<0.0001$), and LVESV ($P=0.01$).¹¹ The antioxidant effect of carnitine can prevent the formation of superoxide in heart muscle and excessive inflammation, which results in changes in heart structure.⁴

There was no impact on the mortality of patients with heart failure, both in intention to treat analysis and per protocol. From a total of ten literature, six literatures showed no side effects of carnitine administration in patients with heart failure, while four studies report side effects such as dry mouth and gastrointestinal disorders. One literature reported that there was skin rash as a side effect, but it did occur in both treatments, both the control group and the intervention group.¹¹

Based on the article in this evidence-based case report, it can be concluded that administration of carnitine can improve the quality of life of patients with heart failure, improve heart function and serum levels of BNP and NT-proBNP, with minimal side effects. Carnitine can be given orally by using carnitine supplements, and using food sources. Examples of food sources of carnitine are beef, with carnitine of 2320 mg/kg dry weight, duck meat with carnitine 732 mg/kg dry weight, skim milk with carnitine 400 mg/kg dry weight, condensed milk 396 mg/kg dry weight, and yogurt 142-139 mg/kg dry weight.

Recommendation:

Patients with heart failure can be given carnitine at least 1 g/day to 6 g/day. In administration of carnitine at a dose of 1 g, it can be given for 1 year, a dose of 1.5 g carnitine with a duration of 3 months, while a dose of 3 g and 6 g can be given for 7 days

Conclusion

Patients included in defined clinical scenario can be given carnitine up to 6 g/day, in the form of supplementation or derived from food sources such as milk, milk products, or meat. Giving carnitine can improve the quality of life of patients, heart function, reduce BNP serum and NT-proBNP levels, with minimal side effects. Giving carnitine has no impact on the mortality of patients with heart failure.

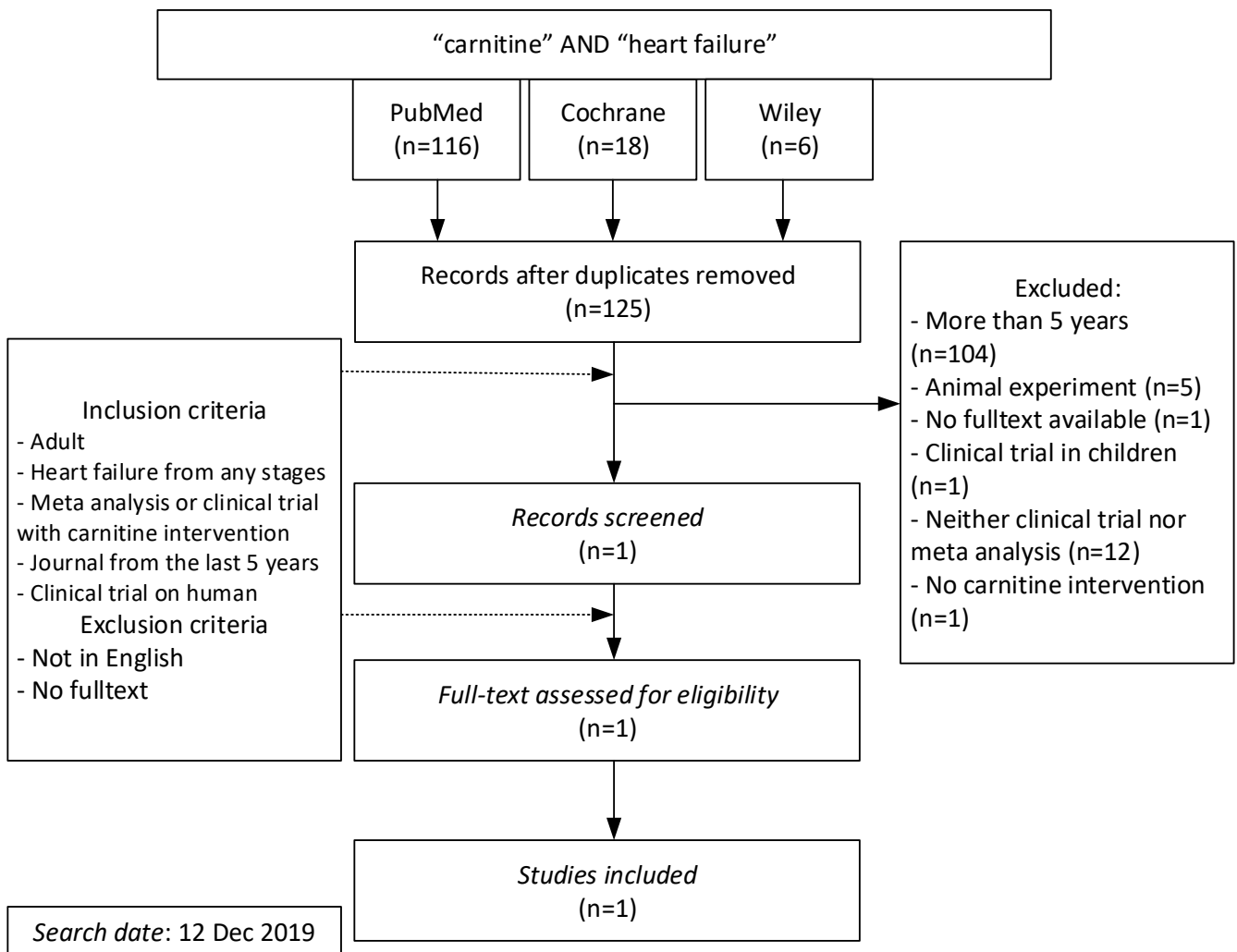


Figure 1. PRISMA flow chart

Table 1. Terminology

Database	Terminology	Hits	Eligible
PubMed	((carnitine[MeSH Terms] OR carnitine[Title]) AND ((heart failure[MeSH Terms] OR heart failure[Title]))	116	1
	ID Search	Hits	
	#1 "heart failure"	28578	
	#2 carnitine	1705	
Cochrane Library	#3 MeSH descriptor: [Carnitine] explode all trees	606	18
	#4 MeSH descriptor: [Heart Failure] explode all trees	8482	0
	#5 #2 OR #3	1719	
	#6 #4 AND #6	18	
Wiley Online Library	"carnitine" AND "heart failure" in Keywords	6	0

Table 2. Study characteristics

Article	Study design	Characteristics of the population	Number of subjects	Age group (years)	Intervention	Control	Outcome	Follow up Period
Song X, et al (2017) ¹¹	Meta analysis	Patients with heart failure	1625	43-78	Carnitine 1-6 grams	Without carnitine	Functional capacity, heart function, BNP and NT-proBNP level, side effects	7 days up to 3 years

Table 3. Validity criteria

Validity	Relevance									Result	Level of Evidence
Artikel	Common point	Follow up	Blind fashion	Sub-group analysis	Outcome	Precise	Apply	Important			
Song X, et al (2017) ¹¹	+	+	-*	+	+	+	+	+	+	A	1

* Only 3 journals stated that there was blinding in patients and study members

Table 4. Relevance criteria

Article	Similarity Population	Similarity determinant/ intervention/ indicators	Similarity Outcome
Song X, et al (2017) ¹¹	+	+	+

Conflict of interest

The authors declare no conflict of interest regarding this study.

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Correlation between intensive phase treatment of antituberculosis drugs with nutritional status of patients with tuberculosis in Kupang city

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Abstract

Background: Indonesia is a country with the third highest tuberculosis incident in the world. Nutritional status is very important to patients with tuberculosis, an optimal nutritional status created an optimal immune system. Lack of adequate nutritional intake, prolonged the anti-tuberculosis drug treatment and caused them to get a slower recovery. Therefore, the writer found the need of knowing the relation of intensive phase treatment of anti-tuberculosis drugs with nutritional status of patients with tuberculosis in Kupang City.

Objectives: To know the relation between intensive phase treatment of anti tuberculosis drugs with nutritional status of patients with tuberculosis in Kupang City.

Methods: This study was an observational analytic study with a nested cohort design conducted by 11 public health centers in Kupang City by taking secondary data from medical records. The sampling technique used consecutive sampling with 84 respondents who met the inclusion and exclusion criteria. The study was analyzed univariately, and bivariately using Mc Nemar.

Results: From 84 respondents, before intensive phase tuberculosis treatment 61 respondents (72.6%) had abnormal nutrition status, and 23 respondents (27.4%) had normal nutritional status, while after intensive phase tuberculosis treatment from 84 respondents it was found that 50 respondents (59.5%) had abnormal nutrition status, and 34 respondents (40.5%) had normal nutritional status. The result of the bivariate analysis test shows a significant different in nutritional status before and after tuberculosis treatment with p value = 0.001.

Conclusions: There was a significant different in nutritional status before and after tuberculosis treatment indicating that anti-tuberculosis drug treatment can affect the nutritional status of patients with tuberculosis.

Keywords anti tuberculosis drugs, nutritional status, Kupang city

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Introduction

Tuberculosis (TB) is one of the deadly communicable diseases and is now become a concern of the public worldwide.¹ TB is currently become one of the world's health problems.² There

are differences in epidemiology of TB between developing countries and industrial countries. In countries with low living standard and poor health resources, the risk of new TB infection happens at productive age (15-59 years old) is 80%. In developed countries where TB incidence has decreased, the majority of TB cases arise as a result of endogenous reactivation of TB. This cause the highest rate of disease to occur in elderly (>65 years old).³

In 1995 the World Health Organization (WHO) recommended a Directly Observed Treatment Short Course (DOTS) as a strategy to control TB in the world. The World Bank declared the DOTS strategy as one of the most cost-effective health interventions, integration into basic health services is highly recommended for efficiency and effectiveness.⁴ Based on data from around the world, TB is one of the 10 leading causes of death. In 2017, TB caused an estimated 1.7 million deaths. Based on data from WHO, TB is present in all countries and all age groups. Globally, TB sufferers are estimated to have as many as 10.0 million people and in 2017 there are 5.8 million men, 3.2 million women and 1.0 million children affected with TB.⁵

TB consist of 2 phases of treatment which is intensive phase for 2 months and continuous phase for 4-6 months. There is a difference between intensive phase treatment and continuous phase treatment, where the intensive phase uses 4 kinds of drugs and the continuous phase uses only 2 kinds of drugs.^{6,7} Therefore based on this background we wanted to conduct a research on the relation between intensive phase treatment of anti tuberculosis drugs with nutritional status of patients with tuberculosis in Kupang City.

Methods

This research was conducted in 11 Public Health Centers around Kupang City, East Nusa Tenggara, Indonesia from June to September 2019. This research is an observational analytical research that examined the relation between each variables. This research aimed to determine the relation between intensive phase treatment of anti tuberculosis drugs with nutritional status of patients with tuberculosis in Kupang City.

This research used the nested cohort method design, which emphasized on time and independent and dependent variables only once at a time. The sampling technique used consecutive sampling with the total 84 respondents who met the inclusion and exclusion criteria. This research was then analyzed univariately and bivariately using Mc Nemar test. The independent variable in this research is intensive phase tuberculosis treatment, and the dependent variable is the nutritional status in patients with tuberculosis.

Results

Table 1. shows the baseline characteristic data of patients with tuberculosis at Public Health Centers around Kupang city, the highest number of respondents was located at Oesapa Public Health Center with the total number of 40 people (47.6%) and the lowest was located at Kupang Kota Public Health Center with the total number of 0 people (0%). Respondents were divided into age groups according to the 2009 Indonesian Ministry of Health, consist of late adolescence (17-25 years), early adulthood (26-35 years), late adulthood (36-45 years), early elderly (46-55 years), late elderly (56-65 years) and over elderly (> 65 years). Based on the data above, the highest age group who suffer pulmonary tuberculosis is the early adult group (25.0%), followed by the late adolescent (21.4%) and late adulthood (17.8%) which is the productive age. The results also showed that the total number of respondents in this research were 84 respondents, consist of 51 male (60.7%) and 33 female (39.3%). Among 84 subjects, 57 respondents (67.85%) had sputum Ziehl-Neelsen staining procedure positive for acid-fast *bacilli* (AFB).

As shown in **Table 2**, 23 people had normal nutritional status before the intensive phase treatment (27.4%), and 61 people had abnormal nutritional status (72.6%). After the treatment, 34 people had normal nutritional status (40.5%), and 50 people had an abnormal nutritional status (59.5%).

Based on statistical analysis using Mc Nemar test, the results showed a significant level of p value = 0.001 (p <0.05) which indicated that there was a significant change in patient nutritional status after the intensive phase treatment of anti tuberculosis drugs (p = 0.001 or p <0.05) (**Table 3**).

Discussion

According to geographical location the research took place around Kupang City, one of the influence factors of TB transmission is temperature, Kupang City has an average temperature of 31°C that is above the standard set by the Indonesian Ministry of Health Regulation No.1077/Menkes/Per/V/2011 that mentioned about the temperature requirement should be at around 18-30°C. The presence of *Mycobacterium tuberculosis* at an inappropriate temperature has the potential to increase the favorable conditions for bacteria to live and multiply and potentially increasing the transmission of tuberculosis as well.^{8,9}

Population density in Kupang city is around 2,289.39 people/km² that apparently does not meet the requirement of an ideal population density that supposed to be <9 m per person, this condition cause new TB cases that occurs due to the increased population density, it resulted in the increasing of TB incidence as well. This is in line with the research conducted by Jimmy Lahabama⁹ in 2013 in Pontianak Indonesia stating that if the density does not meet the requirements then the incidence of TB will be higher in areas with high population, therefore there will be more people affected by TB compared to areas that meet population density requirements.

Nutritional status is one of the most important factor in the body's defense against infection. It has been proven that nutritional deficiencies are associated with impaired immune function. In poor nutritional conditions, the body's immune response will be weakened so that the ability to defend against infection will be decreased.² Malnutrition of protein energy and micronutrient deficiency can cause secondary immunodeficiency which increases one's vulnerability to tuberculosis infection.¹⁰

TB infection increase energy needs at rest called resting energy expenditure (REE) at around 10-30% of the energy needs of normal people. The process of how the infection could affect nutritional status in person with tuberculosis started with an increasing of leptin resulting in a decreased of nutrient intake and malabsorption, while in the process of infection there is an increase in energy needs by the body and there is also an increasing of IL-1 β , IL-6, TNF- α and malondialdehyde (MDA) as a response of

inflammatory process. The inflammatory process will activate the proteolysis pathway of the ATP-dependent ubiquitin intracellular protease and subsequently the protein is destroyed in proteasomes and regulated by TNF- α . The increased production of IFN-IL, IL-6, TNF- α due to TB infection inhibits the activity of the lipoprotein lipase (LPL) in fat tissue. LPL plays a role in the process of triglycerides cleansing. The increasing of LPL will then increase the process of triglycerides cleansing, decrease the synthesis of fatty acid, and increase the lipolysis process of fat tissue, the decreasing of fatty acids synthesis will lower the body weight and nutritional status.^{10,11}

From the results of the study it was found that TB cases are most common in 26-35 years age group with the total of 21 respondents (25%) that are included in the productive age group, this is because those in productive age group are often exposed in a crowd and populous working environment that allow them to contact with many other people, this can increase the risk of TB. Such working conditions make it easier for someone of productive age to get infected by TB.¹²

From the results of the study it was found that respondents with new TB cases were low occurred in the elderly age group above 65 years by only 4 people (4.8%) because in the elderly age group there will be a degradation in physiological function of the body, a decrease in body muscle mass and a decrease in appetite, however to get an optimal immune system the nutritional status and nutritional intake must also be optimal, the infection process require a good nutritional status and nutritional intake to help optimizing the immune system in the body to eliminate TB bacterias. TB infection can increase energy needs to maintain the body's immune system in running the system energy use.¹³

From the results of the study it was found that most respondents who are involved in the study were male with the total of 55 respondents (60.7%) and there are only 31 female respondents (39.3%). Gender is also one of the risk factors of TB, where men has a higher risk than women especially in cases of pulmonary TB because men have high mobility and are often engaged in activities outside of the home so that the possibility of exposure to *Mycobacterium tuberculosis* is higher. In addition, men also prone to bad lifestyle habits such as

smoking and drinking which lower the performance of immune system that later make them more vulnerable to tuberculosis infection, but an increase in nutritional status is faster in men than women, this is according to research conducted by Lestari¹⁴ in 2016 in the Lung Hospital of West Java Province involving 62 respondents stating that after TB treatment the increasing of BMI is higher in men than women, and because of how the immune system is closely related to nutritional status, therefore according to this research the successful treatment will likely higher to happen in men than women.¹⁴

Poor nutritional status will lower patients' immune system that can cause an escalation in the number of TB bacteria inside the body. The result of AFB examination in the majority of this case will likely be positive and with the prognosis of TB that has been given an anti-tuberculosis drugs there will be a conversion of AFB positive to negative, AFB conversion is influenced by nutrient intake, if nutrient intake decreased it will result in calorie and protein deficiency. Lack of protein will cause atrophy and reduce thymus cell proliferation which later resulted in the decreasing number of T lymphocyte cells production. T lymphocytes play a role in activating macrophages to destroy TB bacteria. If there is a decrease in the number of T lymphocytes, this will cause the body's defense system to weakened, macrophages are no longer able to digest TB bacteria, therefore these bacterias will stay in the lung tissue, delaying the sputum conversion and prolong the healing process.¹⁵

Based on the results of the study it was found that there was an increase in the body weight but there was no improvement in nutritional status after an intensive phase treatment, this is in line with the research by Priyatomo et al⁶ in 2014 conducted on 30 people in Indonesia at the Lung Diseases Health Unit in Health Center Pontianak, it was found that there was a difference between the nutritional status in the intensive phase treatment of 2 months and 6 months, in 2 months of the intensive phase treatment the research found that there was an increase in body weight but there was no improvement in nutritional status, while in the 6 months of continuous phase treatment there was an increase in body weight and accompanied by a significant increase in nutritional status.

Based on the results of the analysis it was found that there was a significant change in patient nutritional status after the intensive phase treatment of anti tuberculosis drugs with p value of <0.001 ($p < 0.05$) so the hypothesis of H_0 is rejected while H_1 can be accepted, and it was approved that there was a relation between intensive phase treatment of anti tuberculosis drugs with nutritional status of patients with tuberculosis in Kupang City.

This is in line with the research conducted by Huda et al in 2015 with the title Differences in Body Mass Index Before And After Treatment in Pulmonary Tuberculosis Patients at the Central Institute of Lung Health in Surakarta where this study was conducted on 216 respondents in Indonesia at The Lung Health Center in Surakarta by looking at the average differences between nutritional status before and after being treated with TB intensive phase treatment with p value <0.001 ($p < 0.05$)⁷, research from Rohini et al in 2013 on 40 respondents conducted in The Institute of Thoracic Medicine in India using a retrospective study showed that there were significant changes in nutritional status before and after intensive phase treatment under the DOTS program, with proper food choices that is suitable for the patient's condition can help in increasing the rate of weight gain during the intensive phase treatment with p value <0.001 ($p < 0.05$)¹⁶, and research conducted by Nagpal et al in 2014 in the City of Amristar in India showed that poor nutritional status was associated with the risk of TB and unfavorable outcomes, the burden of malnutrition was very high but the assessment of nutritional intake was often ignored in clinical practice and in a national TB program, so a counseling is needed regarding nutritional intake for patient with TB with p value of <0.435 ($p > 0.005$).¹⁷

Conclusions

Based on the results of the research it can be concluded that there was a significant change in patient nutritional status after the intensive phase treatment of anti tuberculosis drugs.

Table 1. Baseline characteristics of subjects (n=84)

Characteristic	n(%)
Age (years)	
17–25	18 (21.4)
26–35	21 (25.0)
36–45	15 (17.8)
46–55	14 (16.7)
56–65	12 (14.3)
>65	4 (4.8)
Gender	
Male	51 (60.7)
Female	33 (39.3)
AFB (Acid-fast <i>bacilli</i>) sputum examination	
Positive	57 (67.9)
Negative	27 (32.1)

Table 2. Univariate analysis of nutritional status before and after intensive phase treatment

Nutritional status	n(%)
Before treatment	
Abnormal	61 (72.6)
Normal	23 (27.4)
After treatment	
Abnormal	50 (59.5)
Normal	34 (40.5)

Table 3. Bivariate analysis of nutritional status during before and after intensive phase treatment

Nutritional status	Abnormal		Normal		P
	n	%	n	%	
Before	61	72.6	23	27.4	0.001*
After	50	59.5	34	40.5	

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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Efficacy of branched-chain amino acid to increase muscle strength in chronic heart failure patients: an evidence-based case report

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Abstract

Background: Chronic heart failure (CHF) patients can fall into cardiac cachexia (CC), which is marked by the decrease of muscle mass and strength. Cardiac cachexia decreases the functional capacity and quality of life also increases the length of stay, medical fees, complications, and mortality rate. Branched-chain amino acid (BCAA) accounted for 35% of amino acids that build the muscle. We hope that BCAA supplementation can increase muscle strength of CHF patients, especially the elderly who is more prone to fall into CC. Thus, we performed an evidence-based case report to seek an opportunity of BCAA supplementation to an elderly with CHF.

Objectives: To determine the efficacy of BCAA supplementation on increasing muscle strength in CHF patients.

Methods: Literature searching of the evidence-based case report was performed on Pubmed, Cochrane, and Scopus according to the clinical query. Screening on title, abstract, and full text was done based on eligibility criteria (meta-analysis or clinical trials, suitability to clinical questions, English language, full-text availability, and human studies), followed by duplication filter and critical appraisal.

Results: A randomized-controlled trial was found, but it didn't find a significant difference between the experimental and control groups.

Conclusions: BCAA supplementation doesn't give a significant improvement in muscle strength in CHF patients.

Keywords branched-chain amino acid, chronic heart failure, cardiac cachexia, muscle mass, muscle strength

Introduction

Heart failure has become a rising global issue with more than 62 million people affected.¹ The mortality risk is 35% in the first year after diagnosis.² Despite all current and advanced treatment, the 5-year-

mortality rate is still high and increasing.¹ The high mortality rate allegedly related to anorexia, inflammation, and hypermetabolism that occur in CHF, which will result in weight loss and loss of skeletal muscle mass, called CC. This condition not only occurs in the skeletal muscle but also cardiac muscle,³ and was estimated to affect between 8 to 42% of patients with CHF, which responsible to increase mortality rate as high as 20-30% at 1 year. Therefore, it is crucial to preserve and increase muscle mass and strength in CHF patients.⁴

Branched-chain amino acid supplementation has been shown to enhance muscle's mitochondrial biogenesis by activation of the mechanistic target of

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rapamycin kinase (mTOR) signaling. Several studies have found that BCAA can increase the synthesis of protein, reduce the protein breakdown, and increase muscle mass in the elderly and several catabolic states such as burn and trauma.⁵ Therefore, it is hoped that this report can provide consideration for giving BCAA supplementation to alleviate cardiac cachexia.

Clinical Scenario

Mr. B, 60 years old, comes with exertional dyspnea which worsens since a week ago. He complains about orthopnea, fatigue, and ankle edema. He was diagnosed with HF with reduced ejection fraction 5 years ago, after recovering from a heart attack. The patient complains about anorexia and low intake, which makes his weight drops from 70 kg to 65 kg in 6 months. His height is 170 cm, with a calculated body mass index of 22.49 kg/m². Handgrip strength found slightly decreased. Other than having an elevated CRP (6 mg/dL) and high blood LDL (170 mg/dL), the other lab result is normal. After treated with standard medication for CHF for several days, now the patient is stable and ready to be discharged. Based on this clinical scenario, a question arises whether BCAA supplementation will be effective in preserving and increasing muscle mass and strength in CHF patients?

Methods

Literature searching was performed on Pubmed, Cochrane, and Scopus according to the clinical question on the 14th of May 2020. The keywords used were “branched-chain amino acid”, “heart failure”, “cardiac cachexia”, “muscle mass”, and “muscle strength”. Screening on title, abstract, and full text was done based on eligibility criteria (meta-analysis or clinical trials, suitability to clinical questions, English language, full-text availability, and human studies), followed by duplication filter and critical appraisal was shown in **Figure 1**. A critical appraisal is done based on the Center of Evidence-Based Medicine, The University of Oxford for RCT.

Results

Following the search strategy, one original article was eligible for this evidence-based case report. The design and summary of the selected article are available in **Table 1**. Both groups had significant improvement in decubitus intolerance, fatigue, dyspnea, and muscle strength. But other than a marked reduction of hip circumference in the experimental group, there was no difference statistically between the control and intervention group in the rest of anthropometric variables, body composition, muscle strength, and physical endurance.

Discussion

Studies conducted by Juarez et al⁶ had a clear clinical question (PICO) and corresponded to keywords accordingly. The control and intervention groups were similar at baseline, except for fatigue and cancer history. The assignment of patients to treatments was randomized, but not blinded. Aside from the allocated treatment, the groups were treated equally. Drop-out subjects were not analyzed. Overall, we found this study valid, although there will still be bias because the assignment is not blinded.

Although there are many studies about protein and amino acid supplementation in CHF and CC, there is no other study about BCAA supplementation. Apparently, this is the first. This study did not find any impact on muscle mass and strength with BCAA supplementation. The result is the same with a study that did not find a difference in functional capacity after 5 g/day supplementation of carnitine.⁶ A longitudinal cohort also showed that higher protein intake was not associated with protection against muscle loss in the elderly. Even so, other studies found positive results with amino acid supplementation. A study gave 8 g / day of essential amino acid and found improvement in cardiorespiratory fitness. Other studies found amelioration of body weight and muscle mass after giving supplementation of 600 kcal and 20 g of protein per day.⁷

There are several presumptions about this study's result. First of all, perhaps the participants were not in a depleted state of BCAA, so they could

not benefit from BCAA supplementation.⁷ Secondly, excess of BCAA in the blood can cause a rise in BCAA's metabolite, branched-chain- α -ketoacid (BCKA) which can cause elevated levels of ammonia in blood and result in metabolic acidosis. This condition can create mitochondrial dysfunction, oxidative stress, and harm myocyte.¹ Thirdly, the hyper catabolic state of heart failure patients may cause a decrease in gastrointestinal tract absorption, thus BCAA can not be absorbed optimally. This is seen from the increasing level of BUN and urea in the intervention group.⁶ Last but not least, it is plausible that in the elderly with cardiac cachexia, BCAA supplementation is not enough to increase muscle mass without strength training.⁷ However, strength training did not include in other studies, they only gave protein or amino acid supplementation. This study is the first to accommodate strength training with BCAA supplementation. The limitation of this study is the assignment is not blinded, and perhaps it will be fairer to look at the true effect of BCAA supplementation if the assignment of the groups doesn't involve strength training. For example, the experimental group is given BCAA supplementation, and the control group is not.

identify the efficacy of BCAA to prevent and treat CC in CHF.

Conclusion

Although we can not recommend BCAA supplementation for CHF patients to prevent CC in the present, more study and evidence are needed to

Table 1. Literature characteristic

Article	Design	Population	Exposure	Results
Pineda-Juarez et al, 2016 ⁶	Randomized controlled trial	66 patients aged >18 years old from the heart failure clinic in Mexico City who had stable heart failure, no myocardial revascularization, unstable angina, or stroke in the previous 3 months, had no other chronic illness which contributed to a loss of muscle mass, and able to perform an exercise	The intervention group had a personalized diet, a resistance exercise program (RE), and 20 grams of BCAA per day for 3 months. Control group only had a personalized diet and RE program	There were statistically significant improvements in decubitus intolerance, dyspnea (p=0.03), fatigue (p<0.0001), and a tendency to decreased dyspnea (p=0.07) in 2 groups, but there was no statistical difference between the groups. Muscle strength was increased by 34.5% in the subjects (p=0.08), with no difference between groups. Hip circumference in the experimental group was decreased markedly than the control group (p=0.02). But the differences between other anthropometric variables, body composition, and physical endurance were not statistically different between the two groups.

*BCAA = branched-chain amino acid

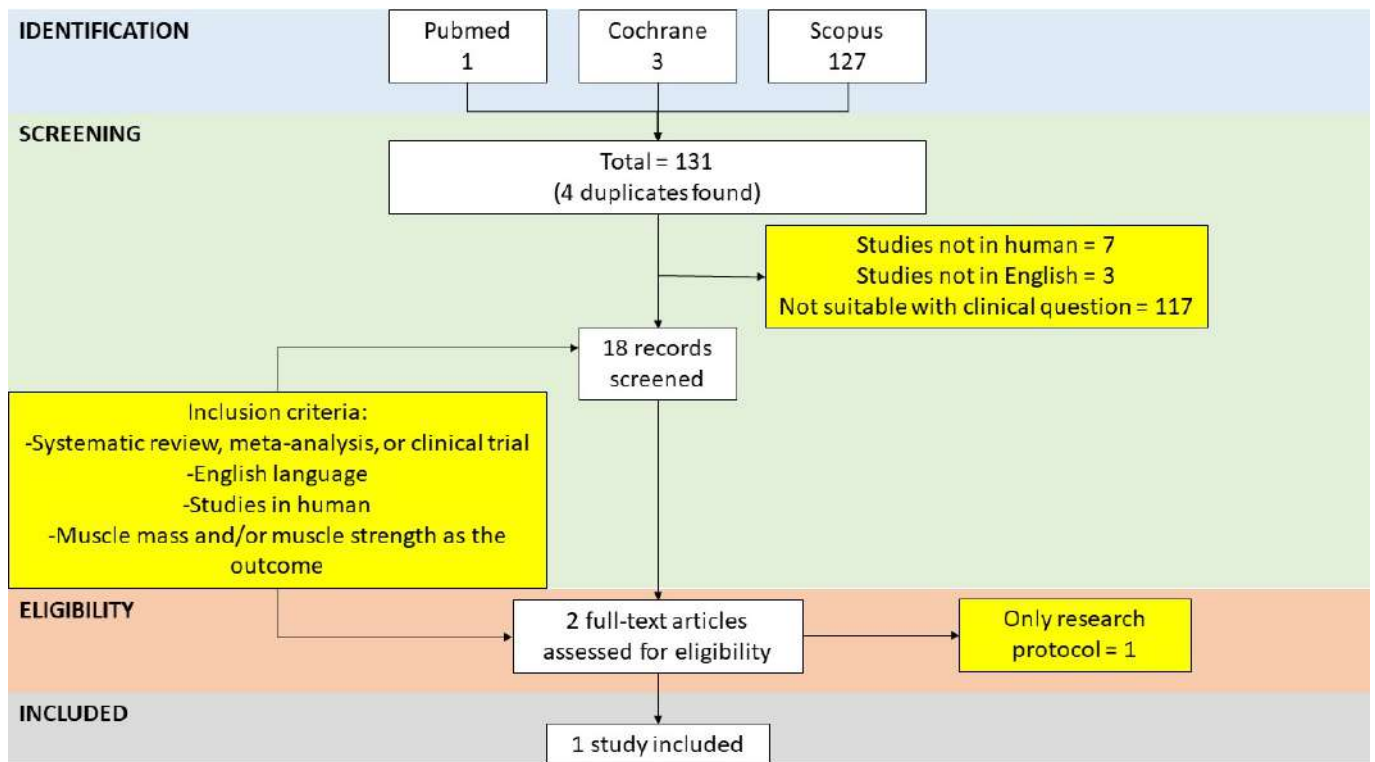


Figure 1. Flowchart of search strategy

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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The effect of omega 3 fatty acid supplementation on HbA1c serum in geriatric patients with type 2 diabetes mellitus: an evidence-based case report

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Abstract

Background: The prevalence of diabetes mellitus as a non-communicable diseases increase annually. The global prevalence doubled from 4.7% to 8.5% in 1980 until 2016. Insulin resistance is the primary cause of type 2 diabetes mellitus. Polyunsaturated fatty acid has a contribution to membrane fluidity as well as the cell signaling system. The result of studies about the correlation between Omega-3 supplementation and blood glucose control in patients with type 2 diabetes is still inconsistent. Meanwhile, we considered to give a 86 year old woman with an uncontrolled type 2 diabetes omega-3 fatty acid supplementation for controlling her blood glucose. Thus, we performed an evidence-based case report to respond this problem.

Objectives: To observe the effect of omega-3 supplementation on glycated hemoglobin (HbA1c) serum of type 2 diabetes mellitus patients.

Methods: Electronic literature searching was performed with Cochrane[®], Scopus[®], and Pubmed[®]. Inclusion and exclusion criteria were applied by MeSH term and title/abstract with clinical trial as the study design. Critical appraisal was performed for eligible article.

Results: There were three articles relevant with the eligibility criteria and clinical question. One study found that omega-3 supplementation did not give a significant effect on HbA1c. The other two studies. found that there were improvement on HbA1c and lipid profile in patients that consumed omega 3.

Conclusions: Omega-3 supplementation has inconsistent results for the improvement of HbA1c. The omega-3 lowering effect of HbA1c depends on the source, dosage, and duration of supplementation.

Keywords type 2 diabetes mellitus, omega-3 fatty acid, geriatric, HbA1c

Clinical scenario

An 86-year-old woman was admitted to the hospital with a chief complaint of decreased of

appetite for three days before admission. She also complained cough and nausea with the absence of fever or vomiting. Her blood glucose level on the first day of care was 161 mg/dl. She was diagnosed with diabetes mellitus since two years ago and hypertension since seven years ago. She also has decreased kidney function since two years ago. She stopped taking oral hypoglycemic drugs since one year ago because of her daily blood glucose was within normal limits. Her blood glucose kept on increasing during the hospitalization that caused her to take oral hypoglycemic drugs to overcome her

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high blood glucose level. Her blood glucose on the second and third admission day reached 241 mg/dL despite her regular oral hypoglycemic drugs intake.

The physical examination revealed that this patient has an irregular heart beat. She was given enteral nutrition by nasogastric tube since the first day of admission. Her nutritional status was mild malnutrition with the body mass index of 18 kg/m². Clinical nutrition specialist planned to give her omega-3 supplementation to decrease HbA1c but whether omega-3 supplementation will give a significant effect on this patient was still on consideration.

Introduction

Diabetes is a chronic disease caused by the inability of the pancreas to produce insulin or insulin-resistant, manifested as high blood glucose level or hyperglycemia.^{2,3} The prevalence of diabetes mellitus as one of non-communicable disease tend to increase annually.³ The global prevalence of diabetes doubled since 1980 from 4,7% to 8,5% in 2016.² Diabetes prevalence in Indonesia is increased 1.7% from 2013 until 2018.⁴

Diabetes mellitus can be classified as type one and type two diabetes mellitus. Type two diabetes is more prevalent than type one diabetes mellitus.² Type two diabetes mellitus is caused by insulin-resistance that occur in the muscle and liver.³ High-fat diet, especially saturated fat, will reduced insulin sensitivity that lead to insulin resistance.⁵ On the other side, high polyunsaturated fat intake will improve insulin secretion and sensitivity. Physiologically, polyunsaturated fatty acid maintains the cell membrane fluidity to facilitate cell signaling pathway that augment insulin sensitivity.⁶

There are many literatures that report the correlation between omega-3 fatty acid supplementation and insulin resistance, but only a few that use HbA1c as a parameter of the study. It is still under debate, whether omega-3 supplementation increase insulin sensitivity in patients with type two diabetes mellitus. Various dosage regimen is one of the reason for this inconsistent result other than difference in length of supplementation.⁷ Whether omega-3 supplementation has a positive effect on blood glucose management, observed with the HbA1c

level in geriatric population as our patient suffered from, is an interesting field to study.

Clinical questions

The inclusion criteria for the subjects in this study are geriatric patients diagnosed with diabetes mellitus type 2. Glycate hemoglobin is the outcome of this study that compose the clinical question. The clinical question of this study: Can omega-3 supplementation reduce HbA1c levels in patients with diabetes mellitus type 2?

P : geriatric patients that is diagnosed to have diabetes mellitus type 2

I : omega-3 supplementation

C : placebo

O : HbA1c

Methods

Search Strategy

Advanced searching was used for this literature searching from three main databases: Pubmed[®], Cochrane[®], and Scopus[®] on December 19th, 2019. MesH Term and abstract/title was used as the searching criteria with the keywords of “omega 3 fatty acid”, “alpha-linolenic acid”, “HbA1c”, “A1c”, dan “diabetes mellitus”. The result of this literature searching was then screened with EndNote[™] application to eliminate duplication. Full text literatures which met the eligibility criteria and PICO were critically appraised.

Strategy of article selection

Eligibility Criteria

The articles were selected based on the inclusion and exclusion criteria, which is in line with the clinical question. The inclusion criteria were: 1) participants diagnosed as type 2 diabetes mellitus; 2) Geriatric patients (aged ≥ 60 years old); 3) Same characteristics subjects; 4) HbA1c measurement was done before and after intervention; 5) Randomized clinical trial 6) HbA1c as the study outcome and 7) publication within the last 5 years. The exclusion criteria were: 1) no available full text and 2) language other than English.

Critical appraisal

Critical appraisal was based on a therapy study, with HbA1c as the outcome measured. All of the relevant articles were assessed for validity, importance, applicability (VIA) with standardized critical appraisal for therapy study.

Results

A total of 793 articles were identified from Pubmed[®], 13 from Cochrane[®], and 43 from Scopus[®] based on keywords, MesH Terms, abstract/title (Table 1).

That literature was screened for titles that contain keywords listed. The result of the title screened was 15 relevant literatures that is eligible for the next screening step. All these relevant literature was screened for inclusion and exclusion criteria, 3 literatures fulfilled the eligibility criteria. Among 12 literatures that excluded, 10 literatures used outcome measure other than HbA1c and 2 literatures included Participants below 60 years of age. (Figure 1).

All of these three literatures used randomized double-blind controlled trials as their study design with a level of evidence of 2. The participants were diagnosed with diabetes and received omega-3 fatty acid. The HbA1c examination was performed to all the participants as one of their clinical outcomes. Study characteristics are shown in table 2. Zeng et al. almost fulfill all the appraisal criteria, followed by Wang et al. that did not fulfill two criteria, and Soleimani et al that did not fulfill three appraisal criteria.

Discussion

Soleimani et al.¹⁰ conducted a randomized double-blind placebo-controlled clinical trial to 60 participants with diabetic foot ulcer grade 3 by Wagner-Meggitt's criteria. Participants included in this study ranged from 40 years old until 85 years old. Participants were divided into two groups with one group was given omega-3 fatty acid from flaxseed oil 1 g/day for 12 weeks and the other one was given placebo both for 12 weeks. Participants were monitored during the 3rd week, 6th week, 9th week, and 12th week. The primary outcome of this

study was wound healing and glucose homeostasis, the secondary outcome was lipid profile, inflammatory biomarker, and oxidative stress. The result of this study was the improvement of wound healing and reduction of insulin serum, HOMA-IR, and HbA1c, also an increase in QUICKI. The secondary outcome was reduction in hs-CRP but there is no significant difference in lipid profile between intervention and placebo group. Omega-3 from flaxseed oil 2 grams/day can reduce of HbA1c from baseline 7.5 +/- 1.5% compare to the end-of-trial 6.6 +/- 1.4% that change about -0.9 +/- 1.5%, (p=0.01).¹⁰

Wang F et al.¹ conducted a randomized, double-blind, placebo-controlled trial, to 100 participants age 65,4 +/- 5,3 years old diagnosed as type 2 diabetes mellitus and central obesity. Participants were divided into an intervention group that was given omega-3 from fish oil 4 grams/day that contains 1.34 g EPA and 1.07 g DHA compared with placebo for 6 months. Participants were monitored for their conformity monthly by returning the empty bottle that was filled by the omega-3 capsule before. The result of this study is that omega-3 fatty acid from fish oil was not significantly different compared with placebo in terms of HbA1 reduction with baseline 7.72 +/- 1.23%, 3rd month 7.85 +/- 1.55%, and 6th month 7.34 +/- 1.51% (p=0.901). There is a significant reduction in triglyceride (p=0,007) and increase in HDL (p=0,006) when compared to placebo in this study.¹

A double-blind randomized controlled trial was conducted by Zheng J.S et al.¹¹ to 185 participants that were diagnosed with type 2 diabetes mellitus aged 35 until 80 years old. The participants were divided into three intervention groups that were fish oil group, flaxseed oil group, and corn oil group. All the participants were given capsules containing EPA and DHA 4 times a day for 180 days. Participants in the fish oil group were given 2 grams of omega-3 fatty acid containing EPA and DHA, meanwhile, participants in the flaxseed oil group received 2.5 grams of alpha-linolenic acid. Participants were monitored on the 90th day and 180th day by returning their omega-3 bottle. Trained nurses make a phone call once a month to make sure every participant consumed the omega-3 capsule that was given. The result of this study is that omega-3 fatty acid from fish oil reduced HbA1c better than flaxseed and corn

oil group ($p=0,037$). Triglyceride, low-density lipoprotein, and total cholesterol decreased more significantly in the fish oil group than the other groups ($p<0.05$). Flaxseed oil group and the corn oil group did not differ significantly.¹¹

The HbA1c lowering effect of omega-3 fatty acid from study of Soleimani et al.¹⁰ can be explained due to the effect of omega-3 fatty acid on modulating peroxisome proliferator-activated receptors and increasing gene expression of G protein-coupled receptor 120 that related to insulin metabolism.¹⁰ Wang F et al.¹ found that there is no significant effect of omega-3 supplementation on HbA1c.¹ Difference between study results might be related to differences in sample size, source of omega-3 fatty acids, dosage of daily omega-3 supplementation, duration of supplementation, or participant disease characteristic.

Zheng J.S et al.¹¹ found that there are different effectivity of omega-3 fatty acids from different sources of omega-3 fatty acids such as fish oil, flaxseed oil, and corn oil. The result of this study explained that fish oil reduced HbA1c better than flaxseed oil and corn oil. Fish oil given in this study was 2 grams for 6 months.¹¹ Fish oil contain eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) as compared to alpha-linolenic acid of flaxseed oil that need to be converted to EPA and DHA.¹²

In our case of geriatric 86 years old woman suffered from type 2 diabetes mellitus with increasing blood glucose during hospitalization. Her age and diagnosis are similar to these studies. We recommended on giving omega-3 fatty acids from 2 grams of fish oil daily besides continuous medical nutritional therapy to improve the patient's HbA1c.

Conclusions

The effect of omega-3 fatty acid to decrease HbA1c still has no consistent result. This can be explained by the difference in the dosage and duration of supplementation. Although there were still inconsistent results, 2 out of 3 literatures in this study conclude that omega-3 fatty acids give a significant effect on the reduction of HbA1c. Omega-3 fatty acids from fish oil give better effect when compared to omega-3 from flaxseed oil and corn oil for HbA1c and lipid profile improvement.

The effect of omega-3 fatty acid for HbA1c reduction depends on the source, dosage, and duration of supplementation. The limitation of this study are no precise dosage and explanation whether age will affect the result of the study, there is no study that explain whether different age population will give different response to omega-3 supplementation. Further research is needed to confirm the effect of omega-3 supplementation on HbA1c.

Table 1. Resources & search strategy

Database	Search Strategy	Hits	Chosen
Pubmed	(((((omega 3 fatty acids[MeSH Terms]) OR omega 3 fatty acids[Title/Abstract]) OR alpha linolenic acid[MeSH Terms]) OR alpha linolenic acid[Title/Abstract]) AND hb a1c[MeSH Terms]) OR hb a1c[Title/Abstract]) OR A1c[MeSH Terms]) OR A1c[Title/Abstract]) AND diabetes mellitus[MeSH Subheading]) OR diabetes mellitus[Title/Abstract]	793	4
Cochrane Library	ID Search Hits #1("omega 3 fatty acids"):ti,ab,kw 2010 #2 MeSH descriptor: [Fatty Acids, Omega-3] explode all trees 2923 #3("alpha-linolenic acid"):ti,ab,kw 0 #4MeSH descriptor: [alpha-Linolenic Acid] explode all trees 226 #5("Hb A1C values"):ti,ab,kw 374 #6 MeSH descriptor: [Glycated Hemoglobin A] explode all trees 5458 #7("glycated haemoglobin levels"):ti,ab,kw 191 #8 MeSH descriptor: [Glycated Hemoglobin A] explode all trees 5458 #9("diabetes mellitus"):ti,ab,kw 59410 #10 MeSH descriptor: [Diabetes Mellitus] explode all trees 28035 #11#1 OR #2 OR #3 OR #4 4317 #12#5 OR #6 OR #7 OR #8 5851 #13#9 OR #10 62938 #14#11 AND #12 AND #13 with Cochrane Library publication date Between Jan 2017 and Dec 2019, in Trials 13	13	6
Scopus	(TITLE-ABS-KEY (omega 3 fatty AND acids) OR TITLE-ABS-KEY (alpha AND linolenic AND acid) AND TITLE-ABS-KEY (hb AND a1c) OR TITLE-ABS-KEY (a1c) AND TITLE-ABS-KEY (diabetes AND mellitus)) AND DOCTYPE (ar) AND PUBYEAR > 2016 AND (LIMIT-TO (DOCTYPE , "ar")) AND (LIMIT-TO (SUBJAREA , "MEDI")) AND (LIMIT-TO (EXACTKEYWORD , "Human")) AND (LIMIT-TO (LANGUAGE , "English")) AND (LIMIT-TO (SRCTYPE , "j"))	43	5

Table 2. Study characteristics

Articles	Study design	Intervention	Population	Outcome
Soleimani Z et al. (2017)	A randomized, double-blind, placebo-controlled trial	Flaxseed oil 1 grams/day for 12 week compared with placebo	60 patients, 45-80 years old diagnosed with grade 3 diabetic foot ulcer grade 3 (Wagner-Meggitt's criteria) with cellulitis and normal distal pulse.	Wound healing, glucose homeostasis parameter (serum insulin concentration, homeostasis model of assessment-insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), Hemoglobin A1c (HbA1c), and fasting plasma glucose), and lipid profiles.
Wang F et al., (2017)	A randomized, double-blind, placebo-controlled trial	Fish oil 4 grams/day compared with placebo for 6 month	100 Participants, >60 years old diagnosed with type 2 diabetes by World Health Organization (WHO) criteria and abdominal obesity by Working Group on Obesity of China (WGOC) criteria.	Waistline, hipline, height, systolic and diastolic blood pressure, serum fatty acid composition and body composition, body composition, serum glucose, HbA1c, insulin, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C).
Zeng J.S et al., (2016)	Double-blind randomized controlled trial	Fish oil 2 grams/day, flaxseed oil 2.5 grams/day.	185 Participants, 35-80 years old for men and between post-menopausal age until 80 years old for woman. Fasting blood glucose >7.0 mmol/L or use of diabetic medications.	Fasting blood glucose, HDL-C, LDL-C, total cholesterol, TG, glucose, uric acid, blood urea nitrogen (BUN), creatinine, liver function markers, blood total protein, globulin (GLB), albumin (ALB), total bilirubin (TBIL), direct bilirubin (DBIL), indirect bilirubin (IDBIL), HOMA-IR, HbA1c

ALB: albumin, BUN: blood urea nitrogen, DBIL: direct bilirubin, IDBIL: indirect bilirubin, GLB: globulin, HbA1c: hemoglobin A1c, HDL-C: high-density lipoprotein cholesterol, LDL-C: low-density lipoprotein, HOMA-IR: homeostasis model of assessment-insulin resistance, TBIL: total bilirubin, TC: total Cholesterol TG: triglyceride, QUICKI: quantitative insulin sensitivity check index,

Table 3. Validity criteria

Articles	Validity							Result	Level of Evidence ⁹
	Randomization	Same characteristic	Same treatment	Intention to treat	Blinded / objective	Applicability	Clinically important		
Soleimani et al ¹⁰	+	+	+	+	+	-	-	A	2
Wang Fet al ¹	+	+	+	-	+	+	-	B	2
Zheng, J.S et al ¹¹	+	+	+	?	+	+	+	C	2

A: Significant reduction of HbA1c in the intervention group (p=0.01)¹⁰

B: Reduction of HbA1c did not differ significantly between the intervention group and placebo group (p>0.05).¹

C: HbA1c significantly decreased statistically in the fish oil group compared with the flaxseed oil and corn oil group (p<0,001).¹¹

Table 4. Relevance criteria

	Similarity Population	Similarity Determinant	Similarity Outcome
Soleimani et al ¹⁰	+	+	+
Wang F et al ¹	-	+	+
Zheng J.S et al ¹¹	+	+	+

Table 5. Result of studies

Articles	Outcome	Key Results
Soleimani Z, Hashemdokht F, Bahmani F, Taghizadeh M, Memarzadeh MR, Asemi Z. (2017) <i>Journal of Diabetes and Its Complications</i> ¹⁰	<ul style="list-style-type: none"> • Wound healing • Serum insulin, homeostasis model of assessment-estimated insulin resistance (HOMA-IR), quantitative insulin sensitivity check index (QUICKI), HbA1c. • Lipid profile: triglyceride, VLDL, LDL, HDL • Inflammation marker: high sensitivity C-reactive protein (hs-CRP), nitric oxide, total antioxidant capacity (TAC), glutathione total (GSH), dan malondialdehyde (MDA) 	<ul style="list-style-type: none"> • The reduction in wound size is more significant in 12 weeks omega-3 supplemented participants • The reduction of insulin concentration, HOMA-IR, and HbA1c is statistically significant. • The result for HbA1c: baseline 7.5 +/- 1.5%, end-of-trial 6.6 +/- 1.4%, change - 0.9 +/- 1.5%, p=0.01 • The increase in QUICKI is also statistically significant
Wang F, Wang Y, Zhu Y, et al. (2016), <i>European Journal of Nutrition</i> ¹⁰	<ul style="list-style-type: none"> • Fasting blood glucose, HbA1c, insulin, HOMA- • Lipid profile such as triglyceride, LDL, HDL 	<ul style="list-style-type: none"> • Omega-3 supplementation for 12 weeks reduced triglyceride level significantly (P=0,007) • Omega-3 supplementation were not statistically significant in affecting HOMA-IR, fasting blood glucose, and HbA1c • The result for HbA1c baseline was 7.72 +/- 1.23%, 3 months 7.85 +/- 1.55%, 6 months 7.34 +/- 1.51%, p=0.901
Zheng JS, Lin M, Fang L,(2016), <i>Molecular Nutrition & Food Research Journal</i> ¹¹	<ul style="list-style-type: none"> • Fasting blood glucose, fasting plasma insulin, HOMA-IR, HbA1c. • HDL, LDL, triglyceride, and total cholesterol • BUN, creatinine, uric acid, ALT, AST, total bilirubin, direct bilirubin, indirect bilirubin, total protein, globulin, and albumin. 	<ul style="list-style-type: none"> • Omega-3 fatty acid from fish oil gives a better statistically significant effects on glycemic control and lipid profile compared with flaxseed oil and corn oil. • HbA1c reduction is statistically significant in fish oil group compared with flaxseed and corn oil. (on day 0: 63.9 +/- 22.9 mmol/mol, on day 90th: 52.7 +/- 13.8 mmol/mol, on day 180th: 54.4 +/- 13.4 mmol/mol, p=0.035)

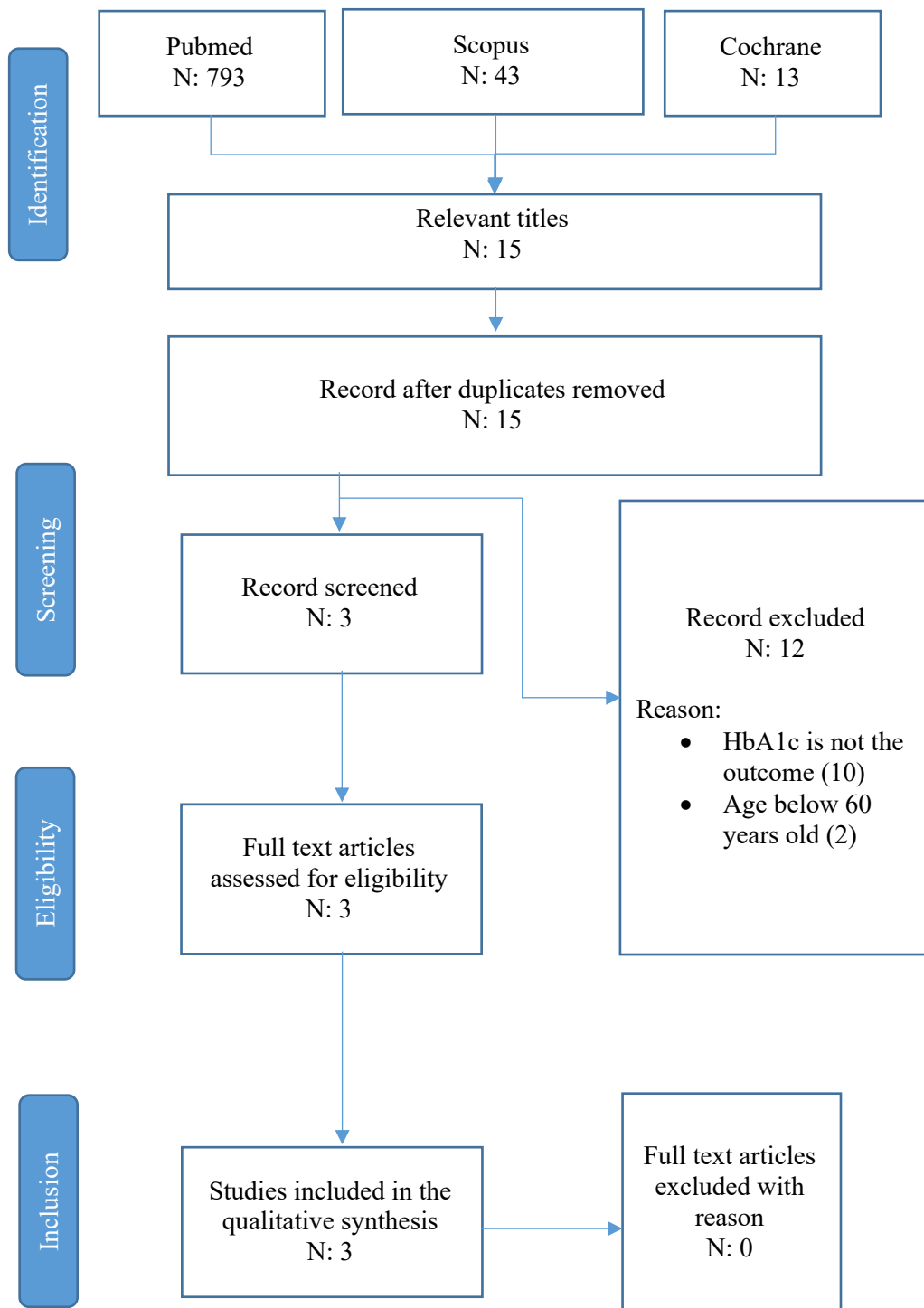


Figure 1. Prima's flow chart of literature searching

Conflict of interest

The authors declare no conflict of interest regarding this study.

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ORIGINAL PAPER

Correlation between serum vitamin C level and COPD assessment test score in chronic obstructive pulmonary disease patients

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Abstract

Background: COPD is a disease due to oxidative stress causing low pulmonary function, resulting in low quality of life. A standard test to measure the quality of life in COPD is COPD Assessment Test (CAT). Vitamin C as antioxidant is widely available in the pulmonary epithelial fluid. This study aimed to investigate the correlation between serum vitamin C level and CAT score in COPD.

Methods: This cross-sectional study was conducted at Persahabatan Hospital, East Jakarta, involving 47 subjects using consecutive sampling method. Interview was used to assess subjects' characteristics and vitamin C intake using semi-quantitative FFQ. Clinical classification, lung function, comorbidity, and CAT scores were gathered from medical records or interview. BMI was used to determine nutritional status, while vitamin C serum level was assessed using spectrophotometry. **Results and conclusions:** All subjects were male, mean age was 66.6 years, mostly ex-heavy smokers, with decreased lung function, and 25% were undernourished. Vitamin C intake was sufficient, but low in serum vitamin C level and CAT score. There was no correlation between serum vitamin C level and CAT score.

Keywords COPD, COPD Assessment Test score, vitamin C, Indonesia

Introduction

Chronic obstructive pulmonary disease (COPD) is a chronic disease that causes high morbidity and mortality.¹ This disease is the fourth leading cause of death worldwide and is projected to be the third leading cause of death in 2020.^{2,3} According to World Health Organization (WHO), in the top 10

causes of death in the world in 2012, COPD was in the third rank with 6% deaths worldwide. In Indonesia, the prevalence is 5.6%, 2.7% in Jakarta, and the highest in East Jakarta as much as 3.8%.^{4,5} Persahabatan Hospital data indicate that COPD patient visits increased from 616 in 2000 to 1735 in the year 2007.⁶

Chronic obstructive pulmonary disease has an impact on the health status-related quality of life of sufferers. COPD ranks 12th as a cause of decreased quality of life (DALY, Disability Adjusted Life Years) in 1990 and is expected to rank 5th in 2020.^{7,8} Patients with COPD have a cough, shortness of breath and tightness in the chest that would make the patients difficult to perform daily activities, giving an impact on the quality of life.⁹ Chronic Obstructive Pulmonary disease Assessment test

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(CAT) is a standard test to measure the impact of disease on quality of life of COPD patients.¹⁰

Pathogenesis of COPD is related to oxidative stress. Oxidative stress occurs when the formation of oxidants is not successfully offset by various antioxidants in the body. Oxidants come from outside the body such as cigarette smoke or air pollution and that comes from the inflammatory process. Oxidative stress will cause lipid peroxidation, which causes damage to the lungs due to decreased lung function.^{11,12} Systemic impact of these mechanisms would affect the quality of life of COPD patients.^{13,14} Various antioxidants are needed to counterbalance the oxidants. Vitamin C is a water-soluble antioxidant that is abundant in the lung epithelial lining fluid. Its ability as an electron donor, enabling vitamin C to scavenge and quench free radicals.^{11,15}

No previous studies had investigated the correlation between serum level of vitamin C and CAT score in COPD. However, some studies show correlation between serum vitamin C level and lung function and CAT scores with lung function.^{8,10,11} The aim of this study was to investigate the correlation between serum vitamin C level and quality of life based on the scores of CAT of patients with COPD.

Materials and methods

This study was a cross-sectional study in 47 outpatients with stable COPD at the Department of Asthma –COPD Persahabatan Hospital East Jakarta, from April to August 2016. Subjects were obtained using consecutive sampling method.

Study subjects were those who met some inclusion criteria of stable COPD patients aged >18 years, was diagnosed with COPD during the previous month, no diabetics, asthmatics, tuberculosis, lung cancer based on medical records, nor vitamin C and multivitamin and minerals supplements. Of 138 subjects who visited, 59 people were excluded, 29 people refused to participate, two people were unable to complete the study procedure, and one blood sample was damaged.

Data on subject's characteristics, smoking history and vitamin C intake using a semi quantitative Food Frequency Questionnaire (FFQ) obtained from interviews. Data on clinical

classification of COPD by the GOLD 2015, lung function by spirometry, CAT scores and history of cardiovascular diseases obtained from interviews and medical records. Anthropometry assessment was done using stadiometer for height and SECA scale 870 for weight measurement. Lung function test was performed using spirometry Microspiro HI 28, Chest Corporation Japan, measuring forced expiratory volume in 1 second (FEV₁%), forced vital capacity (FVC%) and the ratio FEV₁ / FVC%. Vitamin C serum level was assessed spectrophotometrically using Multiskan Ascent. Two mL of non fasting venous serum was stored at -80°C until analysis.

Statistical analysis was performed using the Statistical Program for Social Science (SPSS) for Windows version 20. Data intake of vitamin C and CAT score with a median value (minimum-maximum) and data serum level of vitamin C with a mean \pm standard deviations. Statistical analysis to see the difference in the proportion of two groups using Chi-square / Fisher's exact test and the mean difference between two groups with the Mann-Whitney test. Spearman's rank test was used to see the correlation between serum vitamin C level and CAT score. Significance level was $p < 0.05$. This study has been approved by the Ethics Commission of Research and Health, Persahabatan Hospital, East Jakarta, Indonesia.

Results

Subjects were all males in this study. Figure 1 shows study subject's characteristic: 66.6 ± 8.0 years of age, mostly elderly. (Figure 1A), subjects' income was equally distributed in less or equal to Jakarta's wage index (Figure 1B). Majority of subjects was former smokers (Figure 1C), while half of them was heavy smokers (Figure 1D). BMI of subjects in this study was 21.3 ± 3.8 kg/m², mostly had normal weight, with about 25% were underweight (Figure 1E).

Study subjects' COPD clinical classification according to GOLD 2015 shown in Figure 2. Almost half of study subjects was categorized as severe COPD (Figure 2 A). There was a decrease in lung function, as FEV₁%, FVC% and FEV₁/FVC% ratio was $49.6 \pm 20.7\%$, 66.8 ± 18.6 , and 50.7 ± 10.4 , respectively. Based on spirometry test, about half of

study subjects suffered from severe and very severe degree of lung function (Figure 2B). More study subjects were in the mild category of CAT score, with a median (minimum-maximum) value of 9 (1-29). About half of study subjects suffered from cardiovascular comorbidity of ischemic heart disease, hypertension or congestive heart failure (Figure 2D).

Vitamin C intake of study subjects was 124.2 (18-480.1) mg/L, while serum vitamin C level was 21.1 ± 4.1 $\mu\text{mol/L}$. There was no significant correlation ($p=0.96$) between vitamin C intake and serum level in this study. Almost double proportion of study subjects with sufficient vitamin C intake according to AKG Indonesia 2013 (Figure 3A). However, majority of subjects was in low vitamin C status based on serum vitamin C level (Figure 3B).

A significant difference of vitamin C intake based on CAT score category: study subjects with mild CAT score category had higher vitamin C intake ($p=0.008$) as compared to those with severe CAT score. However, no significant difference of serum vitamin C level between the two CAT score categories, as shown in Table 1.

Proportion of study subjects based on vitamin C intake and serum level based by CAT score category shown in Figure 4. There were more study subjects with low vitamin C intake ($p=0.021$) among severe CAT score category as compared to those with mild CAT category (Figure 4A). However, no difference of serum vitamin C level between mild and severe CAT score category (Figure 4B).

Differences of vitamin C intake and serum level in groups with and without comorbidity shown in Table 2. Serum vitamin C level was lower ($p=0.033$) among those with comorbidity as compared to those without comorbidity.

Proportion of study subjects' vitamin C intake and serum level based on comorbidity shown in figure 5. No difference of study subjects' proportion with low vitamin C intake with or without comorbidity (Figure 5A), however, more study subjects ($p=0.028$) with low vitamin C level among those with comorbidity as compared to those without comorbidity (Figure 5B).

There was no statistically significant correlation between serum vitamin C level and CAT score ($p=0.949$ and $r=0.01$).

Discussion

The mean age of subjects in this study was 66.6 years, mostly elderly.¹⁷ This result was consistent with a study by Draman et al⁸ in Malaysia with similar mean age of 66.4 years, but in contrast with a study by Cristovao et al¹ in Portuguese with a higher mean age of 71.3 years. Age is one risk factor on the development of COPD. The older a person, there will be a decrease in lung function, while more exposure to harmful substances.^{2,18} Fletcher and Peto's study on 792 male workers aged 35-59 years observed for 8 years found that VEP₁ declined throughout life, increasing with age.¹⁹ Kojima et al²⁰ showed data that COPD incidence among non-smokers was lower at 25-49 years of age with a gradual increase at the age of 50-74 years, indicating a decline of lung function by age.

All subjects in this study were male. The result of this study was similar to Ghobadi et al¹⁰ that all subjects were male. Data of previous studies showed that patients with COPD were more among males than females, although lately the number is not much different, due to changes in smoking habits. This may be explained by the smoking prevalence of 16x higher in males (65.9%) as compared to women (4.2%).²¹

Subjects' income in this study was consistent with Ismail et al⁶, despite different socio-economic parameters. Socio-economic is one risk factor of COPD.

In this study, majority (87.2%) of study subjects was former smokers, consistent with Cristovao et al¹ who observed more former smoker patients with COPD than non-smokers, unlike Lin et al²², who found more non-smokers than former smokers. Major risk factor of COPD is smoking. Cigarette contains more free radicals and harmful substances which can increase oxidant load in the body.^{2,13} Smoke as a risk factor for COPD is dose-dependent in nature: the longer and more number of cigarettes, the higher the risks for COPD.²¹

The results of this study were consistent with Ismail et al⁶ who found that 84.6% of study subjects was moderate to heavy smokers. Kojima et al²⁰ showed that increasing incidence of COPD was higher in the group with higher Brinkman index. This supports the hypothesis that smoking is a risk factor for COPD.

The mean BMI of subjects in this study was 21.3 kg/m² considered as normal BMI, which more proportion of study subjects in this category. The results of this study was consistent with Ismail et al⁶ and Lin et al²² studies with normal BMI of 22.13 kg/m² and 22.8 kg/m², respectively. Unlikely, Cristovao et al¹ observed a higher mean BMI of 27.92 kg/m², which was considered as overweight. The difference was also seen in the study by Dhakal et al²⁷ in which most of COPD subjects was with lower BMI of <18.5 kg/m².

BMI assessment was conducted to determine the nutritional status of patients with COPD in connection with the hypothesis that the IMT significantly affects the severity of disease.²⁴ Landbo et al²⁴ states that underweight BMI is a risk factor that stands alone on COPD mortality and had stronger relationship with COPD severity.

The CAT score in this study was 9, categorized as mild, in contrast with two other studies with higher CAT score of 19.6 (Ghobadi et al¹⁰). The result was also different from Draman et al⁸ with CAT score of moderate category (11-20). This indicates that COPD probably provides minor health impact on more than half of study subjects.

This study recorded 23 subjects (48.9%) suffered with comorbidity such as hypertension (14.9%), ischemic heart disease (17%), and congestive heart failure (17%). This study was in line with Negro et al²⁵ who showed that cardiovascular disease was important comorbidity among COPD patients. Cardiovascular diseases exist frequently amongst COPD, which would increase morbidity and mortality.²¹ Smoking is a risk factor for both cardiovascular disease and COPD due to increase oxidative stress and systemic inflammation.¹³ Therefore, the occurrence of comorbidity should be routinely monitored and treated in COPD patient.²

Vitamin C intake in this study was sufficient with median of 124.2 mg/day, with a wide range of 18-480.1 mg/day. This result was different from Lin et al²² and Ahmadi et al²⁶ who showed lower vitamin C intake by COPD patients as compared to healthy individuals. This study found that 66% subjects was with sufficient vitamin C intake, in contrast to Pirabassi et al²⁷ who showed low intake of vitamin C among 94% subjects with COPD in Malaysia.

Low vitamin C intake may also occur due to low consumption of fruit and vegetables,²⁷ as sources of vitamin C. Fruit is a good source of vitamin C because it is consumed directly without undergoing cooking process, which may damage vitamin C content.²⁸

No correlation between vitamin C intake and serum level was observed in this study ($p = 0.96$). Many factors affect the amount of vitamin C in the diet such as processing, long storage as well as high temperature, which will reduce vitamin C content in the diet.^{28,29} Boiling vegetables reduces 50.9% of vitamin C content.²⁹

Vitamin C is absorbed as much as 80-90% in relation to is 30-180 mg of intake, but decreased absorption occurs as vitamin C consumption increases.³⁰ Therefore, the recommendation of vitamin C daily consumption is to consume several times each day with small portions.³¹ Mean intake of vitamin C in this study was 124.2 mg/day, within the range of intake for 80-90% absorption. Therefore, hindering vitamin C absorption was unlikely to occur among our study subjects. The results of this study were different from a study by Dehghan et al³² and Young et al³³ who showed a correlation between vitamin C intake and serum level in healthy subjects. The correlation between the intake and levels of several nutrients, including vitamin C is influenced by age, sex, smoking, alcohol consumption, and comorbid.^{34,35}

Sufficient intake of vitamin C was more observed among subjects with mild CAT score than those with severe CAT score. There was a significant negative correlation between vitamin C intake and CAT score in this study ($p=0.002$; $r=-0.43$). This result was consistent with Grievink et al³⁶ in healthy subjects as vitamin C was significantly associated with symptoms of cough (odds ratio 0.66, 95% CI: 0.50-0.87), and Menaas et al³⁷ also showed an association between vitamin C intake and cough symptoms among healthy smokers. The ability of vitamin C to protect respiratory symptoms such as cough, may explain these findings.

Sufficient intake of vitamin C was observed among subjects without comorbidity as compared to those with comorbidity. Congestive heart failure as observed in this study shows symptoms of reduced appetite, fatigue, and shortness of breath. These

symptoms might cause less sufficient intake of vitamin C in the group with comorbidity. Furthermore, intake of antioxidants such as vitamins C and E has an effect of protecting against cardiovascular disease through stress oxidative reduction.³⁸

The mean serum vitamin C level of 21.1 ± 4.1 mol/L in this study was considered low, observed among 72.3% of study subjects. The result was consistent with Lin et al²², Cristovao et al¹ and Chittimoju et al¹⁵ who found that serum vitamin C level was significantly lower in patients with COPD compared to healthy people. Low serum vitamin C level in this study might be due to vitamin C usage to cope with oxidative stress among COPD patients, through two mechanisms, namely reduction of free radicals, and it is needed for the regeneration of vitamin E, which in turn serves to function in oxidative stress.^{11,12}

The proportion of study subjects with low serum vitamin C level was observed a lot more in the group with comorbidity than without comorbidity. This result was consistent with Padayatti et al³⁹ stated that low level of vitamin C was associated with hypertension and impaired endothelial function, because vitamin C improves endothelial dysfunction, and protects against heart and blood vessel system. The significantly lower serum vitamin C level in the group with comorbidity indicates that comorbid is one of the factors that affect levels of vitamin C serum.

Several studies illustrated a possible relation between serum vitamin C level and CAT score. However, the correlation between serum vitamin C level and CAT score of COPD patients was not significant ($p=0.949$; $r=0.01$) in our study. This maybe due to many factors that affect the quality of life in COPD in addition to symptoms such as shortness of breath, cough, sputum production and limited physical activity. Other factors that can affect the quality of life is age, sex and nutritional status based on BMI, smoking, economic status, degree of disease severity based on pulmonary function, the occurrence of comorbidity, depression and anxiety, as well as other factors such as exacerbations, hospitalizations, number of used drugs, duration of illness and low education.²³ Different proportions of study subjects with serum vitamin C level in the CAT score category was not

statistically significant, indicating that low serum vitamin C level was not associated with increased severity of CAT score.

Pawar et al^{11,12} stated that there was a significant positive correlation between levels of vitamin C serum and lung function. Ghobadi et al¹⁰ stated that there was a correlation between the scores of CAT with FEV₁% and FVC%. These results were corroborated by Draman et al⁸ who showed that there were significant differences of CAT score on every degree of lung function. Salma et al⁴⁰ showed data on CAT score which was positively correlated with the severity of lung function based on FEV₁%. Therefore, lung function is one of the factors that influence the quality of life in COPD,^{23,24} and lung function was positively significant correlated with higher levels of serum vitamin C.^{11,12}

This study showed a significant negative correlation ($p = 0.001$, $r = -0.48$) between CAT score and FEV₁%, but no significant correlation between serum vitamin C level and FEV₁% ($p = 0.59$). FEV₁% indicates level of air obstruction in the respiratory system: the higher the FEV₁% - the lesser the air obstruction which means less burden of respiration experienced by the COPD patients. A burden during respiration influences quality of life as indicated by lower CAT score. Serum vitamin C level is not directly correlated with the level of air obstruction, as the effect of vitamin C in COPD patients as antioxidant is to reduce the destruction effect of oxidants on respiratory organ system. This may explain why unlike FEV₁%, there was no correlation between serum vitamin C level and CAT score in this study as FEV₁% has a more direct influence on CAT score as compared to vitamin C.

In conclusion, no correlation was observed between serum vitamin C level and CAT score in this study. Further study is needed to confirm this finding by assessing oxidative stress as well as anti oxidants among COPD patients of each clinical diagnosis.

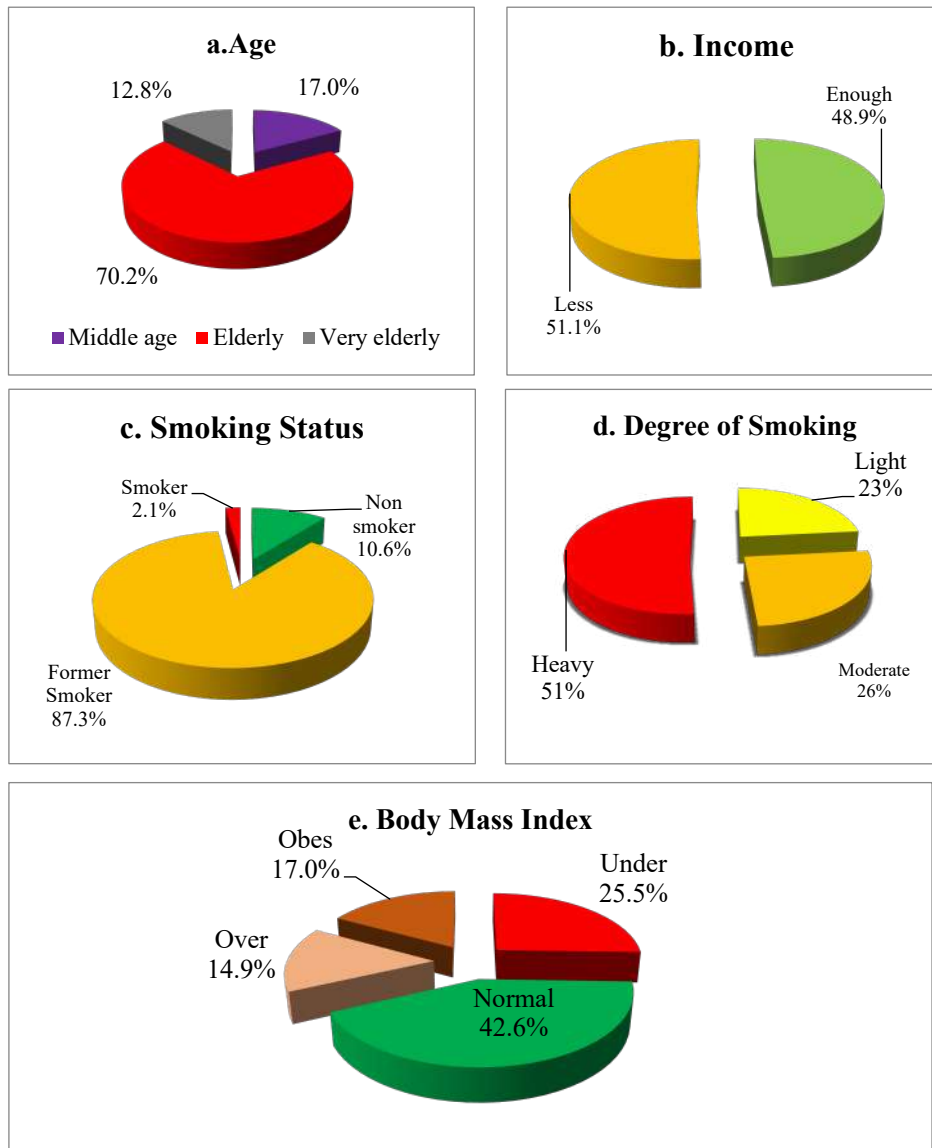


Figure 1. Distribution of Study Subjects by Age, Income, Smoking History, and Nutritional Status Based on BMI

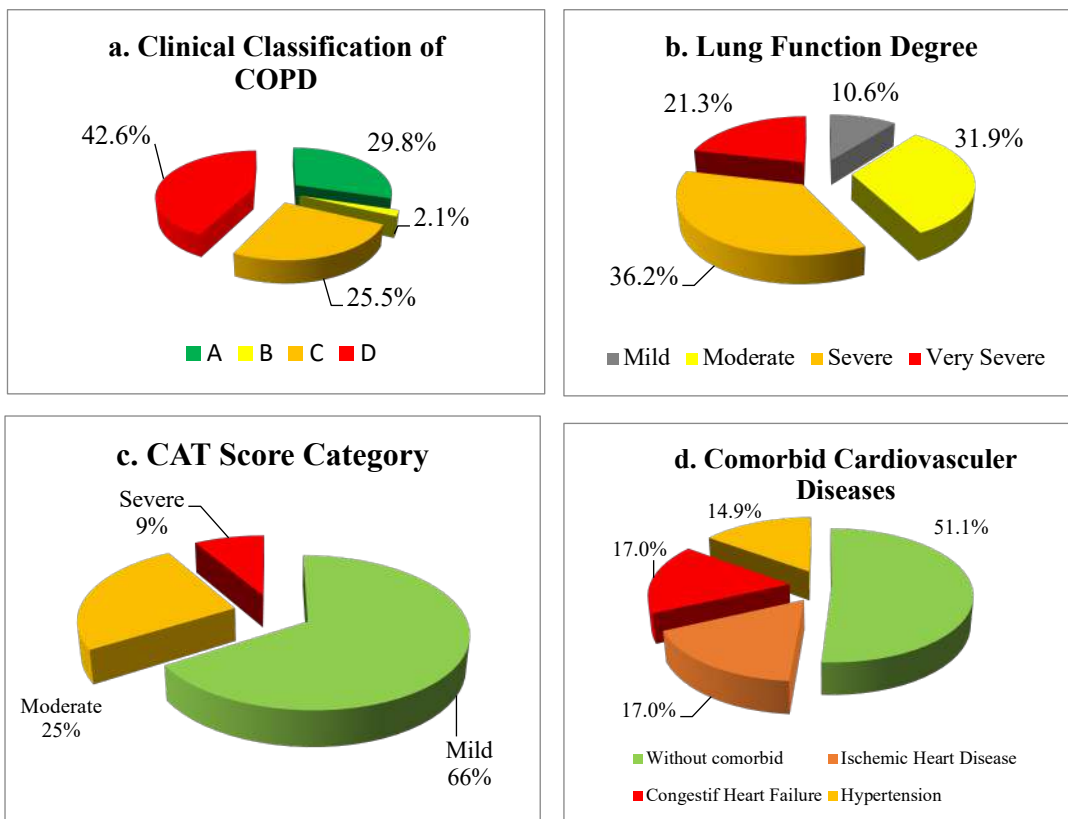


Figure 2. Distribution of Study Subject By Clinical Classification of COPD According to GOLD 2015, Lung Functon Degree Based on Spyrometri, CAT Score and Comorbid Cardiovascular Disease

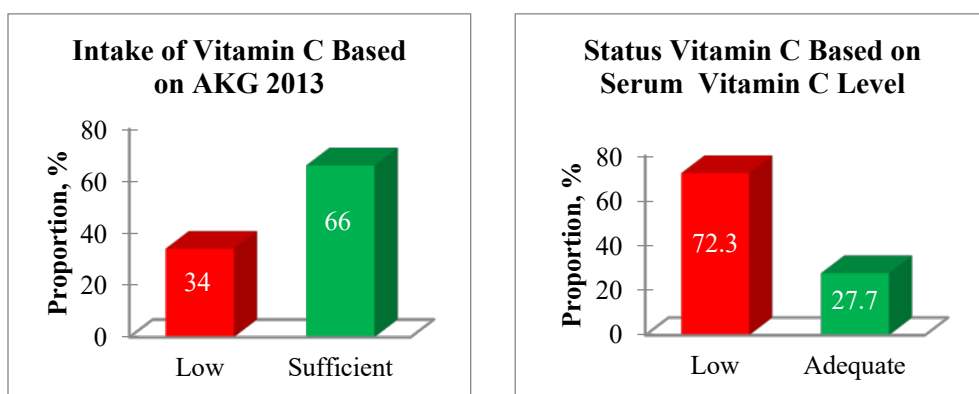


Figure 3. Proportion of Subjects Research In The Intake of Vitamin C Based on AKG Indonesia in 2013 and Status of Vitamin C Based on Serum Vitamin C Level

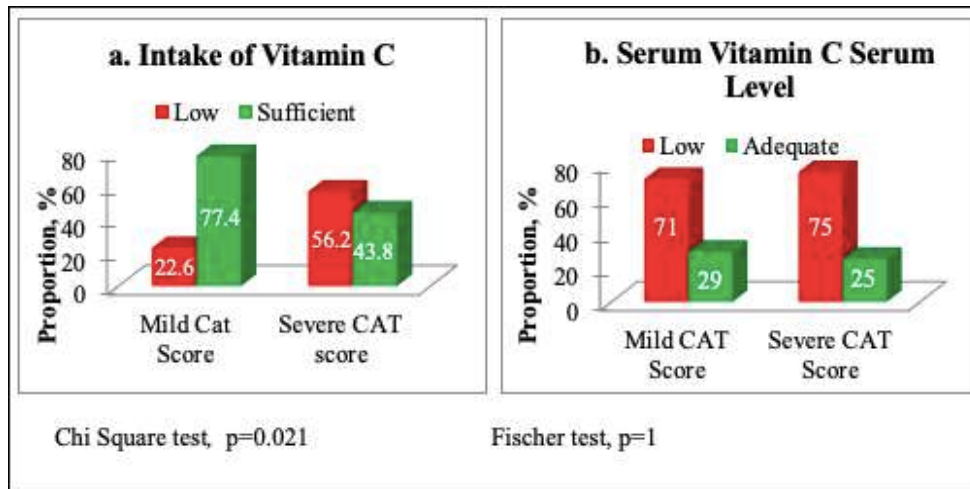


Figure 4. Proportion of Study Subjects in Case of Intake and Serum Vitamin C Level by CAT Score

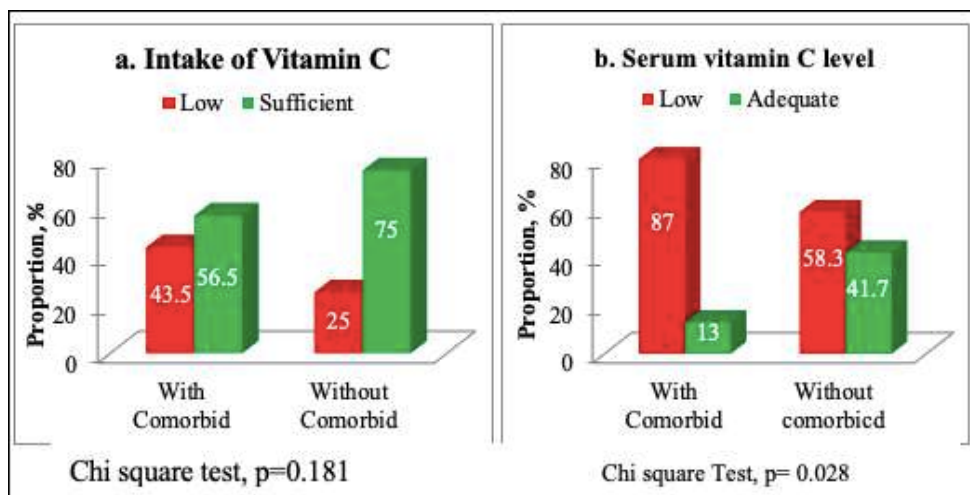


Figure 5. Proportion of Study Subjects in Case of Intake and Serum Vitamin C Level In Comorbid Cardiovascular

Table 1. Distribution of intake and serum vitamin C level by CAT score category

	CAT score category		p**
	Mild (n=31)	Severe (n=16)	
Vitamin C intake, mg/day	^158.9 (20.1-480.1)	*89.9±56.1 *21.2±3.3	0.008 0.787
Serum vitamin C level, µmol/L	^20.7 (13.9-37.6)		

n:number of subject, ^median (minimum-maximum), *mean±standard deviation, **Mann-Whitney test, p value≤0.005, statistically significant

Table 2. Distribution of vitamin C intake and serum vitamin C level based on comorbidity

	Comorbidity		p*
	With (n=23)	Without (n=24)	
Vitamin C intake, mg/day	111.6(18-374.7)	143.4(20.1-480.1)	0.416
Serum vitamin C level, µmol/L	20.2(13.9-25.1)	21.7(14.9-37.6)	0.033

n:number of subject, ^median (minimum-maximum), *Mann-Whitney test, p value≤0.005, statistically significant

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Conflict of Interest

Authors declared no conflict of interest regarding this article.

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Comparison of short-term memory between stunting and non-stunting children in urban and rural elementary school students in Kupang 2019

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Abstract

Background: Inadequate chronic nutrition can cause disruption of bone growth and brain development. Impaired bone growth can cause stunting in children, and a disruption of brain development will affect cognitive function, one of them is short-term memory. This study aimed to compare the short-term memory between stunting and non stunting in urban and rural elementary school students in Kupang.

Methods: This research used analytic observational method with cross sectional design conducted on urban and rural elementary school students in Kupang City. One hundred and sixty students who met the inclusion and exclusion criteria were selected using consecutive sampling method. Characteristics data were collected by the interview, while the stunting data was known by measuring height and assessed by WHO anthropolus application, short-term memory data was obtained from digit span test. Stunting is a nominal data scale, while the short-term memory is an ordinal data scale. This study was analyzed bivariately using chi-square test with significant p value ≤ 0.05 .

Results: Chi-square test results of short-term memory between stunting and non stunting in urban and rural elementary school students obtained p = 0.144, which means there is no significant difference in short-term memory between stunting and non stunting in urban and rural elementary school children in Kupang.

Conclusions: There is no significant difference in short-term memory between stunting and non stunting in elementary school children, both in urban and rural areas of Kupang.

Keywords stunting, short-term memory, rural, urban

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Introduction

Stunting is an impaired growth in children.¹ Stunting represent a chronic malnutrition, which means the pathological process begins in the womb.^{2,3} Stunting is defined as a short or very short body condition with z-score height-for age below -2 standard

deviations from the World Health Organization (WHO) child growth standards median.¹

The highest prevalence of stunting according to WHO, The United Nations Children's Fund (UNICEF) and The World Bank Group are in the developing and third world countries with middle to lower income.^{4,5} In year 2000, stunted children reached 32.7% of the child's population in the world. While in 2015 it reached 23.2% with more than half of the population is in Asia and more than one third in Africa.⁵

In Indonesia, the prevalence of stunted children aged < 5 years in 2018 was 30.8% consists of 11.5% very short and 19.3% short.⁶ If the nutrition of those stunted children is not improved, it can be continued until school age.⁷ The prevalence of stunting in Indonesia of school age children in 2007 was 36.8%, while in 2013 the prevalence of stunting on children aged 5-12 years was 30.7%.^{8,9} The East Nusa Tenggara province is one of the 15 provinces in Indonesia which has a short and very short prevalence above the national prevalence.⁸

Stunting is influenced by the condition of the first 1000 days of life that starts from conception to the first two years of life and this period is called critical windows, because during this period there is a rapid development of body cells including bone so that if nutritional needs is not fulfilled, it can cause stunting.¹⁰ Stunting can cause disruption of child's growth and development, intellectual impairment, lower immunity, vulnerable to risk of non-communicable diseases, decreasing the level of creativity and productivity, increasing the risk of morbidity and mortality.¹¹ Stunting describes as a chronic state of malnutrition in which the supply of nutrients needed by the body including the brain is deficient.^{1,12} This causes unoptimal brain development, therefore it can affect the cognitive function of children.¹³

Stunting is related to decreased cognitive abilities in children. Inadequate nutrient intake for a long time will directly affect the development and maturation of brain function. Disruption of brain development and maturation is associated with decreased cognitive abilities. Decreased cognitive abilities will have an impact on children's learning processes. Short-term memory is important for the learning process and the formation of long-term memory.¹⁴

Short-term memory is the capacity to store a limited amount of information. New information received from the environment will be stored in memory, activated and combined with old memory that has been formed.¹⁵ Memory describes a person's capacity for learning and is closely related to the role of the hippocampus.¹⁶ There are various factors that can affect one's memory including: age, stress, sleep, nutrition and physical activity.¹⁷

The research that was conducted by Horiuchi et al¹⁸ in Cambodia in 2018 on the differences of the nutritional status in urban and rural areas of school-age children found that the children in rural areas had a higher prevalence of stunting than urban areas, this was highly associated with the differences of food intake between the two regions. Another research that was conducted by Addiniya et al¹⁹ in 2014 on the comparison of intelligence based on short-term memory tests in urban and rural students in Jatinangor Region using digit span forward, digit span backward and symbol digit modality tests found that the digit span backward and symbol digit modality tests in children in urban areas were scored higher than those children in rural areas. This shows that stunting rates and short-term memory abilities of elementary school students differ between urban and rural areas.

Based on this background, researcher felt the need to conduct a research on the impact of stunting and the short-term memory in urban and rural elementary school students in Kupang of East Nusa Tenggara Province.

Methods

This research is using analytic observational method with cross sectional design, where the independent variables (stunting and non-stunting) and the dependent variable (short-term memory) are measured at the same time. The instrument that was used to measure the independent variable was the WHO anthropus, the method of measurement is by measuring the height of the student and assessed the data by WHO anthropus application. The instrument that was used to measure short-term memory was digit span, the method of this measurement is by mentioning a few numbers and then asking the student to reiterate the figures. The measurements of stunting and short-term memory

were carried out by researchers. Digit span questionnaire was tested for validation and reliability. Measurements of sleep quality, physical activities, socioeconomic parents, and occupation were collected by a direct interview with questionnaires asked by researchers, since these are some factors that could affect child's short-term memory. Measurement of food intake was measured using a food frequency questionnaire. This research was conducted in two places, Inpres Bertingkat Kelapa Lima 1 elementary school (urban) and Inpres Noelbaki elementary school (rural) from September to October 2019.

The population in this study were elementary school students grades three through five in Inpres Bertingkat Kelapa Lima 1 elementary school and Inpres Noelbaki elementary school with the total number of 452 people. There are 160 elementary school children who met the inclusion criteria that currently on grade 3-5, aged 9-11 years, children were able to hear and talk and willing to be the subject of the research. The exclusion criteria were children who suffer from disability, experiences stress or have a mood feeling questionnaire score (MFQ > 11), history of head trauma, seizures, central nervous system infection, comma, spinal disorders and congenital *equinovarus* (clubfoot), diarrhea and intestinal worms. The sampling technique in this research used consecutive sampling technique. This study was analyzed univariately and bivariately. The bivariate analysis using Chi Square test with significant p value ≤ 0.05 . This study has been approved by the Research Ethics Committee of the Medical Faculty Nusa Cendana University (Approval Number: 64/UN15.16/KEPK/2019).

Results

A total of 160 children participated in this study. **Table 1** shows the baseline characteristic data of subjects. **Table 2**, **Table 3**, and **Table 4** shows physical activities, quantity and quality of sleep, parents' income and occupation, respectively. As for food consumption patterns, it is shown in **Table 5**.

Table 6 shows the univariate analysis results of stunting and non-stunting children, based on WHO child growth chart for height-for-age. Comparison

of short-term memory between stunting and non-stunting group of children is shown in **Table 7**.

Discussion

This study found that (1) the variation of food from the daily intake of the subjects in urban and rural areas is still low. According to UNICEF and WHO the variation of food for children should be at least consist of 4-5 kind of foods.²⁰ The results from Food Frequency Questionnaire (FFQ) shows that subjects only consumed 2-3 food ingredients each day. (2) There was an inadequate sources of omega 3 food such as salmon, mackerel, catfish, sardines, shrimp, squid, fish oil and nuts. Omega 3 plays an important role in morphological, biochemical and molecular development of the brain, so that if the daily intake of omega 3 is insufficient, it will reduce the intelligence of children that can be seen by their low short-term memory.²¹ Based on FFQ results, the daily consumption of fish which is a source of omega 3 in urban and rural areas were still relatively low.

Bone growth in school-aged children is influenced by food intake, if the child's food intake is inadequate, the bone growth will be disturbed and the child will be stunted. Food ingredients that contain nutrients for bone growth are protein, calcium, phosphorus, vitamins, magnesium and zinc.²²⁻²⁴ Protein is important to form new bone tissues and replace the damaged bone tissue. Protein sources are divided into 2 types, (1) animals-source such as beef, chicken, eggs, and fish and (2) vegetables-source such as tofu, tempeh and beans.²² Based on the results of FFQ, subjects in rural areas often consume animal protein i.e. fish and subjects in urban areas often consume vegetable source protein such as tofu and tempeh. The essential role of calcium is to form bones and teeth, the main source of calcium comes from milk.²⁴ Based on FFQ results, daily milk consumption in urban areas was higher than in rural areas.

Phosphorus plays a role in bone and tooth mineralization. Food sources that contain phosphorus are tofu, spinach and cassava leaves.²³ Based on the results of the FFQ, the daily consumption of tofu in urban areas and in rural areas was still relatively low. Vitamins that play a role in helping bone growth are vitamin A and vitamin C. Vitamin A plays an

essential role for bone development, while vitamin C is optimizing the absorption of calcium which can affect the bone growth. Food which contain lots of vitamin A are carrots while lots of vitamin C can be found in oranges.²⁴ Based on FFQ results, the daily consumption of carrots and oranges is still low.

Magnesium and zinc have the same function as phosphor in the role of mineralization of bones and teeth.^{22,24} Food sources that contain lots of magnesium are green vegetables.²⁴ Food sources that contain zinc are animal protein.²² Green vegetables that are included in the FFQ questionnaire were cassava leaves, spinach and kale. It was found that there are 93 subjects who consumed kale based on the results of FFQ in urban and rural areas. From the discussion above, it can be concluded that the daily consumption of the subject's nutrients to meet the ideal needs of bone growth is still relatively low.

The results found that there is no significant difference in short-term memory between stunting and non stunting in elementary school students, these results are same with the research conducted by Sadikin¹⁴ in Indonesia, especially in Jatinangor Region in 2015 about the comparison of short-term memory in 60 elementary students grade 3-5 who were stunting and not stunting, it was found that there was no significant difference in short-term memory between stunting and non-stunting students.¹⁴ Table 7 shows the pattern of how stunting subjects tend to have relatively low short-term memory. The table also shows that the total of stunting subjects in urban areas was 25% with low short-term memory, while in rural areas 46.2% of stunting subjects had low short-term memory. This shows that the percentage of stunting subjects in rural areas who has short-term memory is lower by 21% compared to stunting subjects in urban areas.

Low short-term memory in rural subjects may be influenced by internal and external factors. Internal factors include the quality and quantity of nutrient intake, sleep quality and physical activities.^{17,25} While the external factors are stimulation or training.²⁶ Based on the distribution of the data it can be seen that the daily consumption of fish in rural areas was higher than in urban areas. However, not all subjects in rural areas consume fish every day. Fish is a source of omega 3, where omega 3 plays a role in increasing the intelligence, if the

consumption of omega 3 is inadequate then the intelligence will also be impaired.²¹ The quality of sleep on subjects in rural areas was better than in urban areas, which means that the correlation of low-term memory with low-quality of sleep can be removed. Physical activity of subjects in rural were higher regularity and frequency compared to urban areas. Regular physical activities often has positive impact on short-term memory but it must be followed by adequate food consumption to optimize the subject's short-term memory.¹⁷ External factors such as stimulation / repetitive exercise will improve the ability of short-term memory of the subject.²⁷

A research conducted by Sadikin was also supported by the research conducted by Sokolovic et al²⁸ in India of 1040 elementary school students who were stunted after a nutritional intervention for six months found that the short-term memory abilities, retrieval abilities, and visuospatial abilities were not significantly different before and after the intervention with the p value > 0.1.

In contrast to the results of the research conducted by Woldehanna et al¹³ in 2017 in children aged 5-8 years with a total sample of 2000 children in Ethiopia was found that the stunted children had lower cognitive abilities (which can also be described by short-term memory function) with a significance value of $p < 0.01$ compared with children who are not stunting.

Some studies suggest that the hippocampus is assumed to have a crucial role in determining the power of the brain in capturing and storing the memory. This adequate nutrition early in life will affect the hippocampus. Based on these findings, height-for-age correlates with inadequate nutrition at the beginning of growth because height reflects the nutritional status in the past.^{16,29}

Short-term memory is the capacity to store a limited amount of information. Low short-term memory in children will affect the learning process of children in school, children who have low short-term memory must be given a stimulus repeatedly so that the new information obtained can be stored in their memory.²⁷ The ability that can be disrupted in children who have low short-term memory is the ability to read and write, while in elementary school children this ability is taught as the basis of their knowledge which will be applied to further

education. If the ability to read and write is disrupted it will have an adverse effect during adult.³⁰ The results of this study indicate that stunting and non-stunting children don't have significant differences in cognitive abilities, especially in short-term memory. This is caused by various factors such as parental education, socioeconomic and environment.³¹ Parental education background was not examined by the researcher. However, the socioeconomics factors obtained in the characteristics is that the majority of parents have a low income <1 million rupiah which illustrates that most of the subjects has a low economy capacity, this could affect their food availability in household which then resulted in low nutritional intake of the subject.³² The intake of omega 3 nutrients that affect the short-term memory in stunting and non-stunting children was still very low. So there was no significant difference between stunting and non-stunting children. For the occupational factors, the majority of subject's father worked as a farmer and the mother as a housewife. Having most of the

subject's mothers as a housewives is a positive thing because mothers have enough time for parenting, rising, and caring for their children. Parental genetic factors can also contribute to cognitive development. In general, these factors will affect the child's growth and development process. However, it depends on different stimulations and responses that can affect the child's growth and development process.³¹

Conclusions

Based on the results of the study it can be concluded that there is no significant differences in short-term memory between stunting and non stunting in elementary school children, both in urban and rural areas of Kupang, but in rural elementary schools the prevalence of subjects in stunting group with short-term memory abilities is relatively low, 21.2 % higher compared to urban elementary schools.

Table 1. Baseline characteristics of subjects (n=160)

Characteristics	n(%)
Age (years)	
9	85 (53.1)
10	59 (36.9)
11	16 (10.0)
Elementary school grade	
3	18 (11.3)
4	81 (50.6)
5	61 (38.1)
Gender	
Female	80 (50)
Urban	44 (55)
Rural	36 (45)
Male	80 (50)
Urban	36 (45)
Rural	44 (55)

Table 2. Characteristics of subjects based on physical activity

Physical activity		n(%)
Type of activity		
Light		36(22.5)
	Urban	21(26.3)
	Rural	15(18.8)
Moderate		109(68.1)
	Urban	46(57.5)
	Rural	63(78.8)
Heavy		15(9.4)
	Urban	13(16.3)
	Rural	2(2.5)
Constancy		
Irregular		47(29.4)
	Urban	25(53.2)
	Rural	22(46.8)
Regular		113(70.6)
	Urban	55(48.7)
	Rural	58(51.3)
Frequency		
< 3x/week		75(46.9)
	Urban	41(54.7)
	Rural	34(45.3)
≥ 3x/week		85(53.1)
	Urban	39(45.9)
	Rural	46(54.1)

Table 3. Quantity and quality of sleep of subjects

Quantity and quality of sleep		Percentage (%)
Lenght of sleep:		
<9 hours		46(28.8)
	Urban	29(63)
	Rural	17(37)
≥ 9 hours		114(71.3)
	Urban	51(44.7)
	Rural	63(55.3)
Nap:		
Yes		69(43.1)
	Urban	43(62.3)
	Rural	26(37.7)
No		91(56.9)
	Urban	37(40.7)
	Rural	54(59.3)
Often wake up in the middle of the night		
Yes		74(46.3)
	Urban	47(63.5)
	Rural	27(36.5)
No		86(53.8)
	Urban	33(38.3)
	Rural	53(61.7)

Table 4. Parents' income and occupation

Socioeconomics conditions		n(%)
Parents income :		
< 1 million rupiah/month		93(58.1)
1-5 million rupiah/month		57(35.6)
> 5 million rupiah/month		10(6.3)
Father's occupation		
Entrepreneur		26(16.3)
Government employee		14(8.8)
Farmer		40(25.0)
Laborer		17(10.6)
Teacher		6(3.8)
Seller		4(2.5)
Doesn't work		13(8.1)
Other		40(25.0)
Mother's Occupation		
Entrepreneur		6(3.8)
Government employee		12(7.5)
Farmer		7(4.4)
Teacher		7(4.4)
Seller		11(6.9)
Housewife		109(68.1)
Other		8(5.0)

Table 5. Food consumption patterns

Food Material	Frequency										Total	
	> 3x/day		≤ 3x/day		> 3x/week		≤ 3x/week		Never		n	%
	n	%	n	%	n	%	n	%	n	%		
Staple Food												
Rice	32	20	124	77.5	4	2.5	0	0	0	0	160	100
Noodles	4	2.5	27	16.9	20	12.5	98	61.3	11	6.9	160	100
Bread	10	6.3	51	31.9	16	10	73	45.6	10	6.3	160	100
Side Dishes												
Wet Fish	7	4.4	36	22.5	10	6.3	80	50	27	16.9	160	100
Dried Fish	7	4.4	46	28.8	13	8.1	78	48.8	16	10	160	100
Egg	8	5	49	30.6	16	10	81	50.6	6	3.8	160	100
Chicken Meat	6	3.8	17	10.6	16	10	107	66.9	14	8.8	160	100
Meat	2	1.3	15	9.4	15	9.4	106	66.3	22	13.8	160	100
Tofu	13	8.1	61	38.1	14	8.8	63	39.4	9	5.6	160	100
Tempeh	13	8.1	62	38.8	17	10.6	62	38.8	6	3.8	160	100
Vegetables												
Cassava Leaves	5	3.1	13	8.1	8	5	81	50.6	53	33.1	160	100
Spinach	6	3.8	36	22.5	11	6.9	75	46.9	32	20	160	100
Kale	7	4.4	86	53.8	13	8.1	47	29.4	7	4.4	160	100
Carrot	6	3.8	26	16.3	14	8.8	74	46.3	40	25	160	100
Cabbage	8	5	23	14.4	8	5	72	45	49	30.6	160	100
Cauliflower	3	1.9	10	6.3	7	4.4	63	39.4	77	48.1	160	100
Mustard Greens	7	4.4	40	25	10	6.3	60	37.5	43	26.9	160	100
Long beans	4	2.5	17	10.6	13	8.1	75	46.9	51	31.9	160	100

Table 5. Food consumption patterns (continued)

Food Material	Frequency										Total	
	> 3x/day		≤ 3x/day		> 3x/week		≤ 3x/week		Never			
	n	%	n	%	n	%	n	%	n	%	n	%
Fruits												
Banana	11	6.9	49	30.6	12	7.5	80	50	8	5	160	100
Orange	1	0.6	23	14.4	12	7.5	99	61.9	25	15.6	160	100
Watermelon	3	1.9	25	15.6	12	7.5	96	60	24	15	160	100
Papaya	7	4.4	41	25.6	5	3.1	85	53.1	22	13.8	160	100
Pineapple	0	0	8	5	5	3.1	61	38.1	86	53.8	160	100
Mango	5	3.1	104	65	15	9.4	29	18.1	7	4.4	160	100
Drink												
Tea	10	6.3	73	45.6	12	7.5	36	22.5	29	18.1	160	100
Coffee	0	0	17	10.6	5	3.1	43	26.9	95	59.4	160	100
Milk	11	6.9	67	41.9	13	8.1	48	30	21	13.1	160	100

Table 6. Univariate analysis of subject according to WHO growth chart for height-for-age

Height-for-age	n(%)
Stunting	52(32.5)
Non stunting	108(67.5)

Table 7. Comparison of short term memory between stunting and non-stunting group

Height-for-age	Short term memory		p value*	
	Low n(%)	Moderate n(%)		
<i>Stunting</i>				
Urban	13(25)	8 (15.4)	0.144	
Rural	24 (46.2)	7 (13.4)		
<i>Non stunting</i>				
Urban	32 (29.6)	27 (25)		
Rural	32 (29.6)	17 (15.8)		

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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ORIGINAL ARTICLE

Effect of *Moringa oleifera* leaf powder supplementation on weight gain of toddler in the working area of Naibonat health center, Kupang regency

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Abstract

Introduction: Undernutrition prevalence in East Nusa Tenggara is very high. One of the intervention to overcome this problem is by providing foods enriched with vitamins and minerals. One of the plant that contains great amount of vitamins and minerals is Moringa which thrives in almost all of the mainland of Timor. This study aims to determine whether there is an effect of Moringa leaf powder supplementation on weight gain of children under five years of age at the working area of Naibonat Health Center in Kupang Regency.

Methods: Experimental study with pre-test post-test control group design was conducted among children aged 2-5 years in the working area of the Naibonat Health Center in Kupang Regency. The study was conducted with consecutive sampling technique with a total subjects of 50 children consisting of 25 children in the treatment group and 25 children in the control group. The intervention group was given 25 grams of Moringa leaf powder for 14 days. **Results:** There was a significant increase in body weight of the treatment group after supplementation of 25 grams of Moringa leaf powder for 14 days ($p < 0.001$). In the control group, there was no significant difference of body weight after the study. **Conclusions:** Moringa oleifera leaf powder supplementation of 5-10 grams has been able to increase body weight by 0.53 kg on children under five years of age at the working area of Naibonat Health Center in Kupang Regency by increasing the child's appetite.

Keywords Moringa leaf powder, weight gain, toddler

Introduction

Children under five years of age are one of the most vulnerable groups to malnutrition. Nutritional status in this group requires special attention because malnutrition that occurs can be irreversible, which can't be recovered and can cause physical growth, mental, and intellectual disruption. Furthermore, the growth process in this phase is relatively fast which make children need nutrients in relatively large quantities.¹⁻³

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Based on data from the Global Nutrition Report, approximately 41 million children under five years old have short stature and 50 million are underweight. Poor nutrition causes death in infants around 45%. It is known that the most severe malnutrition problems are commonly happen to middle to lower countries, including Indonesia.⁴ Based on Basic Health Research data in 2018, the percentage of undernourished children under five years of age in Indonesia in 2007 and 2010 is constantly 13.0% and decreased by 0.1% from 13.9% in 2013 to 13.8% in 2018.⁵

Based on the data of weight and nutritional status of children under five years old in East Nusa Tenggara were 11.6% in 2016 and 10.6% in 2017. Therefore, East Nusa Tenggara was ranked as second highest number of malnutrition in Indonesia. However, based on nutritional status measured by weight for age, East Nusa Tenggara was ranked as the province with the highest malnutrition rate with the percentage of 21.3% in 2016 and 20.9% in 2017.^{6,7} This result shows that the case of malnutrition in East Nusa Tenggara is very serious and needed proper handling.

The problem of malnutrition in East Nusa Tenggara spread throughout the region. Based on the data of the East Nusa Tenggara Food Security and Vulnerability Map, Kupang Regency is one of the districts with the highest prevalence of malnutrition in children under five years old in 2013 with the percentage of 33.39%.^{8,9} Based on the survey results, the Naibonat Public Health Center in Kupang Regency has the highest prevalence of malnutrition compared to any other Public Health Centers. The average number of children aged 2 to 5 years with malnutrition is 134 children in 2017, 88 children in 2018, and 231 children in 2019.¹⁰

One of the solutions to overcome the problem of malnutrition in Indonesia is to provide nutritional interventions, such as adding the supplementary micronutrients to food.¹¹ Moringa leaves are rich of minerals, vitamins, amino acids and antioxidants. Moringa leaf powder has excessively higher nutrient content than a fresh Moringa. Therefore, Moringa can be a solution to overcome the problem of malnutrition.^{12,13}

Based on Dudi Krisnadi,¹⁴ entrepreneur of Moringa from West Java, Moringa varieties of East Nusa Tenggara are superior compared to other

regions.¹⁴ Analysis results of Nutritional Standard of Moringa leaf powder per 100 g in Moringa leaves from East Nusa Tenggara is higher than Moringa leaves in general.¹⁵ This makes the potential use of Moringa is very possible in East Nusa Tenggara.

There are several studies on the effect of Moringa on weight gain. Research conducted by Srikanth et al¹⁶ showed that the addition of Moringa leaf powder as a supplementary food for toddlers can improve the nutritional status of the toddlers.¹⁶ Research by Zakaria et al¹⁷ also showed that there was an increase in body weight of toddlers when given the South Sulawesi Moringa leaf flour variety in their foods.¹⁷ However, all the studies that have been conducted have different quality of Moringa from the ones in East Nusa Tenggara. Therefore, the writer is interested in examining the effect of Moringa leaf powder supplementation in undernourished children under five years old in the working area of the Naibonat Health Center, Kupang Regency.

Methods

The research was conducted in the working area of the Naibonat Public Health Center, Kupang Regency from February to December 2019.

This is an experimental study with pre test-post test with control group design. This study used consecutive sampling. The subjects were children aged 2-5 years which was divided into 2 groups, the treatment group and the control group, each group consist of 25 children. The treatment group, were given 25 gram Moringa leaf powder supplementation for 14 days. Furthermore, at the beginning of the study, the body weight was measured to determine the nutritional status based on weight for height indicator and 2x24 hours food recall was conducted. The body weight measurement and 2x24 hours food recall were also conducted, in the middle and at the end of the study. The study then analyzed by using paired T test to see if the data distribution was normal and Wilcoxon test as an alternative if the data distribution was abnormal, this test used to assess differences in the average before and after treatment in each group. To see the difference in the average changes between the two groups the paired T test was used if the data distribution was normal and the Mann-Whitney as

an alternative test if the data distribution was abnormal.

Results

Characteristics of research subjects in the treatment group and the control group based were classified based on gender, nutritional status, and energy intake. Table 1 shows that from the sample there were more females than males. Females are more vulnerable to nutritional problems than males. This could be caused by higher priority in terms of food for males because of their higher rate of activity than women.¹⁸

Table 2 shows that from 50 research samples that were taken, subjects with poor nutritional status based on weight for height indicators are more than samples with good nutritional status. Factors that may affect the nutritional status of children are inadequate nutrients in food, poor family economy, poor knowledge of providing good nutrition for children, and availability of nutritious and affordable food by the community.¹⁹

Table 3 shows that the majority of children have less energy intake (54%), then followed by more (28%) and enough (18%) energy intake.

Toddler energy intake is obtained from the average food recall (kcal) of children for 2x24 hours. When doing a food recall, the researcher found that most mothers were unable to provide their children high protein source of food, especially animal protein. The following graph shows the comparison of children's energy intake before and after treatment for 14 days in the treatment and control groups.

Data obtained from observations for 14 days in each group were analyzed by Wilcoxon test in the treatment group showed that there was significant differences in the changes of energy intake before and after treatment ($p < 0.000$). However, in the control group it was found that there was no significant difference ($p = 0.545$). Mann-Whitney test is used to see whether there is a significant difference of energy intake between the treatment and control group. The result showed a significant difference ($p=0.001$). The energy intake from the treatment and control groups also showed a significant difference ($p=0.037$).

The following is a comparison chart of toddler weight before and after the intervention in both

groups. In the treatment group, there was a weight gained with an average of 0.61 kg after the intervention of Moringa leaf powder for 14 days. However in the control group, the increase of average body weight was 0.03 kg.

Data obtained from observations for 14 days in each group were analyzed by paired T test. Test results in the treatment group found a significant difference before and after the intervention ($p \leq 0.001$). However in the control group there was no significant difference ($p=0.678$). Data analysis was continued by conducting an unpaired T test to compare the difference in mean changes between the two groups by using a weight difference value before and after the intervention and the result was a significant difference ($p \leq 0.001$), however the result of the comparison between the weight after the intervention between both groups was not significantly difference ($p=0.662$).

Discussion

A child's nutrition can be influenced by various factors. One of the factors that might contribute to the nutritional status of children in the working area of the Naibonat Health Center, Kupang Regency is the inadequate food nutrients. After taking 2x24 hour food recall data at the beginning, middle, and the end of the study, most mothers admitted that their children didn't consume enough of high protein-source foods, especially animal protein. Even though protein is very important for children's growth, height and weight as well as the child's development.²⁰ This might be caused by the inability of the mother to afford the food.

The biological environment might also affect the nutritional status of children in the working area of Naibonat Health Center, Kupang Regency. Dense population can cause limited food availability. Population density in the working area of Naibonat Health Center is 233 inhabitants/km.^{2,21} Based on Indonesian National Standards 03-1733-2004, population density in this region is considered as high population density so the biological environment is probably one of the factors that is responsible to the nutritional problems that occurred.²² Furthermore, another factor that might affect a child's nutrition is the level of parental knowledge. Based on the health profile of the

Naibonat Health Center Kupang Regency, in general, the parental educational levels in the working area of the Naibonat Health Center is still low.²¹

Adding foods enriched with micronutrients is one of the intervention to overcome the nutritional problem among toddler. Moringa is one of the plant that is rich with minerals, vitamins, amino acids and antioxidants. In the treatment group, 25 grams of Moringa leaf powder were given to 26 children for 14 days, but there was 1 child who had diarrhea for 3 days when the study took place so the child was excluded, and added in the drop-out criteria.

In the treatment group, only 4 of 25 children in the treatment group used up all of Moringa leaf powder for 14 days with an average weight gain of 1.05 kg, while the other 21 children only spent 5-10 grams of Moringa leaf powder. This is because these children did not like the scent of Moringa leaf powder. This is because these children did not like the scent of Moringa leaf powder. Research by Zakaria et al¹⁷ stated that at the beginning of the administration of Moringa leaf flour, children also did not like the scent of Moringa leaf flour, but after it is given continuously little by little, the children start to like and get used to it.¹⁷ Even so, the weight of these 21 children increased by an average of 0.53 kg.

Energy intake in the treatment group increased and also gained the level of energy sufficiently. Qualitatively, parents of children in the treatment group stated that the child's appetite increased after the administration of Moringa leaf powder. This is in line with research conducted by Zakaria et al¹⁷ which stated that the Moringa leaf flour can increase child's appetite.¹⁷

The increased of appetite in children may be caused by vitamins and minerals contained in Moringa. Based on research by Lili and Mitriya²³ about the effect of giving papaya to the appetite of children aged 2-5 years in the working area of the Kuranji Public Health Center showed that the increased in appetite in infants was because papaya fruit contains vitamins and minerals. Vitamins and minerals restore the digestive system so that the child's appetite increases and improve nutrients absorption. The content of vitamin A can prevent keratinization of the gastrointestinal tract. Vitamin A in Moringa leaf powder is known to be 10 times

higher than in carrots. Children with vitamin A deficiency can cause symptoms of anorexia. The content of vitamin A in Moringa can prevent anorexia and have an impact on increasing appetite as well.²³

In the working area of Naibonat Health Center Kupang Regency, there are 1,734 children under five years old with good nutritional status and 104 children under five years old with undernourished status. In the treatment group there were 12 children with good nutritional status who experienced a weight gain with an average of 0.64 kg. While 13 other children with poor nutritional status experienced a weight gain with an average of 0.59 kg. In the control group, there were 12 children who experienced weight loss with an average of 0.2 kg, 12 children who experienced weight gain with an average of 0.3 kg and 1 child whose weight remained constant.

After the research, the body weight before and after the intervention in each group was analyzed and the result showed a significant increase in body weight in the treatment group, but not in the control group. The results of the comparison analysis of the average differences between the two groups also showed a significant difference. This proves that the weight of the subjects increased due to the supplementation of Moringa leaf powder for 14 days. While the results of the weight comparison analysis test after the intervention showed no significant difference. This is probably caused by the initial body weight in the treatment group that was lower than the control group.

The results of this study are not in line with the journal by Susanto et al²⁴ which stated that Moringa leaf powder of Madura variety can reduce body weight because it contains isothiocyanates.²⁴ The article by Wahyudi and Nurhaedah²⁵ with the title Variety of Benefits of Moringa Plants (*Moringa oleifera* Lamk) for the community also stated that Moringa leaves can cause weight loss because it gives effect to stimulate and launch metabolism in the body so that it can burn calories faster.²⁵ Several studies that support the results of this study, including research by Srikanth et al¹⁶ showed that the addition of Moringa leaf powder as a supplementary food for toddlers can improve the nutritional status of these toddlers. Moringa leaf powder was given as much as 30 grams to 30

toddlers with a lack of protein energy in the treatment group for 2 months.¹⁶ Of all 30 children, there were 3 children who gained weight more than 40%, 9 children with 30-40% weight gain, 10 children with 20-30% weight gain, 5 children with 10-20% weight gain, and 3 children with less than 10% weight gain. Research conducted by Zakaria et al¹⁷ also showed that there was a weight gain in 15 children aged 1-3 years in the treatment group when given the addition of 10 grams of South Sulawesi Moringa leaf flour variety for 30 days on their foods¹⁷. From the 15 children, there were only 13 children who were measured and found 10 children who gained weight after 14 days, 2 children who remained with their constant weight, and 1 child who loss weight.

In conclusion, Moringa oleifera leaf powder supplementation of 5-10 grams was able to increase body weight by 0.53 kg in children under 5 years old in the working area of Naibonat Health Center Kupang Regency ($p \leq 0.001$) by increasing the children's appetite.

Table 3. Characteristic of samples based on energy intake

Energy Intake	Group		Total
	Treatment	Control	
Less	14	13	27
Enough	4	5	9
Over	7	7	14
Total	25	25	50

Table 1. Characteristic of samples by gender

Sex	Group		Total
	Treatment	Control	
Male	11	10	21 (42%)
Female	14	15	29 (58%)
Total	25	25	50 (100%)

Table 2. Characteristic of samples based on nutritional status

Nutritional Status	Group		Total
	Treatment	Control	
Good	12	12	24 (48%)
Poor	13	13	26 (52%)
Total	25	25	50 (100%)

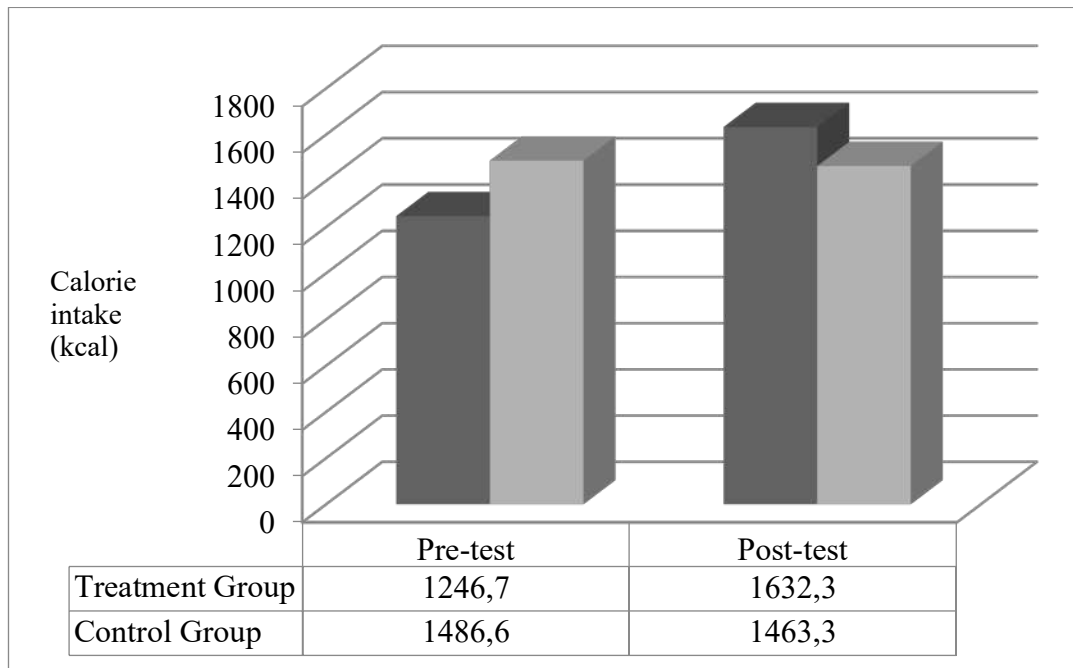


Figure 1. Subjects' energy intake before and after the intervention in the treatment and control groups.

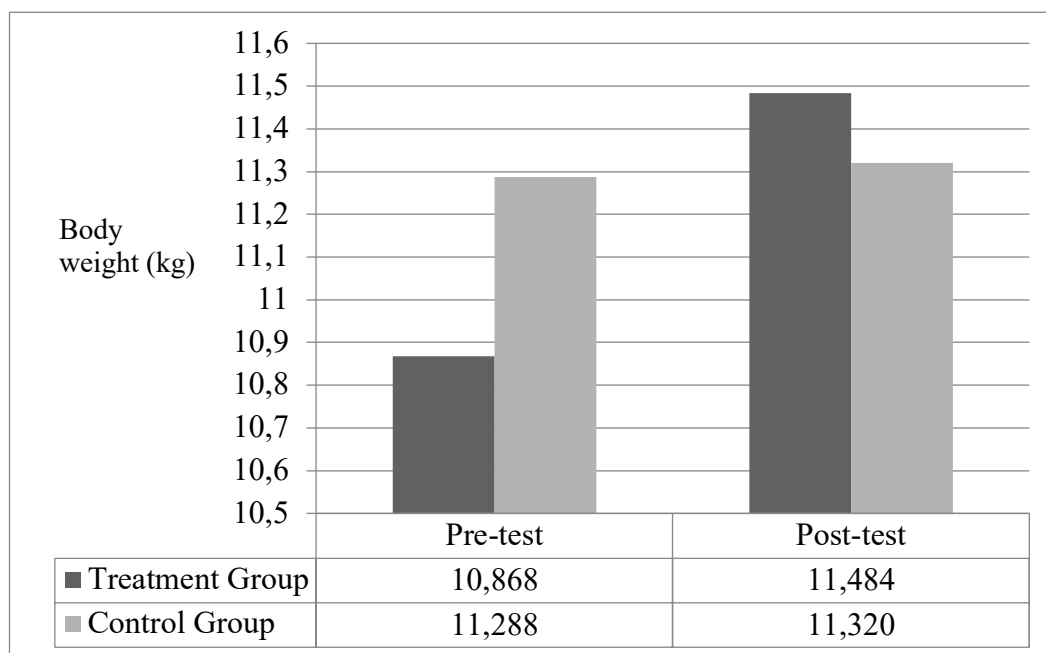


Figure 2. Increase of average body weight of subjects before and after the intervention in the treatment and control groups.

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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Effect of isoflavone consumptions on the recurrence and survival rate among breast cancer patients: an evidence-based case report

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Abstract

Background: isoflavones possess both anti-estrogenic and estrogenic-like properties. Many traditional dishes from Indonesia are rich in isoflavones, such as tempeh, tofu, and soymilk. It remains controversial whether women diagnosed with breast cancer should be advised to avoid or increase the intake of isoflavone food to improve survival.

Objective: to identify the association between post cancer diagnosis isoflavone food consumption with the recurrence and survival rate among women with breast cancer.

Methods: the search was conducted with advanced searching on *PubMed*, *Cochrane*, *Scopus*, and *ProQuest* according to the clinical question. The screening of title and abstract using inclusion and exclusion criteria, double filter, and reading full text led to six useful articles. The selected studies were critically appraised for validity, importance, and applicability.

Results: five prospective cohort studies and one meta-analysis were found with comparable validity. Women at the high level of isoflavone intake (>10 mg/day) had a significant reduction in the risk of recurrence and mortality of breast cancer.

Conclusion: isoflavone food intake is associated with better survival, low recurrence, and low mortality among both ER-positive and ER-negative breast cancer patients.

Keywords isoflavone, breast cancer, prognosis, survival

Introduction

Breast cancer is the most common malignancy affecting women, and its incidence and mortality rate is increasing worldwide. The prevalence of breast cancer in Asian countries, including Indonesia has been rapidly increasing during the past few decades.¹ Migration studies have shown

that breast cancer incidence in Asian women becomes similar to that of Western women because of westernization diet. The GLOBOCAN study in 2018 reported for 17% of new cases and 11% of mortality rate of breast cancer each year.² The number of women who develop breast cancer is more than two times the number of women who die of breast cancer, and this is thought to be related to the relatively high survival rate. Therefore, breast cancer survivors are expected to improve their quality of life through optimal nutrition.

Isoflavones show both anti-estrogenic and estrogenic-like properties. In Asian countries, the average daily intake of isoflavones is 25–50 mg, while in the United States and Europe is less than 3 mg.³ Isoflavone has been suggested to inhibit breast

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cancer development by decreasing estrogen production and inhibiting cell proliferation.^{4, 5} However, isoflavones may exert an estrogenic effect by binding to estrogen receptors in the breast and enhance cellular proliferation.^{4, 6} As a consequence, clinicians frequently suggest women with breast cancer to either avoid isoflavone foods entirely or use them in moderation. Isoflavone containing foods are easily found in Indonesia, such as tempeh and tofu.^{7, 8} Consumption of that product is high because of the high nutritional value, easy preparation, and affordable price. Tempeh is contained the highest amount of total isoflavone (daidzein and genistein) compared to other soy products.⁷

Data on the association of post-diagnosis isoflavone food consumption with breast cancer prognosis are still conflicting. Experimental studies suggest that isoflavones may interact with tamoxifen therapy, with some studies showing a potential benefit of combined dietary isoflavone intake and tamoxifen use on the inhibition of breast cancer growth, whereas other studies have reported a reduction in the anti-cancer effects of tamoxifen on breast tissue.^{6, 9, 10} A concern has been raised whether women should be advised to avoid or increase intake of isoflavone food to inhibit cancer progression. Therefore, we conducted the evidence-based case report to critically evaluate the effect of isoflavones food consumption on the recurrence and mortality rate among women with breast cancer from different ethnicities.

Clinical question

A-52 years old woman admitted to the clinic after being referred by an oncologist with a decrease in food intake and three kilograms of weight loss within one month. She was diagnosed with stage IIIB breast cancer six months ago and had undergone a right radical breast mastectomy and chemotherapy. The patient was malnourished. Previously, she liked to consume tempeh or tofu until the doctor advised her to avoid intake of isoflavone foods (tempeh, tofu, or soybeans) to inhibit her breast cancer progression.

In women with breast cancer, does consumption of isoflavone foods cause a higher risk of breast cancer recurrence or increase mortality?

Methods

A search of literature was done on March, 15st 2020 in four databases including Pubmed, Cochrane, Scopus, and ProQuest using terminology listed in Table 1. The results obtained from four sites were screened by title and abstracts using inclusion and exclusion criteria, double filter, and checked for full-text availability. Eligible articles were cohort prospective, meta-analyses, and systematic reviews that point breast cancer prognosis (recurrence, survival, and mortality rate) as the primary outcome. Review articles were excluded. The search strategy, inclusion-exclusion criteria, and results shown in Figure 1. After article selection, a critical appraisal was done by two authors using guidance for prognostic study from the Center of Evidence-Based Medicine.

Results

Following the search strategy, six original articles were eligible for this evidence-based case report. Two of them (Zhang YF et al., 2012 and Kang HB et al., 2012) were from China; three studies (Caan BJ et al., 2011; Nechuta et al., 2012; and Zhang F et al., 2017) from US, Canada, and Australia; also one meta-analyses among Asian-American women (Chi et al., 2013). Characteristic for stratification, determinant, and results are available in Table 2. The critical appraisal is shown in Table 3. Five articles were cohort prospective with a level of evidence 2 and one article was meta-analysis by Chi and colleagues with a level of evidence 1. All studies considered to have good validity, although the study groups of Zhang, et al.⁵ were not similar. The groups were clearly defined and had an adequate follow-up time. From the aspect of importance and applicability, all studies had a relative risk (RR) below 1, which means that higher consumption of isoflavone foods did not increase the risk of recurrence and mortality rate among women with breast cancer.

Discussion

Soybean is rich in isoflavones, which are phytoestrogens with potent anticancer effects.¹¹ Isoflavones possess anti-estrogenic and

nonhormonal properties that enable them to inhibit the development of breast cancer by decreasing estrogen production, inhibiting cell proliferation, and reducing reactive oxygen species (ROS).⁵ Furthermore, isoflavones have anti-angiogenic, activation of natural killer (NK) cells, and antioxidants effects.¹ Experimental studies suggest that isoflavones may interact with tamoxifen, with some studies showing a potential benefit of combined dietary isoflavone and tamoxifen therapy on the inhibition of breast tumor growth.^{6, 12} Several reports indicate that the occurrence of breast cancer is considerably lower in Asian individuals compared with other populations because of high levels of isoflavones as part of their regular diet.³

Controversy regarding the implementation of dietary isoflavones for breast cancer patients is still debatable. Other than anti-estrogen activity, isoflavones may have estrogen-like properties including the ability to bind to estrogen receptor (ER) in the breast and stimulate cellular proliferation.⁶ Taylor et al.¹³ showed that isoflavones may enhance the proliferation of breast cancer cells in-vitro. Therefore, clinicians frequently suggest breast cancer patients to avoid isoflavone foods, especially in women with estrogen-sensitive breast cancer. The three isoflavones (genistein, daidzein, and glycitein) account for approximately 50%, 40%, and 10%, respectively, of the total isoflavone content. Each of them has different ER binding affinities and genistein is considered to be the most potent.¹⁴ Genistein has been shown to enhance the proliferation of breast cancer cells in vitro; specifically in ER-positive and promote estrogen-dependent mammary tumor growth in animal studies.^{15, 16}

Critical appraisal of six literatures shows no increase in recurrence or mortality among breast cancer patients with high isoflavones consumption. Otherwise, several studies indicate significantly lower risk of recurrence, metastasis, development of new breast cancer, and mortality with high isoflavones consumption.^{5, 6, 10, 17, 18} This association was observed across all ethnics groups. A prospective study conducted by Shu et al.¹⁵ showed that Asian women who continued to consume soy after being diagnosed with breast cancer had significantly lower levels of recurrence compared with women who consumed little to no soy.

Likewise, a report by Guha and colleagues in 1954 Californian female breast cancer survivors found a trend for a reduced risk of cancer recurrence with increasing quintiles of daidzein and glycitein intake among postmenopausal women ($p=0.08$ for daidzein, $p=0.06$ for glycitein).¹⁹ In analyses stratified by ER status; tamoxifen therapy; and menopausal status, we found the inverse association of isoflavone intake with recurrence and mortality appeared among all women with breast cancer. Only one study, Can et al.⁴ showed the non-statistically significant reduction of mortality rate among breast cancer women with consumption of isoflavones >16.3 mg/day. Furthermore, there were no negative effects from consumption of isoflavones >35 mg/day or equivalent to the average consumption in Asia.

Isoflavones are usually present in the form of glycosides in soy foods. Isoflavones glycosides have a complex structure, it needs biochemical processes to simplify the structure so it will easily absorb. After being ingested, isoflavones are hydrolyzed to aglycones and carbohydrates by β -glucosidase and other enzymes in the lower small intestine.⁷ Aglycones are absorbed from the intestinal tract by the actions of intestinal bacteria. Therefore, inter-individual variability in isoflavone metabolism might be depending on intestinal flora.¹⁰ Daidzein can be further metabolized to dihydrodaidzein, equol, and O-desmethylangolensin which has a higher biological activity compounds.^{1, 7} However, individual differences exist in this conversion ability, depending on ethnicity, lifestyle, and genetic polymorphisms.^{1, 6}

Traditional soy foods contain approximately 3.5 mg of isoflavones per gram of protein and highly processed soy can lose as much as 80% of its isoflavone content. On average, traditional soy foods contain 20-30 mg of isoflavones per serving (e.g 250 mL of soymilk made from whole soybeans or 100-gram tofu or 75-gram tempeh).¹⁴ Asian diet is rich in soy products. Isoflavones are present in a variety of soy foods but significantly higher amounts are found in tempeh. Tempeh is a traditional fermented product, which often used *Rhizopus oligosporus*, *R. microsporus*, or *R. oryzae* for its fermentation. Fawwaz, et al.²⁰ show that genistein level in tempeh is 5 times higher compared with soymilk. That finding proves that the fermentation process can

release sugar on isoflavones to produce genistein. The content of daidzein and genistein in tempeh will increase with 3 days fermentation process. After the third day, the growth in the amounts of aglycones was not statistically important. Generally, depending on the strain, the content of genistein in the fermented product was 8-10 times higher than in unfermented product and the fermentation process will increase their bioavailability.⁷

Isoflavones show a competitive role with endogenous estrogens in estrogen binding receptors. This would increase the synthesis of sex hormone-binding globulin (thus lowering the biological availability of sex hormones), inhibit 17 β -hydroxysteroid dehydrogenases (thus reducing estrogen synthesis), and increase clearance of steroids from the circulation. This anti-estrogenic effect may play a positive role in better breast cancer outcomes.¹⁸ Another speculation that the positive result of breast cancer recurrence is dependent on differential gene expression induced by the isoflavones.¹⁶ In our case report, the high intake of isoflavones was positively associated with a better prognosis, which was in line with the previous hypothesis.

Several studies in this case report have examined the effect of soy intake with stratification by ER but reported different findings. The possible anticarcinogenic effect of isoflavones comes from their anti-estrogenic or estrogenic activity mediated by their affinity for ER. However, isoflavones can exert hormonal and anti-estrogenic effects in many ways independently of the ER, and thus further studies are needed to elucidate the underlying mechanism.¹⁸ Tamoxifen is an anti-estrogen widely prescribed to women with ER-positive tumors as long-term adjuvant therapy to prevent recurrences. Experimental studies suggest that isoflavones may interact with tamoxifen therapy with inconsistent findings.¹⁸ In this case report, we did not identify any bad effects on recurrence and mortality for those breast cancer patients who use tamoxifen.

Conclusions

In conclusion, some studies showed that dietary intake of isoflavone is safe and was associated with lower recurrence and mortality among both ER-positive and ER-negative breast cancer patients.

However, it required further studies to ensure its interaction with anti-cancer therapy. The results of the study could be applied in Indonesia because most studies include Asian ethnic breast cancer women as subjects. Research showing that approximately 10 mg/day of isoflavones is required to inhibit breast cancer recurrence. Breast cancer patients may beneficially advise to consume one portion of isoflavone foods (e.g 75 g tempeh, 100 g tofu, or 250 mL soy milk each day) and avoiding high processing methods.

Table 1. Terminology used in four database

Database	Terminology	Hits	Results
Pubmed	(((((((isoflavone [MeSH Terms]) OR isoflavone [Title/Abstract]) OR tempeh[MeSH Terms]) OR tempeh[Title/Abstract]) AND (((((((breast cancer[MeSH Terms]) OR breast cancer[Title/Abstract]) OR breast neoplasm[MeSH Terms]) OR breast neoplasm[Title/Abstract]) OR breast carcinoma[MeSH Terms]) OR breast carcinoma[Title/Abstract]) AND (((surviv*[MeSH Terms]) OR surviv*[Title/Abstract]) OR prognos*[MeSH Terms]) OR prognos*[Title/Abstract]) Filters: Free full text; published last 10 years; Humans; English	38	3
Cochrane	#1 MeSH descriptor = isoflavone OR tempeh, N= 758 #2 MeSH descriptor = breast cancer OR breast neoplasm OR breast carcinoma, N= 36064 #3 MeSH descriptor = survival OR prognosis, N=121186 #4 = #1 AND #2 AND #3, N= 9	7	2
Scopus	<i>TITLE-ABS-KEY ("isoflavone" OR "tempeh" AND "breast cancer" OR "breast neoplasm" OR "breast carcinoma" AND "survival" OR "prognosis") AND (LIMIT-TO (ACCESSTYPE(OA))) AND (LIMIT TO (PUBSTAGE , "final")) AND (LIMIT TO (DOCTYPE, "ar")) AND (LIMIT TO (SUBJAREA, "MEDI")) AND (LIMIT-TO (LANGUAGE, "English"))</i>	23	4
ProQuest	<i>ab (isoflavone OR tempeh) AND ab("breast cancer" OR "breast neoplasm" OR "breast carcinoma") AND ab(prognosis OR survival)</i>	15	1

Table 2. Design and results of the selected articles

Articles, year	Stratification analysis	Determinant	Results
Caan. BJ et al 2011	Analyses stratified by: 1. ER/PR status (ER+/PR+ ER-/PR-) 2. Tamoxifen use (yes or no)	A second breast cancer event (local and distant recurrences and new breast primaries) and all-cause of mortality	<ul style="list-style-type: none"> - Isoflavone intake was unrelated to the risk of a second breast cancer event overall (0.78; 95% CI: 0.46-1.31) or within strata of women defined by hormone receptor status or tamoxifen therapy. - The risk of death tended to be lower as isoflavone intake increased. Women at the highest level of isoflavone intake (>16.3 mg/day) had a non-significant 54% reduction in risk of death compared with the lowest quintile (0.46; 95% CI:0.2-1.05, P for trend= 0.02).
Kang. HB et al 2012	Analyses not stratified by menopausal status, ER/PR status, and tamoxifen use	Survival time which calculated from the date of diagnosis to the date of last follow-up from any causes and cancer-specific death	<ul style="list-style-type: none"> - The highest soy isoflavone intake (>35.3 mg/day) was associated with a decreased death risk of breast cancer (OR= 0.25, 95% CI: 0.09-0.54).
Nechuta. SJ et al 2012	Analyses stratified by: 1. Menopausal status (pre and postmenopausal) 2. ER status (ER+ or ER-) 3. Tamoxifen use in ER+ breast cancer (yes or no)	Total mortality, breast cancer-specific mortality, and recurrences (or metastasis or development of new breast cancer)	<ul style="list-style-type: none"> - Consumption of ≥ 10 mg isoflavone/day was associated with a significantly reduced risk of recurrence (HR: 0.75; 95% CI: 0.61-0.92) but a non-significantly reduced risk of all-cause and breast cancer-specific mortality. The inverse association appeared to be stronger among postmenopausal, ER- and tamoxifen use. - In China, consumption of ≥ 10 mg/day was associated with a marginally significant reduced risk of recurrence compared with < 4 mg/day (HR: 0.59; 95% CI: 0.47-1.01; p= 0.06), while in the US the reduction was significant (HR: 0.76; 95% CI: 0.58-0.99).
Zhang. YF et al 2012	Analyses stratified by ER status (ER+ or ER-)	Survival time which was determined from the time of biopsy proven diagnosis to cancer-specific death	<ul style="list-style-type: none"> - The average intake of soy isoflavone >17.32 mg/day was associated with reduced breast cancer-specific death (HR: 0.64; 95% CI: 0.45-0.93) and the trend of survival was increased with the increasing dosage of soy isoflavone. Better prognosis of breast cancer was found among women with ER+ breast cancer (HR: 0.59; 95% CI: 0.40-0.93)
Chi et al 2013	Analyses stratified by: 1. ER status (ER+ or ER-) 2. Menopausal status ((pre and postmenopausal) 3. Tamoxifen use	Recurrence and mortality in breast cancer patient	<ul style="list-style-type: none"> - Soy isoflavone intake >17.32 mg/day was associated with reduced mortality compared with <7.56 mg/day (HR: 0.64; 95% CI: 0.45-0.92), especially in ER-, ER+, premenopausal, postmenopausal, and patients with tamoxifen. - Soy isoflavones were associated with reduced recurrences at consumption >10 mg/day compared with <4 mg/day (HR: 0.74; 95% CI: 0.59-0.92). The highest soy foods intake after diagnosis was associated with reduced recurrence (HR: 0.74, 95%CI: 0.64-0.85) compared with the lowest intake, especially in ER- and postmenopausal or patients with tamoxifen.

Table 2. Design and results of the selected articles (continued)

Articles, year	Stratification analysis	Determinant	Results
Zhang. FF, et al 2017	Analyses stratified by: 1. Tumor hormone receptor status (ER+PR+, ER+PR-, ER-PR+ and ER-PR-) 2. Hormonal therapy 3. Race/ ethnicity (non-hispanic white, blacks, hispanics, Asians) 4. Menopausal status (pre and post)	All cause of mortality	- Women in the highest quartile of isoflavone intake (≥ 1.5 mg/day) had a 21% decrease in all-cause mortality compared to women in the lowest quartile (< 0.3 mg/day) (Q4 vs. Q1: HR: 0.79, 95% CI: 0.64-0.97) - In stratified analyses, reduced risk of all-cause mortality associated with high isoflavone intake was statistically significant for women with ER-/PR- tumors (HR:0.49, 95% CI: 0.29-0.83) and women who did not receive hormonal therapy (HR:0.68, 95% CI: 0.51-0.91)

CI= confidence interval; ER= estrogen receptor; PR= progesteron receptor; HR= hazard ratio; mg= miligram; OR= odds ratio; Q= quartile

Table.3 Critical appraisal of the six studies based on criteria by Center of Evidence-Based Medicine, Oxford University

Articles	Validity							Level of Evidence*	
	Common point	Follow up	Outcome	Adjustment	Outcome over time	Precision	Applicability		Clinically important
Caan.BJ et al	+	+	+	+	-	+	+	+	2
Kang.HB et al	+	+	+	+	+	+	+	+	2
Nechuta.SJ et al	+	+	+	+	-	+	+	+	2
Zhang.YF et al	+	+	+	+	-	?	+	+	2
Chi et al	+	+	+	+	-	?	+	+	1
Zhang.FF et al	-	+	+	+	-	+	?	+	2

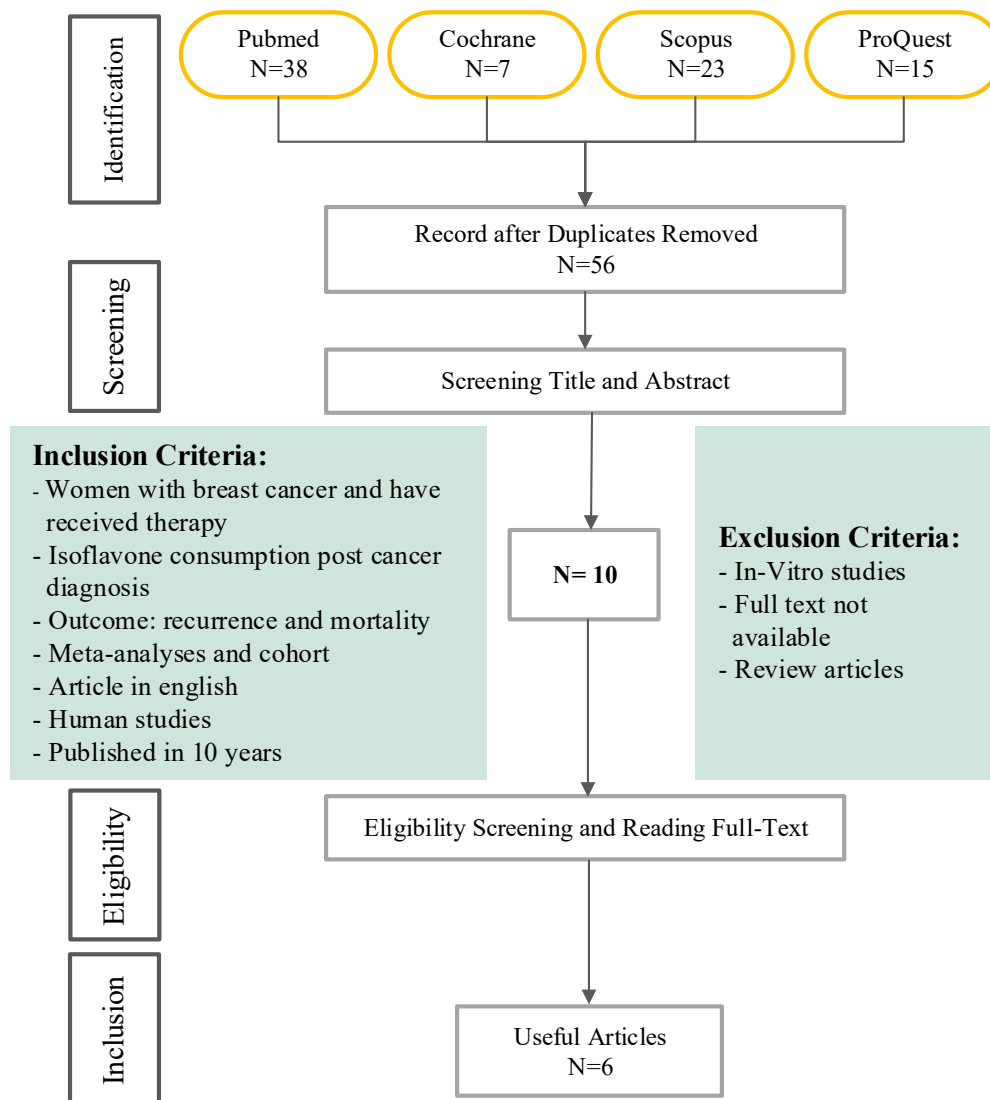


Figure 1. Flowchart of search strategy

Conflict of Interest

Authors declared no conflict of interest regarding this article.

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