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EDITORIAL

Harmonising Food Frequency Questionnaire (FFQ) for South East Asia for Accurate Dietary Data Interpretation

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South East Asia (SEA) is an ethnically diverse region but still share some similarities with regards to food intake[1]. Each country within SEA can be considered as food heaven with its diversity of dietary choices and creativity in food preparations. Within SEA, each individual country is also unique due to its culture, tradition and food choice. Additionally, cross country immigration for economic purpose also demand healthcare providers of host country some additional tasks for evidence-based dietary advice as their training were mostly focused at local foods. For researchers on regional dietary intake huge challenge appears when comparison between countries are made with regards to dietary intake. It raises two pertinent questions. Is it correct to compare food date collected using unstandardized dietary intake tool? Is it possible to harmonise the dietary data and produce a FFQ as a standard tool?

Generally, food frequency questionnaires (FFQs) are designed to assess habitual dietary intake by asking about the frequency and portion intake with which food items of specific food groups are consumed over a set period.[2] The advantage and disadvantages of FFQ compared to other dietary tools are well documented.[3] Nevertheless, FFQ is well accepted in some large studies as the appropriate tool for dietary data collection.[4] However, these large studies are isolated to specific countries and any dietary intake findings is refrained to the specific country only. Recently, there are initiatives to merge and harmonise multiple FFQ result into a single data set. The biggest initiative so far is led by research team at the Tufts University with the Global Dietary Database Consortium (www.globaldietarydatabase.org).[5] Another initiative is the NutriGen Alliance which combined FFQ data from 4 ethnically diverse birth cohorts within Canada[4]. The latter group reported strong association of "plant based" diet with the modified Alternative Healthy Eating Index. These are excellent initiative and important findings as the results are generated from huge dietary datasets with appropriate statistical techniques. However, one limitation of these initiative is the dietary data results are obtained through different set of FFQ's which were designed according to each researcher's objective. Nevertheless, such initiatives should be encouraged but other possible options should also be explored. The idea of designing FFQ starting from

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early stage by considering local dietary elements of the countries should be tested. With the advancement for internet technology, researchers from SEA could communicate actively in designing a standard FFQ which could be tasted among population in individual countries. Perhaps, this approach may produce more accurate data with fewer variations and could be applied in multiple countries any may benefit populations in this region.

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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NARRATIVE REVIEW

Probiotics as Prevention for Gastro-intestinal Disorders in Pediatrics

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Abstract

This is a narrative review of largely randomized trials on the impacts of probiotics. It concludes that evidence for beneficial effects of selected probiotics in the prevention of gastrointestinal disorders is limited mainly to acute gastroenteritis, antibiotic-associated diarrhea, infantile colic and necrotizing enterocolitis. However, there is no broad consensus to recommend the use of probiotics in the prevention of these conditions, mainly because of the different designs used in different studies, resulting in limited evidence for specific strains, dosages and indications. More well-designed studies utilizing standardized methodologies are needed before recommendations can be proposed. At this stage, there is insufficient evidence to recommend the routine use of probiotics in infants and children for the prevention of gastro-intestinal disorders.

Key points:

Data indicate that selected probiotic strains are likely to prevent acute gastroenteritis, antibiotic-associated diarrhea, infantile colic and necrotizing enterocolitis.

- However, relevant studies differ in design.
- As a consequence, there is insufficient evidence for a global recommendation.
- Since adverse effects are extremely rare, one might also recommend these products that were shown beneficial in the above mentioned indications, considering that patients may only profit since "there is no harm and since there may be some benefit."

Keywords probiotic, prevention, prophylaxis, gastrointestinal disorder, infant, child, pediatric

Introduction

The microbiome is the totality of all the microbial cells that colonize the human body and their genes. The microbiota genes are far more predominant than the human genome.[1] A balanced microbiome is associated with eubiosis and health, while an unbalanced microbiome or dysbiosis is related to health problems, within and outside the gastro-intestinal (GI) tract. A lot of research is done on how to manipulate the gut microbiome to treat disease and improve human health. Diarrheal illness is the main one examined; it is the second leading cause of mortality among children younger than five years worldwide, causing an estimated 1.5 to 2 million deaths annually. On average, every child under the age of 3 years is reported to develop at least one episode of infectious gastroenteritis per year.[2]

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The gut microbiota can be altered by medications such as antibiotics and proton pump inhibitors, but also by probiotic supplements. Probiotics are live microorganisms, which when administered in adequate amounts, confer a health benefit on the host.[3] While some authors have published strong evidence to support general effects of probiotics as a group rather than focusing on strain specific effects, others question this approach and yet conclude that there is insufficient evidence to guide the selection of the most effective strains for any specific purpose.[4-6] The aim of this review was to review recent literature regarding the evidence for a health benefit of probiotic administration in the prevention of GI disease in infants and children.

Search strategy and selection criteria

The following data-bases were searched for randomized controlled trials between Jan 1, 2000 and April 30, 2019: The Cochrane Library, MEDLINE, and EMBASE. Search terms used were: "probiotics" and/or "prevention" and/or "prophylaxis" and/or "prophylactic use" and "gastrointestinal disorder" and/or "gastrointestinal disease" and "infant" and/or "child" and/or "pediatric". Languages selected were "English".

Probiotics and prevention of diarrhea

Acute gastroenteritis

Acute gastroenteritis (AGE) is one of the most frequent infectious diseases during early childhood. The effect of the administration of probiotics has been tested in the prevention of AGE.

In a RCT carried out in residential care settings, *Bifidobacterium (B.) lactis Bb 12*, when added to an acidified infant formula, was shown to have some, albeit very modest, protective effect against acute diarrhea in healthy children (Table 1).[7] The difference in the incidence of diarrhea during the study was not statistically different in the probiotic supplemented and control group (28.3 vs 38.7%). The number of days with diarrhea did not differ between the groups. Feeding infants with the *B. lactis BB12* reduced the risk of getting diarrhea by a factor of 1.9.[7] In another RCT, *B. animalis subsp. lactis BB-12* given over a period of 3 months had no preventive effect on GI and respiratory tract infections in healthy children who attend day care centers. Overall, the impact on the incidence of diarrhea was not significant.[8] In a community based double-masked, randomized controlled trial in India of children 1-3 years of age who were randomly allocated to receive either control milk or the same milk fortified with 2.4 g/day of prebiotic oligosaccharide and $1.9x10^7$ CFU/day of the probiotic *B. lactis* HN019, there was a significant reduction in dysentery, respiratory morbidity, and febrile illness.[9] In another RCT, daily administration of a combination of *B. animalis subsp lactis BB12* and *Lactobacillus (L) rhamnosus GG (LGG)* for 6 months in healthy infants did not reduce the number of episodes of diarrhea, or the number of days the child was absent from child care.[10] In a multicenter trial, infant formulae containing *B. lactis* and galacto- and fructo-oligosaccharides (GOS/FOS) did not reduce infection rates compared to formulas with only *B. lactis*.[11]

A placebo-controlled trial with *LGG* showed a decreased incidence of diarrhea in undernourished formula-fed children in Peru, but not in breastfed children.[12] It is tempting to hypothesize that the difference in GI microbiota development in breastfed vs formula fed infants may in part explain this observation. But breastmilk is also a source of protective IgA antibodies,[13] which might protect the infant from developing infectious diarrhea.

Outcomes in prevention may differ from outcomes in treatment, since two recent therapeutic trials concluded that probiotics (a mixture of *L. rhamnosus* R0011 and *L. helveticus* R0052, and *LGG*) did not shorten the duration of acute gastroenteritis.[14,15]

The incidence of diarrhea was significantly reduced with a fermented milk supplement containing *L. casei* DN-114 001 (15.9%) compared with yoghurt (22.0%).[16] Child care infants fed a formula supplemented with *L. reuteri* (American Type Culture Collection 55730) or *B. lactis BB 12* had fewer and shorter episodes of diarrhea than children fed regular formula, with no effect on respiratory illnesses.[17] Healthy children attending day care centers, with daily administration of *L. reuteri* DSM 17938 showed a significant effect in reduced episodes and durations of diarrhea and respiratory tract infection compared to placebo, with

Table 1. Probiotics and prevention of acute gastroenteritis

Author (year)[ref]	Strain	Incidence acute gastroenteritis		p
		Probiotic	Placebo	
Chouraqui (2004) [7]	*B lactis Bb* 12	28.3 %	38.7 %	NS
Hojsak[a] (2016) [8]	*B animaliss Bb* 12	64.4%	61.3%	NS
Sazawal (2010) [9]	*B. lactis* HN019 (+ prebiotic)	5.26 ep	5.44 ep	NS
Laursen (2017) [10]	*B. lactis* BB12 *L. rhamnosus* GG	64%	56%	0.14
Bocquet[a] (2013) [11]	*B. lactis* BB12	4.5 + 3.0 ep	4.9[b] + 3.2 ep	0.18
Oberhelman (1999) [12]	*L. rhamnosus* GG	5.21	6.02	0.028
Pedone (2000) [16]	*L. casei* DN-114 001	15.9%	22%[c]	0.03
Weizman (2005) [17]	*L. reuteri* ATC 55730	0.02 ep	0.31 ep	<0.001
	B. Lactis BB12	0.13 ep		

[a]common infections reported (not only acute gastroenteritis)
[b]prebiotics group
[c]yoghurt
ep=episodes
B=Bifidobacterium
L.=Lactobacillus

consequent cost savings for the community [18]. The number of doctor visits, antibiotic use, absenteeism from day school and parental absenteeism from work were significantly reduced in the *L. reuteri* group ($P < .05$).[18] According to a review, *L. reuteri* is reported to be effective in reducing the incidence of diarrhea in children attending day care centers.[19]

Should administration of probiotics to prevent AGE be recommended? Evidence from literature is limited and differs in design, strains administered, and outcomes measured. Preventive administration of some specific probiotic strains seems to decrease the incidence of AGE--although there are also negative trials[7,8] in regions with a very high incidence of the condition.

Nosocomial diarrhea

In 1994, the first report that showed a benefit of supplementation of infant formula with *B. bifidum* and *Streptococcus thermophilus* in reducing the incidence of acute diarrhea and rotavirus shedding in infants admitted to a chronic medical care hospital (Table 2) was published by Saavedra et al.[20] In contrast, *B. animalis subsp. lactis BB12* was not effective in preventing nosocomial infections when given to children of more than 1 year during an acute hospitalization.[21]

Data regarding *LGG* are contradictory. Prophylactic use of *LGG* was shown significantly to reduce the risk of nosocomial diarrhea in infants, particularly nosocomial rotavirus gastroenteritis, resulting in a number needed to treat of 4.[22] However, formula supplementation with *LGG* appeared ineffective in preventing nosocomial rotavirus infections, whereas breastfeeding was effective.[23] A randomized controlled trial showed that *LGG* (6×10^9 colony forming units (CFU)/day) together with vitamins B and C and zinc given for 15 days, starting on the first day of hospitalization, to children ranging from 0.5-5.0 years of age resulted in a reduced incidence of nosocomial infections.[24]

According to a review, administration of *LGG* and *B. bifidum* and *Streptococcus thermophilus* compared with placebo reduced the risk of healthcare-associated diarrhea.[25] Administration of two other probiotics (*L. reuteri* DSM 17938 and *L. delbrueckii* H2B20) was ineffective.[25] Currently there is sufficient evidence showing that *LGG* administrated in a dose of at least 10^9 CFU/day during a hospital stay can significantly reduce the risk for nosocomial diarrhea in a regular

Table 2. Probiotics and prevention of nosocomial diarrhea

Author (year) [ref]	*Strains*	Incidence nosocomial diarrhea		p
		Probiotic	Placebo	
Saavedra (1994) [20]	*B. bifidum* *Str. thermophilus*	7%	31%	0.035
Hojsak (2015) [21]	*B. animalis* BB12	8.0%	6.0%	NS
Szajewska (2001) [22]	*L. rhamnosus* GG	6.7%	33.3%	0.002
Mastretta (2002) [23]	*L. rhamnosus* GG	25.4%	30.2%	0.432
Bruzzese (2016) [24]	*L. rhamnosus* GG	9%	33%	0.016
Urbańska (2016) [27]	*L. reuteri* DSM 17938	6.4%	7.7%	NS
Wanke (2012) [28]	*L. reuteri* DSM 17938	33%	31%	NS

B=Bifidobacterium, Str=Streptococcus, L=Lactobacillus

pediatric ward.[26] So far, research has found no evidence of effectiveness of *L. reuteri* DSM 17938 in preventing nosocomial diarrhea in children.[27,28] Based on currently available evidence, there is evidence to recommend *LGG* when the use of probiotics for preventing nosocomial diarrhea in children is considered, as recommended by the Working Group on Probiotics from the European Society of Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).[29,30]

Antibiotic associated diarrhea

The prevention of antibiotic associated diarrhea (AAD) has been the subject of many investigations, both in children and adults. Most commonly used probiotics are *LGG*, *L. acidophilus*, *L. casei*, *B. ssp*, *Streptococcus ssp*, and the yeast *Saccharomyces boulardii* (*S. boulardii*). In general, most of these trials do show clear evidence of efficacy, with the two most effective strains being *LGG* and *S. boulardii*. Evidence is also emerging on the importance of the dose in reducing the incidence of this type of diarrhea, as well as the incidence of *Clostridium difficile* (*C. difficile*)-associated post-antibiotic diarrhea.[31] A yogurt combination of *LGG*, *L. acidophilus* and *B. BB12* was reported to be an effective method to reduce the incidence of AAD in children (Table 3).[32] *L. plantarum* DSM9843 was not better than placebo regarding the incidence of loose/watery stools, mean number of loose/watery stools, or the incidence of abdominal symptoms during antibiotic administration.[33] *L. reuteri* DSM 17938 was not effective in the prevention of diarrhea or AAD in children.[34] *S. boulardii* was shown to prevent AAD in children hospitalized because of a respiratory tract infection, and to be effective in the treatment of AAD in children that developed it in the placebo group.[35]

According to a review, moderate-quality evidence suggests that probiotics are associated with lower rates of AAD in children (aged 1 month to 18 years) without an increase in adverse events.[36] A Cochrane systematic review, analyzing data from 23 studies (3938 participants), estimates a pooled probiotic effect (RR 0.46; 95% CI: 0.35-0.61) with a number needed to treat of 10 [37]. A post hoc subgroup analysis to explore heterogeneity indicated that probiotics are effective among trials with a *C. difficile* associated diarrhea baseline risk >5%. The weakness of this kind of meta-analysis is that all probiotic strains are grouped together, while some strains might be more effective than others. Among the various probiotics evaluated, *LGG* or *S. boulardii* at 5–40 x 10^9 CFU/day may be appropriate given the modest number needed to treat and the likelihood that adverse events are very rare.[33] In a meta-analysis, *LGG* was reported to be effective in preventing AAD in children and adults treated with antibiotics for any reason, although with a moderate to low quality of evidence.[38] Moderate quality evidence suggests that probiotics are associated with a lower risk of *C. difficile* infection and very-low quality evidence suggests that probiotics are associated with fewer adverse events than either placebo or no treatment.[39] ESPGHAN recommends that, if the use of probiotics to prevent AAD is considered because of the existence of risk factors such as class of antibiotic(s), duration of antibiotic treatment, age, need for hospitalization, comorbidities, or previous episodes of AAD diarrhea, *LGG* (moderate Quality of Evidence

Table 3. Probiotics and prevention of antibiotic associated diarrhea

Author (year) [ref]	Strains	AAD		p
		Probiotic	Placebo	
Fox (2015) [32]	*L. rhamnosus* GG *B. lactis* Bb-12 *L. acidophilus* La-5[a]	0 %	18%	0.025
Olek (2017) [33]	*L. plantarum* DSM9843	39%	44.5%	NS
Kołodziej (2018) [34]	*L. reuteri* DSM 17938	6.5%	11.4%	NS
Shan (2013) [35]	*S. boulardii*	4.3 %	19.4%	<0.001

[a]both probiotic and placebo groups received yoghurt;
AAD=Antibiotic Associated Diarrhea
L.=Lactobacillus
B.=Bifidobacterium
S.=Saccharomyces

(QoE), strong recommendation) or *S. boulardii* (moderate QoE, strong recommendation) should be used.[40] *LGG* survival is sensitive to penicillin which might make this probiotic ineffective in when this type of antibiotic is in use.[41]

A Cochrane analysis included 33 studies with 6352 participants, assessing the following probiotics: Bacillus spp., Bifidobacterium spp., Clostridium butyricum, Lactobacilli spp., Lactococcus spp., Leuconostoc cremoris, Saccharomyces spp., or Streptococcus spp., alone or in combination.[42] The overall evidence suggests a moderate protective effect of probiotics for preventing AAD. The number needed to treat for an additional beneficial outcome was 9 (95% CI 7 to 13).[42BB] If only studies with high doses of probiotics are considered (≥ 5 billion CFUs per day), the number needed to treat for an additional beneficial outcome to prevent one case of diarrhea is reduced to 6 (95% CI 5 to 9).[42]

If the use of probiotics to prevent *C. difficile*-associated diarrhea is considered, *S. boulardii* (low QoE, conditional recommendation) is recommended.[30,40] Other strains or combinations of strains have been tested for this purpose, but evidence for efficacy is insufficient.[40] Despite the need for further research, hospitalized patients, particularly those at high risk of *C. difficile* associated diarrhea, should be informed of the potential benefits and harms of probiotics.[30] *S.* boulardii, and more recently fecal microbiota transplantation have become valid forms of prevention and/or therapy for *C. difficile* colitis.[43] Analysis has shown that the potential for using *S. boulardii* as AAD prophylactic treatment in adult hospitalized patients in Belgium would, based on 831,655 hospitalizations with antibiotic administration in 2014, result in a € 50.3 cost saving per patient.[44] Generalized use of *S. boulardii* in hospitalized adults treated with antibiotics could result in total annual savings up to € 41.8 million for the Belgian health care.[44] There are no data on the economic impact of prophylactic probiotic administration to prevent AAD in children.

Probiotics and prevention of infantile colic

Infantile colic describes excessive crying of unknown cause in otherwise well infants.[45] The incidence is approximately 10% to 40% of infants worldwide and is similar among formula-fed and breast-fed infants. Proposed causes include alterations in fecal microbiota, allergy to cow's milk protein, lactose malabsorption, gastrointestinal immaturity or inflammation, increased serotonin secretion, poor feeding technique, and maternal smoking or nicotine replacement therapy.[46] The vast majority of published articles concerning treatment of infantile colic have evaluated probiotics as a therapeutic tool and have shown that *L. reuteri* DSM 17938 was effective in reducing infantile colic mainly in breastfed infants.[47] Six studies included for subgroup meta-analysis on probiotic treatment, notably *L. reuteri*, demonstrated that probiotics appear an effective treatment, with an overall mean difference in crying time at day 21 of -55.8 min/day (95% CI -64.4 to -47.3, P=0.001).[48]

Only limited data are available regarding the use of probiotics in the prevention of this common entity in infancy, since only two clinical studies have been published. The first trial included 468 infants, breastfed as well as formula-fed, revealing that compared with placebo, the daily administration of *L. reuteri* DSM 17938, from day 3 for 90 days, resulted in a significant reduction in crying time by approximately 51 minutes per day at 1 month, and by 33 minutes per day at 3 months. There were also significantly less emergency room visits, lost parental working days and use of additional medications in infants who received the probiotic agent. A cost-benefit analysis revealed significant savings as well.[49] Although almost half of the infants were breast fed, results are not given separately for breast or formula fed infants. Preventive administration of *L. reuteri* was shown to reduce the number of consultations because of colic, and to reduce health care cost, both for the family (88 €) and for the community (104 €).[50,51] The second study was based on a secondary analysis of data from a trial of *LGG* supplementation, for the first 6 months of life in 184 infants. No significant differences were found between the infants exposed to early *LGG* supplementation, versus infants exposed to the control intervention.[52] In a third small study, with poorly-defined methods, preventive administration of *B. breve* B632 and BR03 resulted in a mean duration of crying of 12.14 minutes on average in the probiotics group and of 46.65 minutes in the placebo group during the third month of supplementation. However, no significant differences were noticed during the first or second months of supplementation [53]. In view of these conflicting results, further controlled large-scale strain-specific trials are warranted. *L. reuteri* DSM17938 has been recommended at a dose of 10^8 CFU once daily as preventive strategy of infantile colic (level I evidence).[30]

A Cochrane review including six studies with 1886 participants, compared probiotics with placebo: two studies examined *L. reuteri* DSM 17938, two examined multi-strain probiotics, one *examined L. rhamnosus,* and one examined *L.paracasei* and *B.animalis*.[54] No clear evidence could be found that probiotics are more effective than placebo at preventing infantile colic; however, daily crying time appeared to reduce with probiotic use compared to placebo.[54] In summary, although there is insufficient evidence for a recommendation, available data suggest that specific probiotics strains such as *L. reuteri* DSM 17938 may prevent infantile colic in some infants. Since *L reuteri* administration is reported to be safe, the major issue of concern is the cost-benefit.

Probiotics and prevention of necrotizing enterocolitis (NEC)

NEC is in some countries among the most common and devastating diseases in neonates and thus has become a priority for research.[55] The pathophysiology of classic NEC is incompletely understood, but epidemiologic observations strongly suggest a multifactorial cause.[56] Inappropriate initial microbial colonization in preterm infants is considered to be an important risk factor for NEC,[57] particularly since NEC does not occur until at least 8 to 10 days postpartum, at a time when anaerobic bacteria have colonized the gut. Furthermore, experimental NEC does not occur in germ-free animals,[58] and infants with NEC frequently have concomitant bacteraemia and endotoxemia.[59] *C. perfringens* is associated with NEC from the first meconium till just before NEC onset.[60] In contrast, post-meconium, increased numbers of staphylococci were negatively associated with NEC.[60]

L. reuteri DSM 17938 administered to preterm infants was shown to be safe and to reduce significantly feeding intolerance.[61] No significant differences were found for any other secondary outcomes such as necrotizing enterocolitis (NEC), hospital stay, sepsis and diarrhea.

In contrast, a meta-analysis concluded that bifidobacteria administration reduced the relative risk of developing NEC (RR 0.38, 95% CI 0.25-0.58; $P < 0.00001$) or death (RR 0.74, 95% CI 0.60-0.92; $P = 0.006$), but no significant difference in the incidence of sepsis was found (RR 0.87, 95% CI 0.73-1.03; $P = 0.11$).[62] In a retrospective observational study, the incidence of NEC in 640 very low birth weight infants with a median gestational age of 28.7 weeks that were given LGG was 12 % compared to 10.2 % before the implementation of the probiotic administration.[63] The conclusion of this trial was that *LGG* increased the risk to develop NEC.[63] However, another group

came to an opposite conclusion with a comparable protocol in a retrospective observational study performed in a resource limited setting: *LGG* reduced significantly NEC ≥ Stage II and the composite outcome of NEC ≥ Stage II/mortality in preterm infants.[64] According to a strain-specific network meta-analysis, only 3 of 25 studied probiotic treatment combinations (the combination of *B.bifidum* NCDO 1453 and *L. acidophilus* NCDO 1748 (based on 2 studies with 494 infants); the combination of *B. bifidum, B. infantis, B. longum, and L. acidophilus* (based on 1 study with 186 infants); and the combination *of B. infantis, L. acidophilus, L. casei, L. plantarum, L. rhamnosus, and S. thermophilus* altogether (based on 1 study with 150 infants) showed significant reduction in mortality.[64] Seven treatments reduced NEC incidence (*B.lactis* Bb-12 or B94, based on 5 trials with 828 infants; *L. reuteri* ATCC 55730 or DSM 17938, based on 4 studies with 1459 infants; *L. GG,* based on 6 studies with 1507 infants); the combination of *B. bifidum, B. infantis, B. longum, and L. acidophilus,* based on 2 studies with 247 infants; the combination of *B. infantis* ATCC 15697 and *L. acidophilus* ATCC 4356, based on one study with 367 infants; the combination of *B. infantis* Bb-02, *B. lactis* Bb-12, and *S. thermophilus* TH-4, based on 2 studies with 1244 infants; and the combination of B.longum 35624 and *LGG,* based on 2 studies with 285 infants, 2 reduced late-onset sepsis (combination of *B. bifidum, B. infantis, B. longum,* and *L. acidophilus* (based on 2 studies with 247 infants); for the combination of *B. longum* R00175, *L. helveticus* R0052, *L. rhamnosus* R0011, and *S. Boulardii* CNCM I-1079, based on 3 studies with 241 infants, and 3 reduced time until full enteral feeding (*L. reuteri* ATCC 55730 or DSM 17938, based on 3 studies with 626 infants); for the combination of *B. bifidum, B. infantis, B. longum,* and *L.acidophilus,* based on 2 studies with 247 infants; and for the combination of *B. longum* BB536 and *LGG,* based on 1 study with 94 infants.[64] There was no clear overlap of strains, which were effective on multiple outcome domains.[64] The network meta-analysis showed efficacy in reducing mortality and morbidity in only a minority of the studied strains or combinations. This may be due to an inadequate number or size of randomized controlled trials, or due to a true lack of effect for certain species.[65] The importance of strain specificity and a demonstration of safety is highlighted since a specific product (Infloran™) was reported to increase the incidence of NEC.[66] Further large and adequately powered randomized controlled trials using strains with the greatest apparent efficacy will be needed to define more precisely optimal treatment strategies.

Compared to formula feeding, breastmilk protects for NEC. However, both in breast and formula fed preterms probiotics seem to be one of the most significant advances in NEC prevention at present because of the significant range of beneficial effects at various levels of gut function and defense mechanisms.[4,30] While some authors published strong evidence to support general effects of probiotics as a group, rather than focusing on strain specific effects, others do question this approach and conclude that there is insufficient evidence to guide the selection of the most effective strains.[4-6]

Probiotics and prevention of regurgitation

Regurgitation is one of the most common functional gastrointestinal disorders in infants, with a significant impact on quality of life of the infants and the family.[67,68] Administration of *L. reuteri* DSM 17938 prevented regurgitation episodes during the first month of life in exclusively breastfed infants, when compared to historic controls.[69,70] Prophylactic use of *L. reuteri* DSM 17938 from birth to 3 months resulted in a decreased number of episodes of regurgitations per day, compared to no probiotic (2.9 vs 4.6; $P < .01$).[49] This finding is likely to be related to the faster gastric emptying induced by the probiotic.[70] A synbiotic infant formula, supplemented with *B. lactis* and fructo-oligosaccharides, with lactose and a whey/casein 60/40 protein ratio was tested in 280 infants over 3 months and resulted in a lower incidence of daily regurgitation (10.9% of all infants) compared to the median prevalence for a similar age according to historic data from literature (median value of 26.7%).[71] Some probiotic strains may enhance gastric emptying and therefore have a beneficial effect on functional gastro-intestinal symptoms of the esophagus and stomach.

L. reuteri DSM 17938 decreased dysbiosis in children treated with proton pump inhibitors.[72] After

12 weeks of treatment with a proton pump inhibitor, dysbiosis was diagnosed according to the results of a glucose hydrogen breath test in 56.2% of the children in the placebo group, compared to 6.2% of the children in the probiotic group ($P < 0.001$).[72] Bacterial overgrowth was detected in 5% of controls, which is similar to the group treated with *L. reuteri* and proton pump inhibitors.[72]

There is insufficient evidence from literature to recommend routine administration of some specific probiotic strains for the prevention of regurgitation. However, no study suggested that probiotics may increase the risk for regurgitation. *L. reuteri* DSM 17938 may decrease the adverse effects of proton pump inhibitors on the GI microbiota.

Probiotics and prevention of constipation

A meta-analysis concluded that there is insufficient evidence to recommend pre-, pro- or synbiotics in the treatment of children with functional constipation.[73] Another meta-analysis showed that some probiotic strains increase stool frequency in Asian children.[74] A synbiotic infant formula, supplemented with *B. lactis* and fructo-oligosaccharides, was tested in 280 infants over a 3-month period and showed a lower incidence of constipation (3.2%) than the incidence reported in literature (7.8%).[71] *L. reuteri* DSM 17938 administration resulted in a statistically significant increase in mean number of defecations per day compared to placebo in infants (4.2 vs 3.6; $P < .01$).[48] Although there is insufficient evidence for a recommendation, there are some data that preventive administration of probiotics to infants may increase the number of defecations per day.

Probiotics and prevention of *Helicobacter pylori*

Lactobacilli, as an adjunct to triple therapy, increases *Helicobacter pylori* eradication rates and reduces the incidence of therapy-related diarrhea in children.[75] According a meta-analysis of data obtained with *S. boulardii* in 11 RCTs (2200 participants, among them 330 children), the yeast probiotic is likely to increase the eradication rate by about 10 percent and to decrease the adverse effects of the eradication therapy.[76] A meta-analysis of 5 studies (434 participants), concluded that the lactobacilli strains differed among studies: *L. acidophilus* and *L. rhamnosus*, *L. reuteri*, *L. casei*, *LGG*, and compound lactobacillus but detailed information was rarely provided of the strains used.[75] However, there are no data on the prevention of *Helicobacter pylori* infection by the administration of probiotics.

Probiotics and small bowel bacterial overgrowth

There are a few studies in adults showing that the clinical consequence of small intestinal bacterial overgrowth can be treated effectively by administration of probiotics.[77] However, *L. rhamnosus* R0011 (1.9×10^9 CFU) and *L. acidophilus* R0052 (0.1×10^9 CFU) failed to decrease the incidence of small bowel bacterial overgrowth in children treated with omeprazole.[78] However, we could not find any information on the use of probiotics in the prevention of this condition.

Probiotics and prevention of irritable bowel syndrome

Although there are some data that some specific strains alleviate pain in children with irritable bowel syndrome,[79,80] we could not find information on prevention.

Probiotics and prevention of inflammatory bowel disease

No randomized controlled trials were found evaluating if preventive administration of probiotics may decrease the number of flares of inflammatory bowel disease in children.

Conclusion

The authors of this review strongly believe in strain and product specificity in probiotic research. Extrapolation from studied strains to unstudied strains and products could lead to erroneous conclusions. Clinical trials using commercialized products should give attention to influencing factors such as product quality and shelf life.

The ability to impact the microbiome with probiotics is an interesting approach in the

prevention of GI diseases, but studies on probiotic administration to prevent GI disorders are limited. Most studies focus on treatment and not prevention. The studies available on prevention of gastro-intestinal diseases in children focus on infectious, nosocomial and antibiotic-associated diarrhea or NEC, and there are some studies on infantile colic. Studies on the prevention of NEC differ in design and strains tested. Partly for this reason, there is no consensus to recommend the routine administration of probiotics to preterm infants to prevent NEC. The possibility of serious adverse effects in preterm infants should also be considered in continuing research.

There is also no consensus if probiotics should be administered routinely to normal infants to prevent acute gastroenteritis, AAD and infantile colic. The best evidence for benefit regards *B. lactis* (for acute gastroenteritis), *S. boulardii* and *LGG* (for AAD) and *L. reuteri* DSM 17938 for infantile colic, for regurgitation and stool composition. Despite the lack of evidence, many infant formulae do contain probiotics and thus many infants are exposed to daily intake of probiotic strains. Research is inadequate to judge whether or not to recommend the use of these products in artificially fed infants.

Overall there are insufficient data to recommend routine administration of probiotics to prevent GI disorders. However, one could also consider that preventive probiotic administration is unlikely to be harmful or cause adverse effects except possibly in very vulnerable infants such as prematures and that preventive administration of probiotics can be considered because of the safety profile even if the evidence suggesting benefit is limited so far.

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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ORIGINAL PAPER

The Impact of Nutritional Status and Body Mass Index on Rehabilitation Outcomes in Patients Receiving Home-based Medical Care

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Abstract

Background: Home-based medical care is expanding rapidly in Japan.
Objectives: We aimed to identify the factors associated with outcomes of therapy in patients receiving home-visit rehabilitation.
Methods: One hundred twenty-one patients receiving home-based rehabilitation were investigated. Nutritional status was assessed by the Mini Nutritional Assessment Short Form (MNA-SF). The Functional Independence Measure (FIM) was employed to assess the activities of daily living (ADL). The body mass index (BMI), medical history, and orthopaedic disease-related pain were also recorded. The primary outcome was the improvement in FIM scores in one year.
Results: A total of 19 (17%) patients were malnourished and 58 (48%) were at risk of malnutrition. Malnourished patients had a lower FIM score at initiation than those at risk of malnutrition or with normal nutritional status. Only changes in patients' BMI and MNA-SF scores over one year were significantly associated with improved FIM scores ($p = 0.0079$ and $p = 0.0049$, respectively). No association was noted with the other factors.
Conclusions: This is the first report to demonstrate that changes in MNA-SF scores and BMI are significantly associated with rehabilitation outcomes in home-based care. Nutritional management is essential along with rehabilitation to improve ADL in the long-term home care setting.

Keywords home-based medical care, nutritional status, body mass index

Introduction

The number of patients receiving home-based medical care in Japan has been steadily on the rise.[1] This is primarily owing to the rapid growth of the older adult population in Japan, which has led to remarkable increases in medical expenses, and subsequent reductions in hospital-based medical care.

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Rehabilitation is the medical care intended to improve quality of life (QoL) in patients with impaired ADL, either due to disease, or disuse. Improvement of ADL is an essential part of acute and convalescent hospital care. Since most patients are able to receive hospital care only for a limited period of time, rehabilitation needs to be continued in the home-based setting. Rehabilitation practiced in the home care setting is offered by visiting therapists. Patients suitable for home- based medical care are either late in the convalescent phase, or in a chronic phase, and are unable to commute to the hospital or neighbourhood clinic due to several reasons including impaired mobility, and severe illness. Consequently, home rehabilitation, intended to improve or maintain ADL, is essential for enhancing social activity, and QoL. In contrast to hospital care, home based medical care is a relatively long- term commitment, which also includes management in the terminal stages.

Malnutrition is common in older people receiving care in long-term care facilities, with a prevalence between 12% and 54%.[2] The prevalence varies, with considerable differences depending on the settings. The prevalence of malnutrition in rehabilitation facilities, general hospitals, nursing homes, and in the community, being 50.5%, 38.7%, 13.8%, and 5.8%, respectively.[3] According to our previous report, the prevalence of malnutrition in the home-care setting is 34%, rising to 75% when at-risk patients are included.[4] Rehabilitation outcomes have been known to be poorer in the hospital setting, among malnourished patients with stroke, chronic heart failure, chronic obstructive pulmonary disease, and a variety of other diseases.[5,6] In a cohort of patients who received rehabilitation in the convalescent ward due to hospital-associated deconditioning, poor rehabilitation outcomes were found in 91% of malnourished patients, which was worse than that of patients with normal nutrition.[7]

Although the number of patients receiving home- rehabilitation has been increasing in Japan's current healthcare scenario, no reports are available from this setting. Therefore, the present study aimed to investigate rehabilitation outcomes, and their relationship with nutritional, and other factors, in patients from the long term home-based medical care setting.

Materials and Methods

This was a retrospective, observational study, conducted on patients who received rehabilitation in home-based medical care settings. All therapists involved in this study were from the single Japanese orthopaedic medical corporation, which has a home visiting rehabilitation division, with 34 home-visit therapists engaged in home-rehabilitation therapy. In order to identify the factors associated with outcomes of long term home rehabilitation, 121 patients who received home rehabilitation, continuously, for one year in the past two years (between January 2, 2016 and January 2, 2018), were analyzed.

The patients were prescribed physical therapy once or twice a week, including motion exercises, resistance training, physical restoration, movement exercises, and ambulation exercises at home. Each session of physical therapy was equal to 1 to 2 units (1 rehabilitation unit equated to 20 minutes of therapy). The nutritional status was assessed by the Mini Nutritional Assessment Short-Form (MNA-SF) at initiation of home rehabilitation, and after one year.[8,9] The MNA-SF comprises six questions that address: (1) the decline in food intake over the past 3 months, (2) weight loss over the past 3 months, (3) mobility, (4) psychological stress or acute disease in the past 3 months, (5) neuropsychological problems, and (6) the body mass index. The ADL were evaluated by the Functional Independence Measure (FIM).[10] The FIM consists of 18 items composed of 13 motor tasks, namely, eating, grooming, bathing, upper body dressing, lower body dressing, toileting, bladder management, bowel management, bed-to-chair transfer, toilet transfer, shower transfer, locomotion (ambulatory or wheelchair level), and negotiating stairs. It also includes 5 cognitive tasks, namely, cognitive comprehension, expression, social interaction, problem-solving, and memory. The tasks are rated on a 7- point ordinal scale, which ranges from total assistance, scored 0, to complete independence, scored 7. The scores range from 18 to 126, according to the independence of the functional level. Patients with FIM scores higher than 108 are considered to be independent, whether they extra time, or a support device.[11] The BMI, main basal disease, history of musculoskeletal disease, existence of

orthopaedic pain, and feeding route (oral intake, enteral nutrition, or parenteral nutrition), were obtained from the interview and the medical records.

The outcome of home rehabilitation was classified into three categories, improved, maintained, and deteriorated, in accordance with the differences of the FIM score between point of initiation, and one year later. The patients were then divided into two groups, the "improved or maintained" group, and the "deteriorated" group. The patients-related factors were then analyzed to identify the factor that was related to the FIM score. Statistical analysis was performed using SPSS for Windows, Version 24 (IBM SPSS, Inc., Chicago, IL, USA). The patients' characteristics were compared using a chi-square test, as appropriate. A p value<0.05 was considered statistically significant.

Results

During the study period, 121 patients including 58 men, and 63 women, continuously received home rehabilitation, for longer than one year. The patients' characteristics are summarized in Table 1. Eleven patients (11%) were younger than 65 years. The remaining 110 patients (91%) were older than 65 years, with an average age of 79. The basal diseases in this cohort were mostly various chronic conditions. The sequelae of strokes were most common in this group, followed by Parkinson's disease, and Alzheimer's disease. Around half of the patients had a history of musculoskeletal conditions, including vertebral compression fractures, hip fractures, and knee arthroplasty. More than half of the patients experienced orthopaedic pain at the point of initiation. The level of pain was evaluated by the visual analogue scale (VAS), and the pain in all patients was not continuous, did not exceed a score of 5 on the VAS, and was self-controlled.

The patients were classified into three groups according to their nutritional status, as assessed by the MNA-SF score (Table 1, 2). Patients with scores of 0–7 were considered to have malnutrition; those with scores of 8–11 were considered at risk of malnutrition, and those with scores of 12–15, were considered to have normal nutrition. At the point of initiation, the prevalence of malnutrition in this cohort was 17%, which rose to 22% in one year. Malnourished patients showed lower BMI and FIM scores, whereas that of patients with better nutritional status was higher (Table 2). The outcomes of continuous 1-year home rehabilitation, is shown in Figure 1. An improvement in the FIM score was noted in 40 patients (34%), while 21 (16%) maintained their scores. Deterioration of existing scores was noted in 60 (50%) patients.

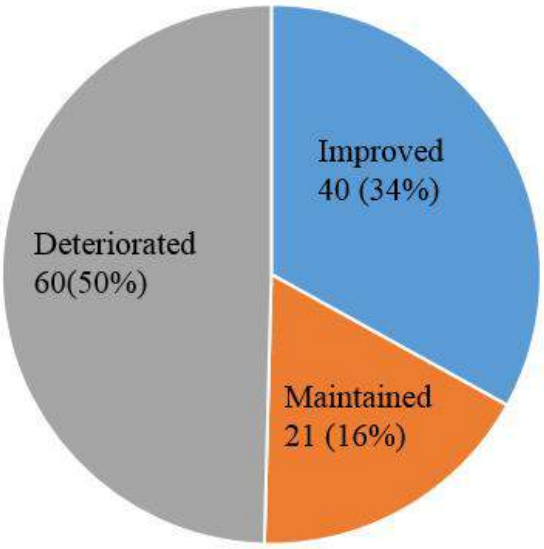

Figure 1. Rehabilitation outcomes after continuous 1-year home-based care (n=121)

We subsequently investigated the patient-factors associated with the rehabilitation- outcomes. As shown in table 3, a change in BMI, and MNA-SF scores, were the factors that were associated with rehabilitation-outcomes. The existence of orthopaedic pain, the age, the gender, the BMI, the FIM scores, and the MNA-SF scores at point of initiation were not found to be associated with outcomes.

Discussion

Japan is undergoing a significant demographic shift, with a large section of adults in the older age group. In addition, birth rate is on the decline. This has led to increases in medical expenses, with considerable impact on the national social economy. Government policies have been implemented to reduce medical expenses, and to deal with this problematic demographic change. These policies include reduction in numbers of hospital beds, and shortening the lengths of hospital stay.

Table 1a. Characteristics of subjects (n=121)

Characteristics	Numbers
Age (y), average (SD)	79±10
Gender, n(%)	
Male	58 (48)
Female	63 (52)
Main basal disease, n(%)	
Cardiovascular diseases	13 (11)
Gastroenterological diseases	3 (3)
Kidney and urological diseases	8 (7)
Cerebral and neurological diseases	61 (50)
Haematological diseases	2 (2)
Respiratory diseases	11 (10)
Metabolic diseases	8 (7)
Gynaecological diseases	2 (2)
Autoimmune disease	4 (3)
No specific basal disease	9 (8)
History of musculoskeletal disease (+), n(%)	61 (50.4)
Hip fractures	12
Knee arthroplasty	11
Vertebral compression fractures	17
Spinal canal stenosis	13
Other	8
Orthopaedic pain (+), n(%)	82 (67.7)
MNA-SF at point of initiation, average, (SD)	9.9±2.7
Malnutrition, n(%)	19 (17)
At risk of malnutrition, n(%)	58 (48)
Normal nutrition status, n(%)	44 (36)
MNA-SF in one year, average, (SD)	9.7±2.9
Malnutrition, n(%)	27 (22)
At risk of malnutrition, n(%)	54 (45)
Normal nutrition status, n(%)	40 (33)
Feeding route, n(%)	
Oral intake only	3 (2.4)
Oral intake and enteral nutrition	118 (97.6)
BMI at point of initiation, average, (SD)	21±3.9
BMI in one year, average, (SD)	21±3.8
FIM at point of initiation, average, (SD)	100±25.8
FIM in one year, average, (SD)	97±27.4

Consequently, home-based medical care has been expanding rapidly, and the number of patients receiving home-based medical care is on the rise. Home care patients receive rehabilitation within their permitted insurance coverage; its duration is usually longer, and frequency lower, than the intensive rehabilitation provided by hospital care. In general, home care patients regularly receive rehabilitation once or twice a week. The impaired ADL of elderly patients in long term care facilities have an adverse impact on their QoL.[12] Home rehabilitation should therefore be considered as a key factor in improving or maintaining patients' ADL, while enhancing their social activities, which contribute to improved QoL.

Rehabilitation outcome in long term home settings is worse than hospital settings. Only 34% of patients rehabilitated at home showed an improvement in FIM scores, compared to 90% in the convalescent hospital setting.[13] As we focused on evaluating outcomes of only long-term home-rehabilitation in this study, patients who received home rehabilitation for less than one year were excluded. A total of 210 patients attending our clinic

Table 1b. Details of main basal diseases (n=121)

Main basal diseases, n(%)	
Cardiovascular disease	13 (11)
Chronic heart failure	6
Chronic artrial flutter	2
Hypertension	3
Other cardiovascular diseases	2
Gastroenterological diseases	3 (3)
Hepatocellular carcinoma	1
Cholangiocarcinoma	1
Gastric cancer	1
Kidney and urological diseases	8 (7)
Chronic renal failure	5
Other kidney and urological diseases	3
Cerebral and neurological diseases	61 (50)
Alzheimer's disease	8
Parkinson's disease	12
Sequelae of strokes	33
Guillain-Barre syndrome	4
Other neurological disease	4
Haematological diseases	2 (2)
MDS (myelodysplastic syndromes)	1
Malignant lymphoma	1
Respiratory diseases	11(10)
Interstitial pneumonia	1
Lung cancer	3
COPD (chronic obstructive pulmonary disease)	1
Other respiratory disease	4
Metabolic disease	8 (7)
Diabetes mellitus	7
Hyperlipidemia	1
Gynecological disease	2 (2)
Uterus cancer	2
Autoimmune disease	4 (3)
SLE (systemic lupus erythematosus)	2
RA (rheumatoid arthritis)	2
No specific basal disease	9 (8)

Table 2. Nutritional status and average of FIM and BMI

MNA-SF at point of initiation	n(%)	FIM, average(SD)	BMI, average(SD)
Malnutrition	19(17)	83±33	18±2
At risk of malnutrition	58(48)	98±26	20±3
Normal nutrition status	44(36)	110±15	24±2

MNA-SF in one year	n(%)	FIM, average(SD)	BMI, average(SD)
Malnutrition	27(22)	75±33	18±2
At risk of malnutrition	54(45)	102±22	20±3
Normal nutrition status	40(33)	107±20	25±3

received home rehabilitation during the two-year observation period. Among them, 121 received continuous rehabilitation for longer than one year, while 89 received shorter rehabilitation care, lasting less than one year. A total of 44/89 short-term care patients demonstrated improved FIM scores, and had discontinued home-based care, as either their rehabilitation goals were accomplished, or they had

Table 3. Analysis of the factors associated with home rehabilitation outcome

		FIM		
		Improved group (n=41)	No-improvement group (n=80)	p value
Age	80>	24	33	0.714
	80<	17	47	
Gender	Male	22	36	0.3669
	Female	19	44	
Orthopedic pain	No	12	27	0.6176
	Yes	29	53	
FIM at the point of initiation	108<	21	46	0.6887
	108>	20	34	
BMI at the point of initiation	20<	29	58	0.5107
	20>	13	22	
BMI change	Increase or no change	28	33	0.0079
	Decrease	10	37	
MNA at the point of initiation	8～14	26	43	0.3094
	0～7	15	37	
MNA in one year	8～14	32	53	0.179
	0～7	9	27	
MNA change	Improve or no change	29	35	0.0049
	Deterioration	12	45	

been transferred to the outpatient rehabilitation services. Considering the entire patient cohort, regardless of the rehabilitation period, outcomes were better, with 40% showing improved FIM scores. The efficacy of physical rehabilitation is not the same in the different phases of rehabilitation therapy. In Japan, owing to the insurance system, cases of stroke or orthopaedic diseases receive acute rehabilitation for two weeks in the acute hospital setting, followed by convalescent rehabilitation for a maximum of six months in the convalescent hospital setting.[14] Most of the recovery of patients' ADL usually occurs in the acute and convalescent phase, with little recovery during the maintenance phase, which is a part of home rehabilitation. Compared to long term care facilities, stroke patients in acute and convalescent hospitals have a higher rate of recovery, as evidenced by improved FIM scores.[15]

Malnutrition is associated with poorer rehabilitation outcomes and physical function in patients with stroke, hip fracture, hospital-associated deconditioning, and a variety of other diseases.[16] The MNA-SF score, and the serum albumin level, have also shown to be significantly associated with ADLs in older in-patients, with hospital-associated deconditioning.[17] In general, the nutritional status at first screening is strongly associated with rehabilitation outcomes in the hospital setting.[17] However, in the present study, the nutritional status, BMI, and FIM at point of initiation, were not associated with rehabilitation outcomes in the long-term home care setting. This was probably because the nutritional status and the ADL scores at point of initiation are better in home-care patients, compared those in the hospital setting. The prevalence of malnutrition is much higher in hospital patients than in home care patients, the rates being 38.7% and 17%, respectively.[3] The average total FIM scores in the convalescent hospital and long term home care settings are 72, and 100, respectively.[18] A study showed that gains of more than 20 points in FIM

scores were noted in 51.4% of patients in the convalescent hospital setting, compared to only 2.4% among those receiving long term home care.[13] Consequently, the association between ADL improvements and patient-related factors are not evident in long term home care. Our results showed that changes in the MNA-SF score, and the BMI were significantly associated with rehabilitation outcomes. Deterioration of the nutritional status and loss of body weight were associated with poorer outcomes. It also indicated that, an improvement in patients' ADL may be expected, regardless of the independence level, and the nutritional status at point of initiation. Monitoring the nutritional status, and maintenance of the body weight are both important in improving the ADL by home rehabilitation, in the long term home care setting. These factors are also important in the hospital setting to ensure better rehabilitation outcomes. Nutritional supplements have been associated with improved outcomes in post-stroke rehabilitation.[19] Patients receiving intensive nutritional supplementation have shown more improvement on scores of total FIM.[19] A randomized controlled trial in acute stroke patients at nutritional risk, compared routine care with individualized nutritional care to prevent weight loss. The results showed that 20.7 % of the intervention group lost at least 5 % body weight compared with 36.4 % of the control group.[20] Nutritional intervention with resistance training during convalescent rehabilitation has been shown to improve skeletal muscle mass, volume, and ADL, in older patients.[21] About 70% of older people living in long term care facilities are malnourished; malnutrition, and total FIM score, were independently associated with the time taken to return home.[22] Reports from literature confirm the findings of this study, demonstrating the benefits of nutritional support on rehabilitation outcomes in patients in the hospital and home care setting.

Interdisciplinary nutrition management is recommended for patients who receive rehabilitation therapy in hospital setting.[16] The term "rehabilitation nutrition" has been coined based on the combination of both, rehabilitation, and nutrition care management.[16] It emphasizes the need for proper evaluation of the nutritional status, and the implementation of nutritional management, to maximize the efficacy of rehabilitation. It enhances the recovery of functionality in the elderly, and the disabled.[16] Management by a dedicated and specialized team has a positive impact on rehabilitation- nutrition, and this team-based medical practice has been expanding within the hospital setting.[23] However, the practice of management by a nutrition support team (NST) has just started in the home care setting, and only few reports are available on the efficacy of nutritional improvement in home-care patients [4]. In order to enhance the efficacy of rehabilitation in long term home care, nutrition care management, which is provided by a specialized team, is essential.

This study has some limitations. Firstly, laboratory data, including levels of albumin, haemoglobin, and cholesterol, were not analyzed in the present study, because therapists do not perform blood tests. There is a possibility of association between these biomarkers and home- rehabilitation outcomes. Secondly, we analyzed the rehabilitation outcome using the total FIM score, as the total FIM comprehensively reflects the patients' level of independence. We did not analyze motor-FIM, and cognitive-FIM separately in this study. Thirdly, the participants were limited to a single medical corporation. Cooperative, multi-institutional research will be required in the future to validate our findings.

Conclusion

In conclusion, home-rehabilitation outcomes in long-term home-based care settings are not as good as that of hospital-rehabilitation. A decrease in the body weight, and the MNA-SF score is associated with poor rehabilitation outcomes, in this setting. Nutritional management should be provided in conjunction with rehabilitation for better outcomes in the home care setting. Further research is needed on the effect of home NST, and multidisciplinary nutritional management, on rehabilitation outcomes.

Conflict of Interest

Statement of Ethics

Written informed consent was obtained from all the patients for the publication of this paper.

The protocol and study design were approved to be ethically acceptable by the chairman of our medical institute.

Disclosure statement
The authors have no conflicts of interest to declare.

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Author Contributions
KE, and NN contributed equally. NN was responsible for the article planning, and the manuscript preparation. KE was responsible for the data collection. All authors have read and approved the final manuscript.

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ORIGINAL PAPER

Selenium in Hyperthyroidism

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Abstract

Introduction: Thyroid gland has the highest selenium content compare with other endocrine organs. Enzyme that catalyzing thyroid hormone activation, iodothyronine deiodinases, were identified as selenocysteine-containing proteins. Selenium levels in soil and rice consumed in Indonesia were lower than in several other countries, which can increase the risk of selenium deficiency that has been associated with various type of thyroid diseases.

Methods: This is an article review of the current literatures published up to November 2018 about the role of selenium in hyperthyroid.

Result: Several studies have shown that selenium supplementation can be beneficial in patients with Graves disease and autoimmune thyroiditis. Selenium has an important immunomodulatory effect, but the effects of selenium supplementation in hyperthyroid has not been conclude. Data regarding selenium intake, prevalence of deficiency, and the relationship between selenium and thyroid disease in Indonesia are limited. Various study of selenium supplementation in thyroid disease provide controversial results, so there are no guidelines that include selenium as standard therapy hyperthyroid. Selenium supplementation can enhance the restoration of biochemical euthyroidism in Graves disease and was associated with a significant decrease in the levels of thyroid peroxidase antibodies in autoimmune thyroiditis.

Conclusions: Micronutrients that play a role in thyroid hormone synthesis and maintain thyroid function in addition to selenium are iodine, iron, zinc, and vitamin A. By correcting the deficit of selenium, and meeting other micronutrient requirements may provide health benefits in patient with hyperthyroid.

Keywords selenium, hyperthyroid, Graves disease, autoimmune thyroiditis

Introduction

Hyperthyroidism or thyrotoxicosis is a clinical condition due to inappropriately high synthesis and secretion of thyroid hormones by the thyroid gland. In the United States, the prevalence of hyperthyroidism is around 1.2%; 0.5% overt, and 0.7% subclinical. The most common cause of hyperthyroidism is Grave's disease, toxic multinodular goiter, and toxic adenoma.[1] *Riset*

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Kesehatan Dasar (Riskesdas) 2013 in Indonesia, stated that the prevalence of hyperthyroidism in the Indonesian population aged 15 years or older was 0.4% or more than 700,000 persons.[2] Thyroid abnormalities occur very frequently in the population, located around 10-15% of the total population.[3]

The thyroid is a gland that contains high selenium compared to other endocrine organs. Selenium in the form of selenoprotein is important to maintain thyroid function.[4] Selenoproteins (glutathione peroxidase and thioredoxin reductase) also act as cellular antioxidants and protect the thyroid gland from damage caused by hydrogen peroxide and reactive oxygen species. The most important enzymes and are directly involved in thyroid hormone activation, iodothyronin deiodinases, are also selenoproteins. Selenium deficiency, especially those that occur in conjunction with iodine deficiency, will interfere with the synthesis and metabolism of thyroid hormones and contribute to the incidence of goiter, hypothyroidism, and autoimmune thyroid disease. Lower selenium levels were observed in newly diagnosed Graves disease and autoimmune hypothyroidism, but correlations of selenium with serum thyroid peroxidase (TPO) and thyroglobulin autoantibodies (TgAb) are less consistent. The exact molecular, cellular and systemic mechanisms contributing to the obvious relationships among Se status, iodine availability and handling, and thyroid function and the maintenance of its integrity remain to be studied.[5]

In Indonesia, previous studies was found that selenium levels in soil was low, likewise the selenium intake and selenium content in rice consumed by Indonesian people were lower than some other countries, which could increase the risk of selenium deficiency.[6,7] Selenium is most commonly found on the ground and a balanced diet should provide enough selenium for thyroid hormone synthesis. Selenium deficiency occurs in patients with impaired gastrointestinal absorption or receiving long-term parenteral nutrition therapy, as well as people living in areas where selenium content in their soil is very low. Providing selenium supplementation is very important in these patients to prevent dysfunction of the thyroid.[8]

In Graves disease, several studies have shown that selenium supplementation can enhance the restoration of biochemical euthyroidism.[9] Selenium supplementation has also been shown to reduce thyroid peroxidase antibodies (TPOAb) in autoimmune thyroiditis.[10] Immunomodulatory effects of selenium may causing a decrease in the release of proinflammatory cytokines,[11] but the effects of selenium supplementation that clinically relevant are still unclear. Research on selenium and its relationship to hyperthyroidism in Indonesia is still very limited. This paper will explain the role of selenium in hyperthyroidism, so that it is expected to increase knowledge about micronutrients that might help in prevention or therapy.

Hyperthyroidism

Hyperthyroidism or thyrotoxicosis can appear if (i) the thyroid is excessively stimulated (Graves disease); (ii) constitutive activation of thyroid hormone synthesis and secretion, that is cause autonomous release of excess thyroid hormone (toxic multinodular goitre, solitary toxic nodule, and familial non-autoimmune hyperthyroidism); (iii) thyroid are released in excessive amounts owing to autoimmune, infectious, chemical, or mechanical insult; or (iv) there is exposure to extrathyroidal sources of thyroid hormone (struma ovarii, metastatic differentiated thyroid cancer) or exogenous (factitious thyrotoxicosis).[1,12]

The common causes of hyperthyroidism are Graves disease, toxic multinodular goitre, toxic adenoma, and painless thyroiditis. Graves disease is an autoimmune disease in which thyroid-stimulating antibodies (*thyrotropin receptor antibodies*, TRAb) will activate thyroid-stimulating hormone (TSH) receptors and triggering thyroid hormone synthesis.[1,13] In addition to TRAb, TgAb and TPOAb can also be detected in patients with Graves disease.[14] Risk factors for Graves disease are female and personal or family history of an autoimmune disorder. Toxic multinodular goitre is the most common cause hyperthyroidism in older persons who are living in iodine deficient areas. Nodules arise from replication of clonogenic cells that leads to a mutation of TSH receptors, if a single nodule detected, it is called a toxic adenoma.[13] Other etiology is painless or silent thyroiditis. It is an

autoimmune that causes a destruction of thyroid follicles and leading to release of preformed thyroid hormones into the circulation.[15] Gestational hyperthyroidism can occur in the first trimester of pregnancy. Placental beta human chorionic gonadotropin (β-hCG), which shares structural features with TSH, has stimulatory action on the thyroid gland. β-hCG mediated hyperthyroidism can also caused by hyperemesis gravidarum or gestational trophoblastic tumor.[16]

The clinical manifestations of hyperthyroidism ranges from asymptomatic to thyroid storm. Increasing of thyroid hormone amplify catecholamine signaling through increased numbers of beta-adrenergic receptors, and resulting adrenergic symptoms (palpitations, heat intolerance, diaphoresis, tremor, stare, lid lag, hyper defecation) are the most common clinical manifestations of hyperthyroidism.10 Despite of an increased appetite, hypermetabolism will induces weight loss in hyperthyroid patients. Other symptoms that can occur are neuromuscular symptoms (weakness of proximal muscles), psychiatric symptoms (range from anxiety to frank psychosis), atrial fibrillation (10% to 15% of patients), or heart failure (5.8% of patients).[13]

If there is clinical suspicion of hyperthyroidism, then laboratory testing should be done (Figure 1). Serum TSH has the highest sensitivity and specificity for hyperthyroidism. Free thyroxine (T4) and total triiodothyronine (T3) levels need to be tested if the TSH level is low (free T3 assays are poorly validated). The physicians can also order all three tests in one time to make the diagnosis more efficiently. To diagnose Graves disease, serum level of thyroid-stimulating immunoglobulins or TSH receptor antibodies helps distinguish from other causes of hyperthyroidism in patients who lack clinical signs and symptoms of Graves disease that pathognomonic and have a contraindication to radioactive iodine uptake and scan.[13]

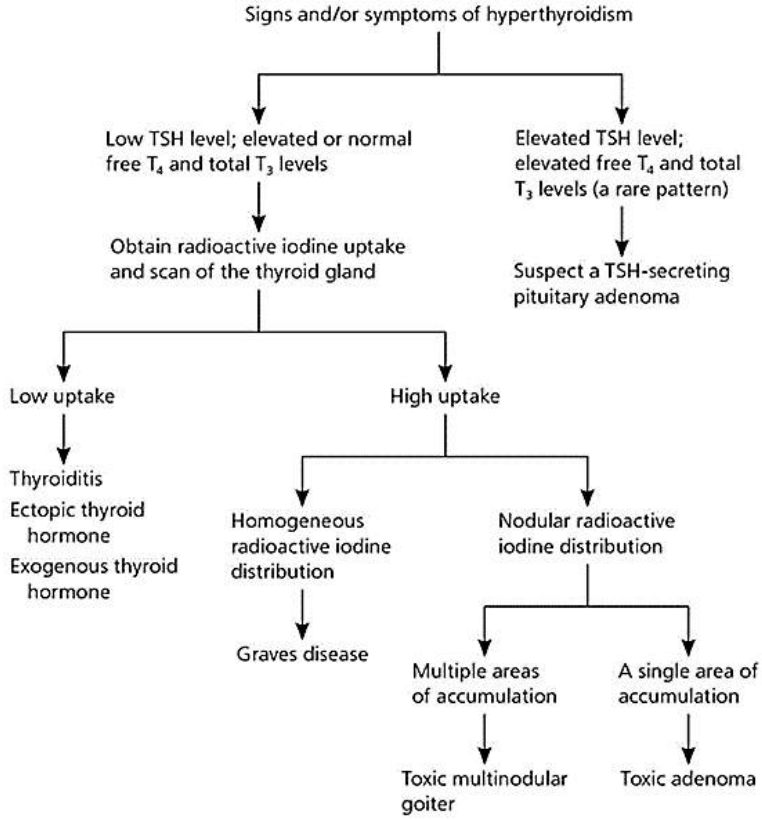

Figure 1. Algorithm for hyperthyroidism diagnosis
T3, triiodothyronine; T4, thyroxine; TSH. thyroid-stimulating hormone
Source: reference no [13]

Metabolism, Daily Requirement, and Food Sources of Selenium

Selenium is a micronutrient that was first discovered in 1817. Selenium from the Greek, would be the "moon", because selenium a sheen similar to that of the moon.[17] Selenium is available both in organic compounds (selenomethionine and selenocysteine) and inorganic compounds (selenite and selenate).[18] Selenium is present in food especially in organic forms, and probably absorbed in the small intestine especially by transcellular diffusion. The inorganic form of selenium, which is selenite or selenate are only found in small amounts in foodstuffs. There is a difference in absorption efficiency and bioavailability of selenium depending on the form (selenomethionine > selenocysteine > selenate > selenite).[19] The biological activity of selenium depends on absorption, retention, and excretion. Selenomethionine is absorbed more quickly and completely (98%) than sodium selenite (84%) and uptake by the liver occurs faster after administration of organic selenium rather than inorganic. In addition, selenomethionine is excreted less than sodium selenite, faecal excretion: 4 versus 18%, urinary excretion: 11 versus 17%, and total excretion: 15 versus 35%. Selenomethionine is retained in the body for 363 days, while sodium selenite 147 days, this slower turnover allows an efficient reutilization of selenomethionine. Because of these properties, high doses of selenomethionine or uncontrolled long-term supplementation should be avoided because this can cause tissue accumulation and selenium toxicity.[17] In other studies, increased selenite absorption occurs when given together with glutathione rather than given alone, this is probably due to to formation of selenodiglutathione, which may be absorbed differently from selenite.[20] Selenium excretion is mostly via urine (in the form of selenosugars and methylated as trimethylselenonium) which is about 60% of total excretion of selenium, 35% is excreted through feces, and in small amounts excreted through sweat, breathing, and saliva.[21,22]

Recommended dietary allowance of selenium in America and from European Commission (Scientific Committee on Food) for both male and female adults is 55 mcg/day. In United Kingdom and Belgium, recommendation for selenium intake is between 60-75 mcg/day. Based on the World Health Organization/Food and Agriculture Organization/International Agricultural Exchange Association, recommendation of selenium intake is only 40 mcg/day in men and 30 mcg/day in women.[6] The maximum recommendation of selenium based on the World Health Organization is 400 mcg/day, and the minimum intake is 10 mcg/day.[7]

Data of selenium intake and selenium content in food ingredients in Indonesia are very limited. The study of Untoro et al.[23] in East Java showed that selenium content in egg yolks (0.15-1.52 mcg/g) and egg white (0.2-2.97 mcg/g) were lower than 1 mcg/g, and that values are below the data from Belgium, Venezuela, and Chile. Eggs contribute about 8% of the estimated daily selenium intake (50 mcg/day for healthy adults).[23] In a study in Bandung that assess selenium levels in rice as the main staple food consumed by populations, the results showed that the mean selenium levels in rice consumed were 0.035 mcg/g, lower than other countries, as can be seen in Figure 2.[6] In another study in East Java, it was found that the mean selenium levels in the soil in the area of the goitre group were lower compared to the control group, respectively 3.2 and 4.6 mcg/kg, but not significantly different.[24] The most recent study showed that selenium levels in the soil in Indonesia is around 0.24-1.31 mg/kg of soil, with the highest content in the Papua area, and the lowest found in Kalimantan area, as can be seen in Table 1.[7]

Until now it is still unknown the reference values of selenium levels that can be use as a parameters to detect the risk of disease caused by selenium deficiency.[25] Large studies are limited because it is difficult to estimate selenium intake from questionnaires due to significant variations of selenium content in the same food ingredients. Measuring the content of selenium in food ingredients is also limited due to the large geographic variability.[26] Food source of selenium and its content can be seen in Table 2.[27]

The greatest selenium concentration (>1 mg/kg) was found in Brazil nuts and offal.[28] In Europe, the average daily intake of selenium is estimated at 40 mcg/day (range 32-62 mcg/day), whereas in America it is 93 mcg/day in women and 134 mcg/day in men.1 The mean selenium intake in

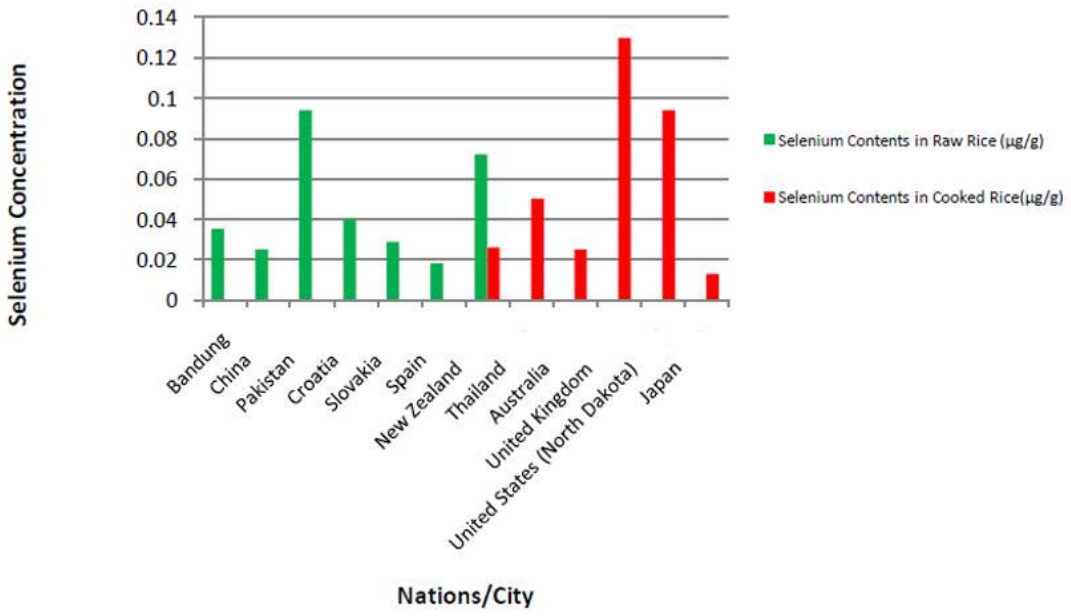

Figure 2. Comparison chart levels of selenium in raw rice or cooked rice in some countries
Source: reference no[6]

Table 1. Selenium concentration in the soil and rice by location in Indonesia

Area	Selenium	
	Soil	Rice
Papua	1.31±0.07	0.068±0.0015
Lampung	1.25±0.08	0.101±0.0059
Kalimantan	0.18±0.03	0.007±0.0012
Java	0.44±0.11	0.022±0.0040
Bali	0.24±0.03	0.007±0.0040
Sulawesi	0.24±0.03	0.024±0.0006

Source: reference no [7]

diabetic patients in several hospitals in Bandung was 74.62 ± 15.46 mcg/day, with a minimum intake was 41 mcg and a maximum was 104 mcg.[29]

The content of selenium in vegetables can be lost during processing and cooking. Refining grains also will reduce selenium content by 50-75%, while boiling can reduce 45% selenium.[30] There are differences in the retention and distribution of selenium derived from broccoli or beef / pork, but administer of foods that is containing high selenium (1.5 mcg selenium/gram diet) did not cause significant changes in selenium bioavailability compared to adequate amounts (0.1 mcg selenium/gram diet).[31]

Selenium Function in Thyroid Gland

Selenium is work actively in the form of selenocysteine amino acids known as a group of proteins known as selenoproteins. The main selenoprotein group is glutathione peroxidase (GPx), thioredoxin reductase (TXNRD), and iodothyronine deiodinase (DIO) as can be seen in Table 3.[17] GPx which have oxidoreductase function and also regulates immune response, it is plays a role in the defense system of the cell against reactive oxygen species and maintains lipid constituents of cell membranes.[25] TXNRD can modulate transcription and signal transduction functions. DIO which catalyzes the conversion of T4 to T3, and rT3 which are very important for thyroid hormone metabolism.[17] Although glutathione peroxidase acts in neutralizing oxidants, other antioxidants such as vitamin E and vitamin C, and Vitamin B2 which is needed by the glutathione reductase also plays a role in synergistic action in oxidative stress neutralization.[32,33]

Table 2. Food sources and content of selenium

Food Source	mcg/portion	%needs/day
Brazil nuts, 1 ounce (6-8 nuts)	544	777
Tuna, yellow fin, cooked, dry heat, 3 ounces	92	131
Halibut, cooked, dry heat, 3 ounces	47	67
Sarden, canned in oil, dried with bone, 3 ounces	45	64
Ham, baked, 3 ounces	42	60
Shrimp, canned, 3 ounces	40	57
Steak, grilled, 3 ounces	33	47
Cow liver, pan fried, 3 ounces	28	40
Chicken, thigh, grilled, 3 ounces	22	31
Brown rice, cooked, 1 cup	19	27
Minced meat, 25% fat, grilled, 3 ounces	18	26
Egg, cooked, 1 egg	15	21
Wheat bread, 1 slice	13	19
Oatmeal cooked with water, 1 cup	13	19
Spinach, frozen, boiled, 1 cup	11	16
Milk, 1% fat, 1 cup	8	11
Yogurt, plain, low fat, 1 cup	8	11
White bread, 1 slice	6	9
Banana, 1 cup	2	3
Potato, baked, with skin, 1 piece	1	1
Carrot, raw, 1 cup	0	0

Source: reference no [27]

Table 3. Main selenoproteins and their function that are found in the thyroid gland

Selenoproteins	Abbreviation	Function
Glutathione peroxidase	GPX	Catalyzes the reduction of H2O2; Protects against oxidative stress
Cytosolic GPx1	GPX1	Antioxidative defence
Extracellular GPx	GPX3	Anti-inflammatory action
Phospholipid GPx	GPX4	Reduces the phospholipids's hydroperoxides; Regulates apoptosis
Iodothyronine deiodinase	DIO	Catalyzes the conversion of T4 and T3
Type I DIO	DIO1	Conversion T4 to T3
Type II DIO	DIO2	Local production (intracellular) of T3 from T4
Type III DIO	DIO3	Production of rT3 from T4, and T2 from T3
Thioredoxin reductase	TXNRD	Oxidoreductase activity having the NADPH as a cofactor
TXNRD cytosolic	TXNRD1	Main antioxidant ''weapon'' at the cellular level
TXNRD mitochondrial	TXNRD2	Regulates cell proliferation
Selenoprotein P	SEPP	Selenium transporter
Selenoprotein K	SELK	Endoplasmic reticulum-associated degradation and immune response
Selenoprotein N	SEP15	Degradation of H_2O_2
Selenoprotein S	SELS	Transmembrane protein, putative role in endoplasmic reticulum stress
Selenoprotein T	SELT	Calcium mobilization
Selenoprotein V	SELV	Testes-specific expression
Selenoprotein W	SELW	Antioxidant role

NADPH = nicotinamide adenine dinucleotide phosphate (reduced form of the redox coenzyme nicotinamide adenine dinucleotide phosphate)
Source: reference no [17]

Selenoprotein P (SEPP) is a source of more than 50% plasma selenium, which is the main plasma transport and distribution system of selenium. SEPP circulates in various forms with different glycosylation patterns. SEPP is produces by hepatocytes and it is very important for maintaining selenium homeostasis as it sustains retention of selenium in the body and increase distribution from the liver to other tissues, especially in selenium deficiency.[34] Inactivation of the SEPP gene in mice actually reduces selenium content in the plasma, kidneys, testis, brain, and the activity of selenoenzyme in various organs drastically.[35] SEPP deficiency can actually trigger neurological disorders (ataxia and seizures), indicating an important role of SEPP to transport selenium in the brain.[36] The thyroid affects the mRNA levels of several enzymes involved in selenoprotein biosynthesis and SEPP concentrations, suggesting that the thyroid hormones can have a positive effect on serum selenium status and regulates the expression of several selenoproteins. Recent data show that single-nucleotide polymorphisms in selenoproteins can increase selenium utilization and effectiveness.[17]

Selenium also has the ability to increase T cell activity and cytotoxicity from natural killer cells, so that it may be effective in viral infections. [17] Selenium supplementation can stimulate the immune system by increasing the differentiation of CD4 + cells into T helper (Th) 1 cells, enhance expression of interleukin-2 and also lymphocyte proliferation.[37] This effect might be effective to eradicated the virus that considered to be involved in autoimmune thyroid diseases.[38] Further, selenium supplementation can also reduce production from CD4+ CD25+ T cells by increasing the regulation of forkhead box P3 (FOXP3) expression and increasing the percentage of regulatory T cells, thereby suppressing excessive inflammation.[11] This studies showed that selenium might have reduce the excessive immune responses in autoimmune thyroid disease.

Selenium in Hyperthyroidism

In the thyroid gland, selenium concentration is very high (0.2-2 mcg/g). In adults, selenium concentration in the thyroid gland (0.72 ± 0.44 mcg/g) was significantly higher than in liver (0.45 ± 0.11 mcg/g).[39] The association of selenium with the functioning of DIO was identified as an enzyme containing selenocysteine, and DIO activity depending on selenium availability. Thyrocytes produce hydrogen peroxide (H_2O_2), which is important for the activity of TPO and iodide oxidation.[17] The formation of H_2O_2 is regulated through the action of TSH via a complex network of second-messenger systems. The iodination of thyroglobulin and formation of H_2O_2 occur on the apical membrane of the thyrocyte. The H_2O_2 formed on the surface of the thyrocyte are available for iodination of thyroglobulin.[40] H_2O_2 will be reduced to H_2O, but if H_2O_2 is present in large quantities, it will cause radical oxygen species damage.[41] In the process of thyroid hormone synthesis, GPX1, GPX3, and TXNRD1 up-regulated, and by acting as antioxidants and modifying redox status, they can protect the thyroid from peroxidation damage. [5,17] In hyperthyroidism, there is significantly increased of malondialdehyde (MDA) levels in erythrocytes, plasma, and urine patients.[42] Selenoprotein protects the thyrocyte from oxidative damage and modulates thyroid hormone biosynthesis, so it is crucial for maintaining the function and integrity of the thyroid gland, although it might not be essential for survival of the thyrocyte.[5,17]

Selenium supplementation (even in non-deficient subjects) can induce immune stimulatory effects such as an increase in the number of activated T lymphocytes and regulates of Th1/Th2 cytokine expression.[43] Combined iodide and selenium deficiency can cause H_2O_2 accumulation; selenium deficiency can reduced cell defense, increasing transforming growth factors β, and fibrosis of thyroid tissue. This will cause thyroid destruction.[44,45] In iodine and selenium deficiency, selenium supplementation can aggravate hypothyroidism due to stimulation of thyroxine metabolism by DIO type I, so selenium supplementation is not indicated without iodine supplementation or thyroid hormone.[46]

In euthyroid healthy subjects with marginal selenium deficiency, selenium supplementation has little and no clinically significant effect on thyroid function.[47] From previous studies it was found that selenium levels were inversely related to thyroid size, [48] and several diseases that might have an effect

on Selenium supplementation is Graves disease and autoimmune thyroiditis. [49]

Selenium in Graves Disease

In a study by giving of 300 mcg/day of selenium supplementation, it was increasing levels of serum selenium and SPP significantly compared to placebo. The serum level of fT3, TRAb, and TPOAb were markedly lower in subject who received selenium supplementation for 24 weeks. Serum levels of SPP correlated with serum selenium and TSH, but negatively correlated with serum fT3 and TPOAb. Serum selenium levels negatively correlated with serum TPOAb. This results indicated that SPP was the more meaningful biomarker of selenium status rather than serum selenium. Although there were a significant increase of the serum levels of selenium and SPP in the selenium group, it did not increase the response or decrease the recurrence rate. There were no significant differences between two groups pertaining to efficacy and clinical course of the thyroid disease. The results obtained in the above study support that there is a relationship between Grave's disease and selenium status, because selenium and SPP concentrations are negatively related to TPOAb, and SPP is positively associated with serum TSH.[11]

Previous study by Leo, et al.[50] there was an increase in serum selenium levels after supplementation 166 mcg/day for 45 days without a difference in serum fT3, fT4, and MDA levels compared to the control group. In this study, the research subjects were selenium-sufficient. From the results of this study concluded that selenium supplementation does not provide short-term benefits in hyperthyroidism, but may be useful in patients with selenium deficiency, so it is necessary to evaluate the selenium status of patients before giving antithyroid therapy, to assess whether the patient might get beneficial effects from selenium.[50]

The study by Calissendorff et al.[37] in patients Graves thyrotoxicosis was found that fT4 levels decreased more in the selenium supplementation (200 mcg/day) group after 18 and 36 weeks, and increase TSH levels after 18 weeks. The concentration of SPP also increased in the selenium group. FT4 and TSH might imply a reduction in disease activity in patients with Graves disease with the addition of selenium. There was no change in TRAb levels in the two groups probably due to other indirect mechanisms. Some factors could be mediated by the immune system, by effects on oxidative stress in the thyroid gland or by deiodinase enzymes. Selenium is important for initiation and enhancing immunity, but it is also being involved in the regulation of excessive immune responses. This is very important to prevent responses that can lead to autoimmunity or chronic inflammation.[37] Selenium supplementation also has a stimulating effects on the immune system by promote the differentiation of CD4 + cells into Th1 cells.[51] The supplementation of selenium also shows an association between enhanced expression of interleukin-2 receptors and lymphocyte proliferation, but whether the immune system can be modulated through selenium in Graves disease remains speculative. In this study there were no significant changes in TRAb or TPOAb during selenium supplementation.[37] Serum selenium levels that increased significantly in selenium supplementation were not accompanied by decreased levels of autoantibodies, indicating a lack of adjuvant effects of selenium supplementation in antithyroid treatment. These results were contrary to Hashimoto's thyroiditis disease, where there was a decrease in TPOAb after selenium.[52] Selenium did not appear to affect immunoglobulins in Graves disease.[37]

The results of meta-analysis of selenium supplementation can enhance the restoration of biochemical euthyroidism and might be useful in Graves disease with selenium deficiency.[9,49] Positive results of the study should be carried out in a larger methodology study before selenium can be included in international guidelines as standard therapy.[9] European Group On Graves Orbitopathy (EUGOGO) provides selenium supplementation in mild and inactive Graves orbitopathy patients in initial management.[53] This is due to the potential efficacy of supplementation 200 mcg/day selenium for 6 months in Graves Orbitopathy. Giving selenium supplementation was significantly improves quality of life, reduces ocular involvement, and slows disease progression in patients with mild Graves orbitopathy.[54]

Selenium in Autoimmune Thyroiditis

In patients with euthyroid autoimmune thyroiditis, supplementation of 166 mcg selenium/day for 6 months did not changes concentrations of TSH, fT4, fT3, TPOAb, thyroid echogenicity, and CXCL-10 (chemotactic cytokines that seems to have a major role in thyroid autoimmunity) levels compared to the control group. Short-term selenium supplementation has a limited effect on euthyroid autoimmune thyroiditis patients. In this study, there was an increase in fT3 levels and a decrease in fT4 in the group given selenium, but not in the control group after 3 and 6 months. This may be due to an increased action of deiodinase induced by L-selenometionin.[55]

This study is different from the results obtained by Nacamulli et al.[10] that 80 mcg selenium supplementation/day may be effective in preventing a decrease in thyroid echogenicity and reducing levels of TPOAb and TgAb, although there were no changes in TSH and fT4 levels for 12 months. This difference in results may be due to differences in the timing of selenium supplementation associated with low selenium intake. The study area where the study subjects lived only had soil with lower selenium levels.[55] Another study with selenomethionine 80 mcg and 160 mcg for 12 months in euthyroid autoimmune thyroiditis patients did not provide changes in TPOAb levels, but there was a significant increase in TPOAb in the group who got a placebo. This shows the potential for selenium effects to protect the progression of the disease in selenomethionine supplementation.[56]

Other studies showed a significant reduction in TPOAb levels after 3 months supplementation of 200 mcg selenomethionine/day.[57] Chemokine CXCL-9 levels decreased significantly after 12 months supplementation of 80 mcg of selenomethionine/day, whereas with supplementation 160 mcg selenomethionine/day, a significant decrease was seen in the 6 month and remain stable. CXCL-10 levels decreased significantly after 12 months of supplementation both in the group that given selenomethionine 80 mcg and 160 mcg. The chemokines are involved in the pathogenesis of autoimmune thyroiditis. The results of that study showed a positive effect of selenomethionine as an immunomodulator by reducing some cytokine regulation.[56]

Study by Farias et al.[52] showed a decrease in TPOAb by giving selenium supplementation for 3 months that occurred after 6 months. Low selenium levels are associated with poor immune function, and it has been hypothesized that mild selenium deficiency may promote the progression of thyroid autoimmunity. Selenium supplementation is associated with decreased levels of serum concentration of thyroid autoantibodies and stabilized the autoimmune response in various variables in different studies and different groups of patients.[52] The decreases in TPOAb may be due to an increase in intra-thyroid selenium levels that will reduce reactive oxygen species damage through enhanced expression of glutathione peroxidase and improvement of redox status in thyrocyte through increasing thioredoxin reductase activity. Selenium supplementation may also reduce the production of CD4 + CD25 + T cells by up-regulating of Fox3p mRNA and increasing the percentage of T regulatory cells, which will decrease some immune responses and restore them to approach normal levels. Selenium requirements are not only influenced by selenium status, but also by selenoprotein gene polymorphisms including SEPP, therefore it is better to rule out the presence of gene polymorphisms before drawing conclusions about activity of selenoprotein in response to therapy. The positive effects of selenium supplementation on chronic thyroiditis autoimmune are obtained both in deficiency and adequacy due to pharmacologic activity.[52]

Meta-analysis by Toulis et al.[58] found that supplementation 200 mcg selenium/day in chronic autoimmune thyroiditis was associated with a decrease in concentration of TPOAb within 3 months. Other systematic reviews of 4 studies showed that supplementation of 200 mcg selenium/day of in chronic autoimmune thyroiditis gave positive and statistically significant results, but the study have a high risk of bias, so evidence to support the efficacy of Hashimoto's thyroiditis is not reliable enough to help make clinical decisions.[59] The latest meta-analysis informs that there have been conflicting reports regarding selenium supplementation in autoimmune thyroiditis patients. With current evidence it is not possible to justify

selenium supplementation in autoimmune thyroiditis patients, but correcting of a selenium deficit might provide other health benefits.[60]

Micronutrients that contribute to thyroid hormone synthesis and maintain thyroid function other than selenium is iodine, iron, zinc, and vitamin A.[8] Study by Guerra et al.[42] in Graves disease patients who were given methimazole and supplemented with antioxidant mixture (200 mg vitamin E, 3 mg β-carotene, 250 mg vitamin C, 1 mg Cu, 7.5 mg Zn, 1.5 mg Mn, and 15 mcg Se) associated with a better biochemical and clinical control of hyperthyroidism in patients given this mixture compared with methimazole alone. In this study, they only gave a small amount of selenium (15 mcg), but patients receiving the antioxidant mixture showed a significant improvement in their clinical score after the first 4 week. Methimazole and the antioxidant mixture affected both urinary and serum malondialdehyde contents.[42] In other study, the fT4 and fT3 levels decreased more rapidly in Graves disease patients who received methimazole, antioxidants and 60 mcg selenium compared to methimazole alone after 30 and 60 days. In the group receiving antioxidants there is also significant increase of TSH after 60 days. [61] This may be due either to the other antioxidative components (vitamin C, vitamin E, and β-carotene) or to selenium given in that study.

Conclusion

Selenium is a micronutrient that needed only in a small quantities by the human body. Amount of selenium in food ingredients depends on the content of selenium in the soil. Studies on selenium levels, intake, and prevalence of selenium deficiency in Indonesia are very limited. In Indonesia, some studies showed that selenium in the soil were low, which might increase risk of selenium deficiency. Selenium has an important function in various metabolisms in the body, especially in the thyroid gland. Selenium works in its active form, namely selenocysteine which is known in the selenoprotein group. Glutathione peroxidase, thioredoxin reductase, and iodothyronine deiodinase are the main selenoproteins that play a role in maintaining the function and regulation of the thyroid gland through antioxidant mechanisms, regulation of immune responses, and signal transcription and transduction.

In hyperthyroidism, the administrations of selenium as supplementation were have different results and the benefits that are clinically relevant are still unclear. Selenium supplementation may improve biochemical hormone in patients with Graves' disease with selenium deficiency, whereas in mild inactive Graves orbitopathy, selenium supplementation might be beneficial. In several studies in patients with autoimmune thyroiditis, it was found that selenium supplementation can reduce autoimmune antibodies, but from the results of existing studies, it cannot be concluded that selenium supplementation can have a positive effect. Perhaps the administration of selenium in hyperthyroid patients with selenium deficiency can provide health effects, accompanied by meeting the needs of other micronutrients that play a role in maintaining the thyroid function such as iodide, iron, zinc, and vitamin A. The exact molecular, cellular, and systemic mechanisms contributing to the obvious relationships among selenium status and thyroid function and the maintenance of its integrity remain to be studied. Further research is needed on the role of selenium in hyperthyroid patients, selenium levels in various foods in Indonesia, as well as the prevalence of selenium deficiency to determine whether selenium supplementation should be given, especially in autoimmune hyperthyroid patients

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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Reference

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EVIDENCE BASED CASE REPORT

Body Mass Index and Survival Rate in Nasopharyngeal Cancer Patient: An Evidence Based Case Report

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Abstract

Introduction: Nasopharyngeal cancer is the most common type of head and neck cancer with prevalence of 6.2/100000 population. Recently, study of prognostic factors for nasopharyngeal cancer still becomes one of research focuses. Several studies have tried to find the relationship between nutritional status (body mass index/BMI) and nasopharyngeal cancer patients' survival rate, but the results are still inconsistent. This study aims to find the relationship between nutritional status represented by BMI and nasopharyngeal cancer patients' survival rate.

Methods: Electronic literature searches were performed in Cochrane®, Scopus®, and Pubmed®. MesH term and title/abstracts were screened based on inclusion and exclusion criteria before relevant journals were reviewed.

Result: Two articles were selected based on the eligibility criteria and relevancy to the clinical question. In the study of Huang et al., the subject was nasopharyngeal cancer patient stage III and IV was included as subject of the study. In the study of Lin et al., nasopharyngeal cancer patient with metastases was also included. Patient with higher BMI has better survival rate than underweight BMI category.

Conclusions: Increasing BMI in underweight cancer patients improves nasopharyngeal cancer patients' survival rate.

Keywords nasopharyngeal cancer, nasopharyngeal neoplasm, body mass index, BMI, survival rate, prognosis

Clinical Scenario

A 40-years-old male patient came to the outpatient clinical nutrition specialist in RSCM National Hospital. He was referred from the ear, nose, and throat (ENT) specialist for nutritional management. He has been suffering from nasopharyngeal cancer since last year. He has lost of appetite since 6 months ago. He experienced unexplained 15 kg weight-loss in one month. The ENT specialist planned to give him chemo radiotherapy. In the past 2 months, he only ate 3–4 tablespoons of porridge per day.

Physical examination showed subcutaneous muscle loss. Based on his history of weight loss, BMI calculation, and physical examination, he was categorized as cancer cachexia. The clinical nutrition specialist gave medical nutrition therapy to increase his intake to overcome malnutrition condition. He asked whether improving his

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nutritional status would increase his chance of survival.

Introduction

Head and neck cancer is the seventh leading cancer in the world. Head and neck cancer can occur in oral cavity, pharynx, and larynx, with squamous cell carcinoma as the most common histopathological findings. Nasopharyngeal cancer (NPC) is one of the most common cancer in South East Asia and North Africa Region.[1] In Indonesia, NPC is one of the most frequent head and neck cancer type (28.4%) with prevalence of 6.2/100.000 population. Nasopharyngeal cancer frequently happens more in male than female.[1]

Risk factors of NPC are smoking habit, alcohol consumption, history of Epstein-Barr virus (EBV) infection, history of human papilloma virus infection, radiation exposure, preserved food, and genetic factor.[2,3] Clinical findings of patients with NPC are hoarseness, feeling of foreign body in their throat, lump at neck area, and abnormal findings in radiology imaging. Diagnosis of NPC is from histopathological findings. Management of NPC depends on the cancer stage, availability of treatment modality, and clinical experts. Treatment for NPC can be divided into surgical, non surgical, and combination therapy. Non surgical treatment consists of chemotherapy and radiotherapy.[3]

Nasopharyngeal cancer patients often suffer from treatment complications such as normal tissue damages. The most common acute treatment complication include mucositis and dysphagia, meanwhile long term effect appears as xerostomia, loss of taste sensation, secondary malignancy, and fibrosis on neck region. Other complications are nausea and vomiting due to chemotherapy. All of these complications can disrupt patient's food intake which result in malnutrition and dehydration.[4]

Many studies currently have focused on the prognostic factors of NPC patients. Some known prognostic factors include cancer stage, EBV DNA findings, and nutritional status.[5] Compared to other methods such as body composition measurement or laboratory examination, BMI measurement is an easy and inexpensive method to determine a patient's nutritional status.[6] Some studies have found the relationship between BMI and survival rate of NPC patients but the results remain inconsistent.[7] For that reason, the relationship between BMI and the survival rate of` cancer patients is an interesting subject as knowing it is necessary to determine the appropriate BMI target for cancer patients.

Clinical Question

Subjects included in this study are adult patients with nasopharyngeal cancer. The factor being analyzed is the influence of BMI to patients' prognosis. The outcome of this study is survival rate. Therefore, this formulates a clinical question: Can BMI affect the survival rate of adult patients with nasopharyngeal cancer?

Methods

Article searching

The literature searching was performed using advanced searching from three large databases: Pubmed®, Cochrane®, and Scopus® on October 9th 2018 that screened by MesH Term and abstract/title. The keywords were "nasopharyngeal cancer", "nasopharyngeal neoplasm", "body mass index", "BMI", "survival rate", and "prognosis". The result of this literature searching was cleaned from duplication by EndNote application. After narrowing down literatures based on their titles and abstracts with the clinical question, the full text literatures which met the eligibility criteria were critically appraised.

Article selection

Eligibility criteria

Article selection was based on the inclusion and exclusion criteria, which addressed the clinical question. The inclusion criteria were: 1) the study subjects were diagnosed as nasopharyngeal cancer; 2) subjects were adult patients (aged ≥18 years old); 3) subject has the same characteristic; 4) BMI measurement was done before patients did chemotherapy and radiotherapy; 5) the study design was systematic review or cohort 6) study's outcome measure was survival rate or prognosis; and 7) publication within the last 5 years. The exclusion

criteria were: 1) no available full text and 2) non-English journal.

Critical appraisal

Critical appraisal was done using cohort methods with BMI as prognostic factor for NPC's survival rate. Every article was assessed by two reviewers for its validity, importance, applicability (VIA) using standardized criteria for prognostic research critical appraisal.[8]

Results

Based on the inclusion and exclusion criteria, journal articles identified were 19 from Pubmed® and 22 from Scopus®. (Table 1)

Those 41 articles were screened for duplication using endnote X7. Eleven out of 41 articles have duplication, thus only 30 articles used for the next step. There were only 2 articles that met the eligibility criteria, meanwhile 28 articles excluded. Among 28 articles excluded, 25 articles used prognostic factors other than BMI, 1 article was therapeutic study, one article as diagnostic study, and 1 article used language other than English (Figure 1).

These articles were retrospective and prospective cohort studies. All studies had a level evidence of 2. The total sample is adequate to represent nasopharyngeal cancer patients. The subjects were taken from single cancer center in endemic area in China. Study characteristics are shown in Table 2. The study by Li W et al. satisfied all appraisal criteria. On the other hand, the study by Huang PY et al. lacked in one of validity criteria (Table 3, 4, and 5).

Discussion

Nutritional status can be assessed by measuring BMI or body composition. BMI is one of the prognostic factor for NPC. Body composition measurement is an accurate method yet expensive, and a specific tool must be used. Meanwhile, BMI is the simple and inexpensive method.[6]

Table 1. Resources and search strategy

Database	Search Strategy	Hits
Pubmed	((((nasopharyngeal cancer[MeSH Terms]) OR nasopharyngeal neoplasm[Title/Abstract])) AND (((body mass index[MeSH Terms]) OR "body mass index"[Title/Abstract]) OR "BMI"[Title/Abstract])) AND (((survival rate[MeSH Terms]) OR "survival rate"[Title/Abstract]) OR prognosis[Title/Abstract])	19
Cochrane Library	***#1 ("body mass index"):ti,ab,kw OR ("BMI"):ti,ab,kw in Cochrane Reviews (Word variations have been searched) N: 93*** ***#2 MeSH descriptor: [Body Mass Index] explode all trees N:9240*** ***#3 #1 OR #2 N:9307*** ***#4 ("survival rate"):ti,ab,kw OR ("prognosis"):ti,ab,kw in Cochrane Reviews (Word variations have been searched) N:230*** ***#5 MeSH descriptor: [Survival Rate] explode all trees N:9443*** ***#6 #4 OR #5 N:9661*** ***#7 #3 AND #6 N:45*** ***#8 (nasopharyngeal cancer):ti,ab,kw OR (nasopharyngeal neoplasm):ti,ab,kw in Cochrane Reviews (Word variations have been searched) N:2*** ***#9 MeSH descriptor: [Nasopharyngeal Neoplasms] explode all trees N:332*** ***#10 #8 OR #9 N:332*** ***#11 #3 AND #6 AND #10 N:0***	0
Scopus	***(TITLE-ABS-KEY(*nasopharyngeal *AND* cancer *) OR TITLE-ABS-KEY (* nasopharyngeal *AND* neoplasm *) AND TITLE-ABS-KEY (* "body mass index" *) OR TITLE-ABS-KEY (* "BMI" *) AND TITLE-ABS-KEY (* survival *AND* rate *) OR TITLE-ABS-KEY (* prognosis *) AND LANGUAGE (* english *)) AND DOCTYPE (* ar *OR* re *) AND PUBYEAR > 2012***	22

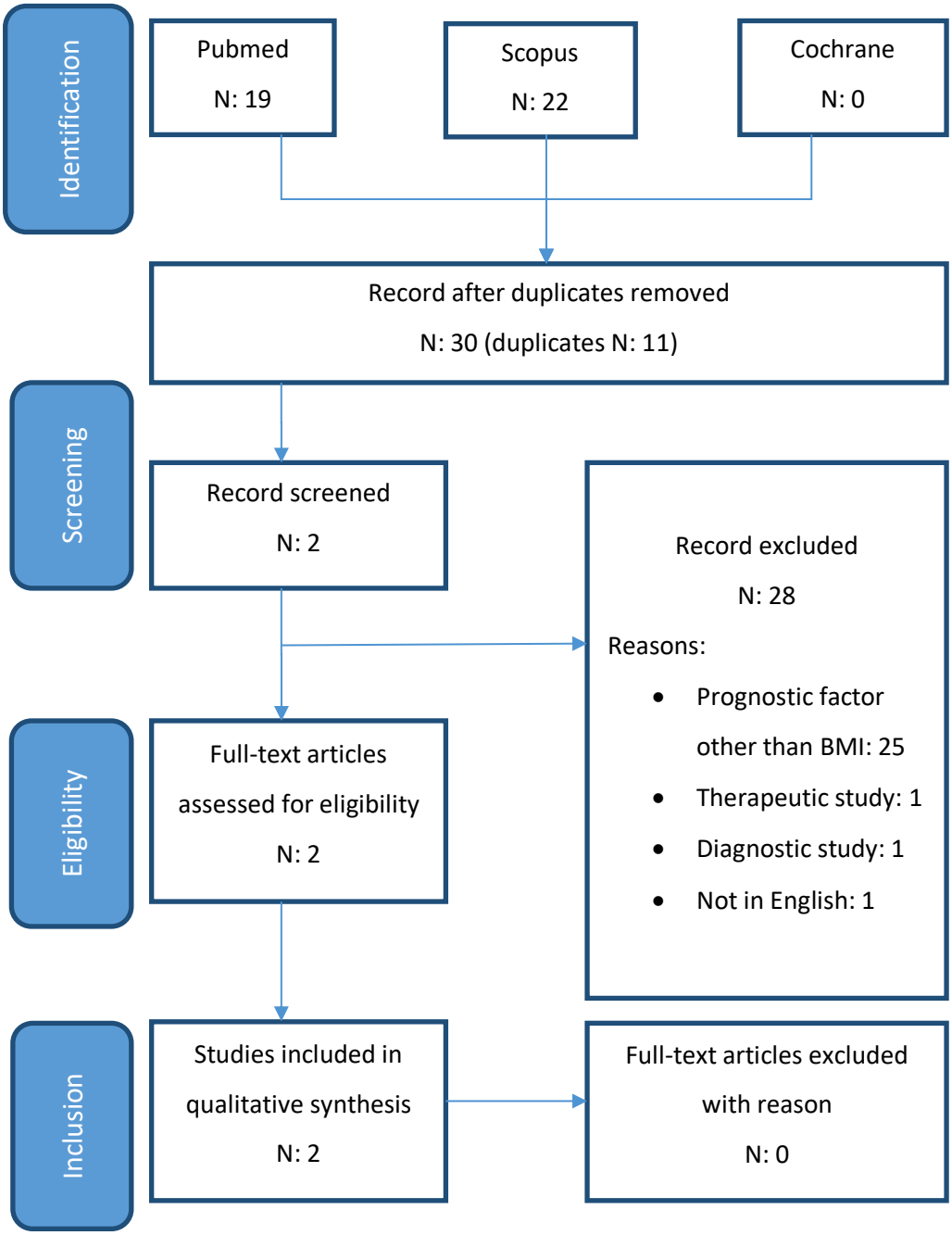

Figure 1. Flow chart of literature searching

Energy Reserve of Hibernation Hypothesis explained that adipose tissue in cancer patients act as nutrient reserve in times of stress such as in patients undergoing cancer treatment. This hypothesis explained the possible mechanism of the relationship between BMI and cancer survival rate.[11]

Li W, et al.[8] conducted a retrospective study to 819 nasopharyngeal cancer patients (median age 45 years old and age range 18–78 years old) with distant metastases whom being treated between 1998 and 2007 at Sun Yat - Sen University Cancer Center, China. During palliative chemotherapy, patients were evaluated by computed tomography or magnetic resonance imaging for response every two cycles and then every 3 months or the last follow-up (June 30, 2014) with OS and PFS as the primary outcomes. Result of this research was higher BMI patients had a significantly longer overall survival compared with underweight patients (HR 0.62; 95% CI 0.48–0.81; $p<0.001$) and normal-weight patients (HR 0.72; 95% CI 0.57–0.90). In contrast, PFS rates had no association with BMI ($p= 0.407$).[10]

Table 2. Study characteristics

Articles	Study design	Population	Outcome
Li W, et al., (2016)	Retrospective cohort study	819 patients >18 years with distant metastasis NPC. Patients were classified into: underweight (n:168), normal weight (n:431), and overweight/obese (n:220)	Overall survival (OS) rates and progression-free survival (PFS).
Huang PY, et al., (2013)	Prospective cohort study	400 patients with NPC stage III and IVa. Patients were divided into: underweight (n:41), normal (n: 184),overweight (n: 83), and obese (n: 33)	Local-regional failure-free survival (LR-FFS), distant failure-free survival (D-FFS), FFS, OS

D-FFS: distant failure-free survival; LR-FFS: local-regional failure-free survival; NPC: nasopharyngeal cancer; OS: overall survival; PFS: progression-free survival

Table 3. Validity criteria

	Relevance									
Articles	Common point	Follow up	Outcome	Adjustment	Outcome over time	Precision	Applicability	Clinically important	Result	Level of Evidence[9]
Li W, et al[10]	+	+	+	+	+	+	+	+	A	2
Huang PY, et al[7]	+	+	+	-	+	+	+	+	B	2

A: Higher BMI patients had a significantly higher 5-year OS rates than underweight patients (p<0,001).[10]
B: Higher BMI patients had a significantly higher 5-year OS rates, FFS rates, LR-FFS rates and D-FFS rates than underweight patients (p=0,001, p=0,014, p=0,045 and p=0,037 respectively)[7]

Table 4. Relevance criteria

Articles	Similarity Population	Similarity Determinant	Similarity Outcome
Li W et al[10]	+	+	+
Huang PY et al[7]	+	+	+

Table 5. Importance criteria

Articles	Outcome	n	Hazard ratio	95% CI
Li W, et al[10]	Overall survival (OS) rates and progression-free survival (PFS)	819	Higher BMI compared with underweight patients: HR 0.62.	0.48–0.81
Huang PY, et al[7]	5-year OS rates in under, normal, overweight, obese group: 51%, 68%, 80%, 72%, respectively (p=0.001). 5-year FFS rates in under, normal, overweight, obese group: 44%, 61%, 68%, 73%, respectively (p=0.014)	400	Higher BMI compared with normal-weight patients: HR 0.57	0.39–0.84

BMI: body mass index; CI: confidence interval; FFS: failure-free survival;; OS: overall survival; PFS: progression-free survival

The prospective cohort study by Huang, et al. was conducted at Sun-Yat-sen University Cancer Centre, China. Four hundred patients with stage III or IVa nasopharyngeal carcinoma were recruited for a randomized clinical trial of induction chemotherapy combined with radiotherapy or concurrent chemo radiotherapy. The mean age was 43 years (range 18–65 years). Patients with different histopathology type and distant metastases were excluded. The subjects were collected from August 2002 to April 2005 and last follow-up was in August 2011. The results showed that higher BMI patients had longer overall survival rates compared with normal weight patients (HR 0.574; 95% CI 0.391–0.845). In a multivariate analysis, whether BMI was calculated as a categorical variable or as a continuous variable, the results showed that BMI was an independent factor for the overall survival of loco regionally advanced nasopharyngeal carcinoma treated with chemoradiotherapy.[7]

In the study of Li W, et al.[8], there are several reasons why higher BMI patients with metastatic NPC had a better survival rate. First, higher BMI patients are less susceptible to malnutrition and/or cachexia than underweight patients with head and neck cancer. Malnutrition and cachexia are associated with reduced tolerance to cancer therapies, impaired immunity, and poor outcomes. Second, based on the preliminary data, higher BMI group received more cycles of palliative therapy after metastasis diagnosis than underweight group. Higher BMI group may prolong the patients' tolerance to continuous treatment because they could receive more aggressive therapy rather than underweight group. However, higher BMI did not necessarily improve therapy's efficacy.[8]

Underweight patients in these two studies may suffer from an advanced stage of tumor. But, the study by Huang PY, et al. did not find significant differences between pre-treatment BMI and the NPC stage distribution.[6] The BMI measurement in this study was taken on day 1 of chemotherapy while Li W, et al. measured within 14 days. In 14 days, patients might experience the therapy's adverse effects such as nausea, vomiting, and decreased appetite so the pre-treatment BMI may be different if taken in last day.

Li W, et al. also observed that BMI level was still significant in predicting OS after analyzing it with age, metastasis onset, bone metastasis, and the number of lesions. However, further comprehensive studies are required to evaluate the relationship between the advanced stage of tumor and patients with low BMI.[8]

Our patient is 40 years old male with NPC. He was categorized as cancer cachexia due to history of weight loss, body mass index, and physical examination. His age is similar with age characteristics in both studies. Researches show that the survival rates of higher BMI patients was better than underweight patients. In this case, we recommend giving the patient continuous medical nutrition therapy in order to increase his chance of survival. This is important because the prevalence of NPC in Indonesia is increasing. To conclude, adult NPC patients must have a better nutritional status while they received treatment.

Conclusion

BMI is one of independent prognostic factors that affect the overall survival of adult NPC patients. This scientific evidence can be the basis to implement nutritional support. Patients with higher BMI compared with underweight patients may have a better quality of life and therefore a higher survival chance. From this evidence-based case report, we conclude that nutritional support should be an integrated part of nasopharyngeal cancer's management. The limitation found in this evidence based case report is the lack of research regarding BMI as a risk factor for NPC. Further studies are required so that the clinician will be able to decide the best BMI target for NPC patients.

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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ORIGINAL PAPER

Correlation between Docosahexaeoic Acid Intake and It's Content in Breast Milk of Lactating Mothers in Jakarta

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Abstract

Objective: Docosahexaenoic acid (DHA) is the predominant structural fatty acid in the brain and crucial for cognitive development in early life. Newborn DHA intake completely depends on preformed DHA in mother's breast milk. In advancing years, globalization has been declining the fish intake of Asian countries. This study aims to determine DHA intake among lactating mothers in Jakarta and its association with breast milk's DHA.

Method: This cross-sectional study was conducted in Grogol Petamburan and Cilincing Public Health Centers, Jakarta. Eighty healthy lactating mothers aged 20–35 years old in 1–6 months postpartum were taken using consecutive sampling method. Characteristics data were taken by interviews and DHA intake was assessed with the semiquantitative food frequency questionnaire. Breast milk specimens were collected in the morning and its DHA content was analyzed using Gas Chromatography with Mass Spectrometry. Descriptive analyses and Spearman rho test were used with a 95% confidence level.

Result: This study showed the median of subjects' DHA intake was 158.5(13.9–719.7) mg/day, i.e., 67.5% of the subjects was below Food and Agriculture Organization (FAO) recommendation. The median of breast milk DHA was 51.7(19–184.7) mg/day, only 42.5 % of the subjects had breast milk DHA to meet the minimal requirement of their infants. A moderate positive correlation was found between maternal DHA intake with breast milk DHA ($r = 0.478$, $p < 0.001$).

Conclusion: Maternal DHA intake has moderate positive correlation with breast milk DHA, more than half of the subject had DHA intake below FAO recommendation.

Keywords: Lactation, Breast Milk, DHA, Nutrition, Indonesia

Introduction

Among all organs in the human body, the brain undergoes the fastest development in the first year of life. The brain volume will increase rapidly to reach 72% of adult brain volume in the first year. Optimal growth of the brain in this period is crucial because it will determine the intelligence of the future, whereas poor brain growth will result in a condition that may not be reversible by intervention after infancy. Because of the rapid growth and

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development, the brain has higher nutritional requirements and very vulnerable to nutritional deficiencies.[1,2]

One of the most critical nutrient that affects brain development is docosahexaenoic acid (DHA). In human cells, DHA is esterified to phospholipid of the membrane cells and serve as the primary structural fatty acid of human nerve cells, especially the brain. It is distributed in various parts of the human brain from the cortex, synaptic membranes, to retinal photoreceptors and serves critical functions of neurodevelopment and brain function, such as neurogenesis, proliferation, impulse transmission, membrane integrity, and gene expression.[3]

Humans were incapable of synthesizing alpha-linolenic acid (ALA) which is the parent of omega-3 fatty acid, but humans have various enzymes which are capable of lengthening and adding extra double bonds to the molecule to form DHA. During early life, this metabolic capability to convert ALA to DHA is very limited. Therefore, infant's requirements of DHA solely depend on the content of preformed DHA in mother's breast milk.[4,5]

The content of breast milk DHA is affected by maternal lipid intake. Dietary fatty absorbed to the bloodstream in the form of chylomicron then delivered to mammary glands to be used as the precursor of breast milk fatty acid. Fishes are rich in preformed DHA which is the best food source to increase breast milk DHA.[3] However, it has been a concerning matter that in many Asian countries, which are known to be fish eaters, are undergoing a reduction of fish intake and increment of the red meat and prepared food intake in the advancing years.[6] In Indonesia, besides the influence of western diet, fish and seafood also have been considered as food taboo for pregnant and lactating mothers.[7] A study in East Jakarta, Indonesia, showed that the adequacy of omega-3 fatty acid intake among pregnant mothers was only 35.8% and 28.4% for DHA intake.[8]

Inadequate maternal DHA intake of lactating mothers could affect the availability of DHA in their breast milk, which is needed for optimal brain development of the infant. However, recent study in Indonesia by Wibowo et al shows that more than 70% of first-trimester pregnant woman had deficient blood DHA concentration.[9] Little is known about the DHA intake of lactating mothers in Indonesia. Only one study by Nahrowi that shows a correlation between fish intake of lactating mothers and breast milk DHA[10]. This study aims to determine the DHA intake of lactating mothers in Jakarta and its association with breast milk DHA content.

Methods

This cross-sectional study was conducted in Grogol Petamburan Public Health Center, West Jakarta, and Cilincing Public Health Center, North Jakarta, from February to April 2019. This study was part of a larger study of nutrient concentration, inflammation status, and oxidative stress in breast milk: specific assessment to DHA, β-carotene, Zinc, C-Reactive Protein (CRP), Superoxide Dismutase, and Malondialdehyde.

This study has been approved by the Committee for Ethics in Research of the Faculty of Medicine Universitas Indonesia (No.1129/UN2.F1/ETIK/2018, protocol number 18-10-1242).

Subjects

The subjects for this research were lactating mothers aged 20–35 years old at 1–6 months postpartum who had single term delivery and consented to join the study. Lactating mothers who had a history of diabetes mellitus, suffered from mastitis or breast tumor, using drugs to inhibit nutrient absorption (lipase and glucosidase inhibitor, laxative agent), statin, and corticosteroid in the previous 2 weeks, and undergo weight loss diet program were excluded. A total of 95 subjects were recruited using consecutive sampling method, but 15 subjects didn't finish the data collection process, thus only 80 samples were analyzed.

Materials and Specimen

The specimen was post-feed mature breast milk. The mothers were asked to empty either breast 2 hours before breast milk extraction. The selected breast cleaned with sterile distillated water, after that about 30 ml of breast milk were collected with manual milk pump Real Bubee® using non-powdered latex

gloves into a sterile container. Collected breast milk then stirred lightly and 6 ml of breast milk was separated to a sterile breast milk bag, stored in -70°C until analysis. The rest of the breast milk was returned to the mother.

Characteristic data

Characteristics data, e.g. identity, age, education, ethnicity, infant sex, postpartum duration, family income, parity, were taken by interview.

Nutrition Status and Dietary Intake Assessment

Anthropometry measurement was taken using Seca 703s digital scale and stadiometer. They were measured according to standardized height and weight measurement protocol. Body mass index (BMI) calculated as weight divided by height squared (kg/m^2). Energy and macronutrient intake were assessed using 24-hour recall for two non-consecutive days, one in the weekday and one in the weekend. Omega-3 and DHA intake were assessed using semi-quantitative food frequency questionnaire.

Laboratory Assessment

Breast milk specimens were analyzed in Prodia Esoteric and Research Laboratory, Kramat, Senen, Central Jakarta.

Docosahexaenoic Acid

Breast milk DHA content was analyzed with Gas Chromatography (GC) and Mass Spectrometry (MS) using a method that was modified from Ren et al,[11]and Lagerstedt et al.[12] The frozen breast milk specimens were thawed and homogenized, then the liquid-liquid extraction with methanol-water-chloroform mixture was used to separate the fat from another macronutrient. The separated fat then undergo transesterification using boron trifluoride and methanol to form their associated fatty acids methyl esters (FAMEs). The separation and identification of FAMEs were performed using Agilent Gas Chromatography System 7890B and Agilent Mass Selective Detector 5977A. Authentic standards were used to identify DHA based on its retention time and mass distribution was calculated from the peak area.

Data Analysis

Data were analyzed using IBM statistical package for the social sciences (SPSS) statistic software version 20.0. Kolmogorov-Smirnov test was used to determine data distribution. It is considered normal if the p-value is above 0.05. Spearman correlation (1-tail) was used to determine the correlation between maternal DHA intake and numerical subject characteristic with breast milk DHA and Chi-square test was used to determine the odds ratio between DHA intake and the adequacy of breast milk DHA, p-value <0.05 was considered significant.

Nutrients database was constructed using Nutrisurvey 2007 by incorporating value from Indonesian Food Composition Table 2017, Indonesian fatty acid composition book,[13] Food Composition Table from United State Department of Agriculture, food composition research form Sukarsa,[14] Jacoeb et al,[15] and Swastawati et al.[16]

Results

A total of 80 subjects data were analyzed. The average age of subjects was 28 ± 4 years old. Most of the subjects had a moderate level of education (67.5%), were Sundanese and Javanese, and were overweight and obese (51.2%). The characteristics can be seen in Table 1.

The adequacy of energy and macronutrient intakes were compared to Indonesian Recommended Dietary Allowances (RDA) 2013 and DHA intake were compared to Food and Agriculture recommendation for lactating mothers (200mg/day).[17,18] Most of the subjects had energy and macronutrient intake below Indonesian RDA. Median of subjects DHA intake was 158.5 (13.9–719.7) mg/day, only 32.5 % of the subjects meet the FAO recommendation. The dietary intakes of the subjects can be seen in Table 2.

The median of breast milk DHA content was 59.6 (22–213) mg/day. There was a weak positive correlation between family income and breast milk DHA (r = 0.220, p <0.025). Correlations between subject characteristics and Breast Milk DHA can be seen in Table 3.

Table 1. Baseline characteristics of subjects (n=80)

Basic Characteristics	Values
Age (years)	28 ± 4†
Education level n (%)	
Low	11 (13.8)
Moderate	54 (67.5)
High	15 (18.8)
Ethnicity n (%)	
Sundanese	20 (25)
Javanese	27 (33.8)
Betawi	13 (16.3)
Melayu	9 (11.3)
Other	11 (13.8)
Infant's sex n (%)	
Male	41 (51.3)
Female	39 (48.8)
Postpartum duration (weeks)	14 (4–24) ‡
Family Income (Rp/months)	3,900,000 (200,000–18,000,000)
Parity (child)	2 (1–4) ‡
BMI (kg/m^2)	23.96 ± 4.19†
Nutritional Status n (%)	
Underweight	3 (3.8)
Normal	36 (45)
Overweight	16 (20)
Obese	25 (31.2)

†: mean ± standard deviation. ‡: median (minimum–maximum)

Table 2. Dietary intakes of subjects

Dietary Intakes	Value	
	24 hours recall	SQ-FFQ
Energy (kcal/day)	1838 (1055–3375) ‡	
Energy adequacy n (%)		
Low	67 (83,8)	
Adequate	13 (16,3)	
Carbohydrate (gr/day)	229.5 (104–420) ‡	
Carbohydrate adequacy n (%)		
Low	74 (92.5)	
Adequate	6 (7.5)	
Protein (gr/day)	67.5 (41–149) ‡	
Protein adequacy n (%)		
Low	53 (66.2)	
Adequate	27 (33.8)	
Fat (gr/day)	77.1 (27–130) ‡	
Fat adequacy n (%)		
Low	43 (53.8)	
Adequacy	37 (46.2)	
DHA (mg/day)		158.5 (13.9–719.7)‡
DHA adequacy n (%)		
Low		26 (32.5)
Adequacy		54 (67.5)
Omega-3 fatty acids (mg/day)		1089 (209–7154) ‡

†: mean ± standard deviation. ‡: median (minimum–maximum)

Table 3. Correlations between subject characteristics and breast milk DHA

Characteristics	Breast Milk DHA	
	r	p (*1-tailed*)
Age	- 0.009	0.468
Postpartum duration	- 0.025	0.414
Family Income	0.220	0.025*
Parity	- 0.113	0.160
Body Mass Index	- 0.38	0.370
Energy Intake	0.117	0.151
Carbohydrate Intake	0.109	0.168
Protein Intake	0.013	0.455
Fat Intake	0.050	0.329

*: statistically significant.

Correlation between subjects fatty acid intakes and breast milk DHA showed in Table 4. There was a moderate positive correlation between maternal DHA intake and breast milk DHA ($r = 0.479$, $p < 0.001$). Omega-3 intake seems to be positively correlated to breast milk DHA, although its not statistically significant.

Table 4. Correlation between fatty acid intakes and breast milk DHA

Fatty acid Intakes	Breast Milk DHA	
	r	p (1-tailed)
DHA	0.479†	<0.001*
Omega-3	0.176†	0.059

Based on the average breast milk intake of Indonesian 0–6 months infant by Winarno, et al.[19], which is 750ml, the minimum value of FAO recommendation for 0–6 months infant DHA requirements (0.1–0 ,18% of total energy intake), and Indonesian RDA 2013 for 0–6 months infant calories intake (550 kcal), we calculated the adequacy of breast milk DHA to meet the recommendation.

We used two different cutoffs (minimum and maximum) from FAO recommendation for DHA intake of 0–6 months infant (Table 5). Only 15% of the subjects had adequate breast milk DHA if the maximum cutoff (0.18% of total energy or 110mg DHA/day) was used compared to 50% of the subjects for the minimum cutoff (0.1% of total energy or 61.1mg DHA/day). There were higher odds to have adequate breast milk DHA if maternal intake exceeds 200 mg/day. Using the minimum cutoff (61.1 mg/day) the odds to have adequate DHA in the breastmilk is 4.265 times higher if maternal DHA intake was above 200 mg/day and it was 5.556 times higher if the maximum cutoff (110mg/day) was used.

Discussion

More than half of the subject in this (51.2%) were overweight and obese. The study by Makela et al.[20] showed that overweight and obese mother have lower breast milk DHA. Obesity has been known to cause low-grade inflammation in the body. This condition could increase the proportion of omega-3 fatty acids converted to anti-inflammatory eicosanoids, reducing the availability of DHA to be transferred into breast milk lipid.[21,22] This study result showed a negative correlation between BMI and breast milk DHA, but it was not statistically significant.

This study found that there is a weak positive correlation between family income and breast milk DHA. Higher family income will ensure food security and the availability of DHA food source for lactating mother. This result is similar with a study by Forsyth et al.[18] showed that food security correlates with omega-3 intake, including DHA, and high-income countries have a better estimation of DHA intake. High DHA intake is a strong factor that determines breast milk DHA content.

The median value of subjects DHA intake in this study (158.5 mg/day) was higher than the FAO

Table 5. Association between DHA intake and Breast Milk DHA adequacy of different cutoff.

DHA intake	Breast Milk DHA Cutoff 61.1 mg/day		p-value[C,1]	Breast Milk DHA Cutoff 110 mg/day		p-value[F,2]
	Adequate	Not Adequate		Adequate	Not Adequate	
Adequate	19	7	0.004	8	18	0.01
Not Adequate	21	33		4	50	

[C]: Chi-Square test; [1]: Odds Ratio = 4.265 (1.531–11.886); [F]: Fisher's exact test
[2]: Odds Ratio = 5.556 (1.491–20.705)

estimation of DHA intake for developing country in South East Asia (134 mg/day), it is also higher than Kim et al.[23] in South Korea. However, it was still below FAO recommendation for lactating mother (200mg/day), only 32.5% of the study subjects meet the recommendation. The median value of omega-3 fatty acid intake in this study was 1.1 (0.2–7.2) gr/day and it was also below the Indonesian RDA for lactating mothers (1.4 gr/day).

This study found a significant correlation between DHA but not omega-3 intake with breast milk DHA. As stated before, this result showed that preformed DHA was a better source of breast milk DHA compared to its precursors. Study done by Nahrowi.[10] in Indonesia, where majority of the lactating mothers lived in coastal areas and had high intake of saltwater fish also have higher average breast milk DHA. On the other hand, study done in Nepal by Henjum et al.[24] showed a lower breast milk DHA that possibly caused by their fatty acids intake mostly came from soybean and sunflower oils, which were abundant in ALA but did not contain preformed DHA.

Indonesia is one of the largest maritime country in the world and it is surprising to see that more than half of our subjects didn't have adequate DHA intake. We suspect that globalization have influenced westernization in Indonesian diet. The other factor that caused this was there were several ethnics in Indonesia that considered fishes and seafoods as a taboo food for among pregnant and lactating. They believe that eating fishes could make their breastmilk smell fishy or delayed the delivery wound healing.[7]

The availability of DHA for brain development in early life solely depends on the mother's breast milk DHA content. Half of the study subjects have breast milk DHA below the FAO minimum recommendation of DHA intake for infants aged 0–6 months, which is 61.1 mg/day. Even though DHA can be stored by infants during pregnancy and we didn't measured the DHA status of the infants, from availability of DHA in their mother breast milk alone we can roughly say that at least half of the subject's infant were at risk of DHA deficiencies.

Adequate DHA is needed to ensure optimal brain development in the early life, especially for cognitive function.[6] Optimal brain growth in this golden period, not only beneficial for the infant in the early age but also affect their future. A study of Lassek and Gaulin.[2] showed that maternal breast milk DHA as strong predictor of the cognitive performance that even greater than educational expenditures.

Breast milk was the primary food and the only natural DHA source for newborn. Breast milk lipid contains a considerable amount of phospholipids in micelle like form, in addition it is also packed with endogenous lipase that make it easier to digest.[25] A study by Meldrum, et al.[26] showed those characteristics of maternal breast milk DHA made it a better predictor to red blood cell DHA of the infant compared to DHA fish oil supplement that contains nearly threefold amounts of DHA. This result suggests that by increasing breast milk DHA content we could secure more DHA for infant's brain development. It also encourages mothers to exclusively breastfed their infants as breast milk will provide higher bioavailability DHA than another source.

This study shows a positive moderate correlation between maternal DHA intake and breast milk DHA. We believe that increasing maternal DHA intake is an effective way to ensure DHA availability in mothers' breast milk. We also found that mothers with DHA intake exceeds 200 mg/day was 4 to 5 times more likely to have adequate DHA in their breast milk to meet their infants' requirement.

There were several limitations to this study. First, there was a possibility of recall and social desirability biases related to nutritional assessment using 24-hour recall and SQ-FFQ. Second, there were limited data of trans fatty acid, omega-3, and DHA in Indonesian food composition table. Indonesian Food Photo Book was used and the standardized procedure has been done during the interview to minimize the possibility and magnitude of biases. Adaptation of nutrient content of several key foods from USDA and food technology research was done to complete the food database.

We conclude that maternal DHA intake during the lactation period positively correlated with breast milk DHA. More than half of our subjects had DHA intake below the FAO recommendation and half of them had inadequate amount of DHA to meet their infants daily intake. Maternal DHA intake

below FAO recommendation associated with higher risk to have inadequate DHA to meet the infant's requirement. Because DHA is important nutrients for brain development in early life. It is crucial for lactating mothers to exclusively breastfed their infants while paying attention to their fatty acid intake to fulfill the infant's DHA requirements.

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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ORIGINAL PAPER

The Effect of a Low-Fat Diet and a Low-Carbohydrate Diet with Aerobic Exercise on Lipid Profile Changes in Adult Women

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Abstract

Background Lifestyle changes become the foundation in primary and secondary prevention of lipid and lipoprotein disorders. The aim of the study was to know the effectiveness of low fat diet and low carbohydrate diet with aerobic exercise toward lipid profile change.

Methods This experimental research was done with pre test-post test control group design. The sample of adult women in the city of Denpasar as many as 33 people, aged 30-50 years, BMI 25-30 kg/m2, allocated to 3 groups. A low-fat diet was applied to Group 1, a low-carbohydrate diet to group 2 and group 3 as controls. Before and after the intervention, blood lipid profile was measured. Changes in blood lipid profile before and after intervention were analyzed by paired t-test. The difference in mean blood lipid profile in all three groups was analyzed by One Way ANOVA test.

Results Low-fat diet and low-carbohydrate diet can lower total cholesterol and low density lipoprotein-cholesterol (LDL-C) significantly ($p < 0.05$). The average decrease in total cholesterol with low fat diet was 16.82 mg/dL and low carbohydrate diet 14.64 mg/dL. The LDL-C decrease was 13.36 mg/dL in low fat diet and 7.45 mg/dL in low-carbohydrate diet group. There was no significant difference in lipid profile changes between low fat compared to low carbohydrate diet ($p>0.05$).

Conclusion Low-fat diet is as effective as a low-carbohydrate diet to improve lipid profile.

Keywords low fat diet, low carbohydrate diet, aerobic exercise, lipid profile

Introduction

Lifestyle changes, namely changes in dietary and physical activity patterns play an important role in lipid profile changes and reduce risk factors for cardiovascular disease. Recommended lifestyle changes for those who have high cholesterol levels include low-fat saturated and low trans-fatty acids diet, exercising regularly and maintaining a healthy weight.[1]

Manipulating the dietary macronutrient content contributes to the beneficial effects of improving the lipid profile even without changes in total calorie intake. Low-fat diet recommendations to reduce cardiovascular diseases (CVD) risk factors, there is still much debate and attention recently to foods that are low in carbohydrates rather than low in fat, it remains to be explained the beneficial effects of each type of diet when providing recommendations for CVD prevention.[2]

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Given the complexity of individual lifestyle choices, observed research results emphasize the challenge of accurately assessing the impact of lifestyle changes, including diet-based intervention or physical activity, on lipid profiles and cardiovascular risk.[1]

Therefore, this study was conducted with aim to determine the effectiveness of low-fat diet and low-carbohydrate diet with aerobic exercise in improving lipid profile in obese women.

Materials And Methods

This was an experimental study with randomized pre-test and post-control group design.[3] The study was conducted in Denpasar City, targeting adult women aged 30-50 years old and body mass index (BMI) of 25-30 kg/m^2. The sample size was calculated using the Pocock formula. The result was 11 subjects. The study used three groups of observation, therefore it required 33 subjects. Group 1 was given low-fat dietary intervention and aerobic exercise; group 2 was given a low-carb dietary intervention and aerobic exercise; group 3 acted as control (no diet nor aerobic exercise).[4]

The population of this study was PKK (Indonesian family welfare programme) members in Kesiman Kertalangu Village, East Denpasar District, Denpasar City, while the sample was part of the population with the following inclusion criteria: 1) willing to become the research subject until completion of the study; 2) healthy based on doctor's examination; 3) age 30-50 years old; 4) body mass index (BMI) 25-30 kg/m^2; 5) did not have a history of obesity; 6) not currently attending a regular physical training program. Subjects who have history of bone injury is excluded. Drop out criteria: suffering from illness or injury during training and did not attend training three times in a row.

The diet applied was a low energy diet i.e energy intake minus 500 kcal from normal needs, with different compositions. Low-fat diet is a low energy diet with 10-15% protein composition, <20% fat and >65% carbohydrates from total energy. On the other hand, low-carbohydrate diet was 10-15% of protein, >30% fat and <55% carbohydrates of total energy. The application of low-fat and low-carbohydrate diets by subjects was done daily for six weeks. Monitoring the implementation of dietary measurement of food intake was done with the food recall method and nutrition counselling three times a week during the study period. Aerobic exercise was moderate in intensity, with 3 times a week frequency and 60 minutes duration. Exercise was held for 6 weeks guided by gym instructors.

Before and after the intervention, lipid profile was taken (total cholesterol, triglycerides, high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C)). Lipid profile changes before and after intervention in each group were analyzed by Paired t-test. Differences in lipid profile changes in the three groups were analyzed by One Way ANOVA Test. Finally, to find out which interventions improved the lipid profile Least Significant Different (LSD) test was used.

Results

The participants recruited in this study were more than 11 people. But 2 people dropped out because they were not present several times at the intervention and 1 person was not measured at the time of the final blood lipid profile level test of the study.

Characteristic of research subjects

Baseline characteristics of study subjects before intervention are shown in Table 1. Comparison of data before intervention between groups 1, 2 and 3

Table 1. Baseline characteristics of the subjects

Characteristics	Group 1	Group 2	Group 3
Age (years)	42.27±5.90	43.82±3.76	39.64±7.57
Cholesterol level (mg/dL)	211.45±41.04	211.91±49.66	200.45±27.60
Triglycerides (mg/dL)	109.09±42.67	150.27±135.58	97.82±49.39
HDL-C (mg/dL)	52.36±9.69	54.64±10.92	66.73±12.51
LDL-C (mg/dL)	138.91±37.23	127.18±30.70	114.10±23.18

were tested with One Way ANOVA at α = 0.05 showing p values for age, total cholesterol, triglyceride, HDL-C and LDL-C greater than 0.05 (p>0.05) which means not significantly different. Thus the condition of the subjects between groups 1, 2 and 3 before the intervention was similar.

The result of normality test with Kolmogorov-Smirnov Test at α=0.05 to the data obtained before intervention showed the p value greater than 0.05 (p>0.05). This means that the distribution of samples from all groups are normal.

Diet application

The average energy recommended in low-fat diet group was 1626.93 kcal, while average energy consumed was 1656.2 kcal. Average percentage of protein intake was 12.08% of total energy, as recommended (10-15% total energy). The average of carbohydrate intake was 66.95%, as recommended (>65% total energy), while fat intake was 20.82% total energy nearly similar to recommended (<20% of total energy).

In low carbohydrate diet intervention group, the recommended average energy was 1592.41 kcal and subjects averagely consumed 1667.80 kcal. The average percentage of protein intake was 14.31% of total energy, as recommended (10-15% total energy); fat intake 32.69% of total energy, as recommended (>30% total energy); and carbohydrate intake 53.26%, as recommended (<65% total energy).

In control group, the average of energy requirement is 2139.34 kcal. Subjects in this group consumed 2185.50 kcal. Average percentage of protein intake was 15.33% total energy, as recommended (10-15% total energy); carbohydrate intake 62.67% as recommended (55-65% total energy) and fat intake 21.67% total energy as recommended (20-25% total energy).

Effect on total cholesterol

The result of t-paired test in Table 2 shows low fat and low carbohydrate diet can significantly decrease total cholesterol (p <0.05). The mean decrease of total cholesterol in low fat diet was 16.82 ± 12.94 mg / dL and on low carbohydrate diet 14.64 ± 14.78 mg/dL.

ANOVA test results showed there was a significant difference of total cholesterol decrease between the three groups (p<0.05). To find out which intervention had greater effect in reducing total cholesterol, further analyzed by LSD test at α=0.05 was done. The test results showed that there was a significant difference of total cholesterol decrease between low fat diet compared to control, with 17.64 mg/dL different value (p<0.05). Similarly there was a significant difference in total cholesterol reduction between low carbohydrate diets compared to controls with different values of 15.46 mg/dL (p<0.05). However, there was no significant difference in total cholesterol reduction between low-fat diet compared to low-carbohydrate diet (p=0.67). Thus low-fat diet is as effective as low-carbohydrate diet to lower total cholesterol.

Table 2. Mean of total cholesterol distribution before and after intervention

Group	Before (mg/dL)	After (mg/dL)	Difference (mg/dL)	p
1	211.45±41.04	194.64±41.97	16.82±12.94	0.00
2	211.91±49.66	197.27±39.00	14.64±14.78	0.01
3	200.45±27.59	201.27±27.10	-0.82±1.87	0.67

Effect on triglyceride

The result of t-paired test in Table 3 showed no significant difference between triglyceride decrease in low fat and low carbohydrate diet group (p>0.05). ANOVA test results also showed no significant difference mean of triglyceride decrease between the three groups (p=0.591)

Effect on HDL-C levels

The paired t-test results in Table 4 showed no significant difference in HDL-C before and after intervention in all groups. ANOVA test results also showed no significant difference in HDL-C changes between the three groups (p>0.05).

Table 3. Mean of triglyceride levels before and after intervention

Group	Before (mg/dL)	After (mg/dL)	Difference (mg/dL)	p
1	109.09±42.67	95.00±25.94	14.09±43.35	0.31
2	150.27±35.58	123.27±63.85	27.00±77.53	0.28
3	97.82±49.39	94.45±41.02	3.36±27.08	0.70

Table 4.Mean of HDL-C levels before and after intervention

Group	Before (mg/dL)	After (mg/dL)	Different (mg/dL)	p
1	52.36±9.69	50.09±7.85	2.27±5.24	0.18
2	54.64±10.92	52.73±13.46	1.91±9.66	0.53
3	66.73±12.51	64.55±12.64	2.18±6.27	0.28

Effect on LDL-C levels

The result of paired t-test in Table 5 shows there is significant difference of LDL-C decrease in low-fat diet (13.36±14.77 mg/dL). ANOVA test results showed there was a difference of LDL-C decrease between the three groups ($p<0.05$). LSD test results showed there was a difference of LDL-C decrease between low fat diet compared to control, the difference was 17.091 mg/dL ($p<0.05$). However, there was no significant difference in LDL-C reduction between low-fat diets compared to low-carb diets, a difference of 5.909 mg / dL ($p>0.05$).

Table 5. Mean of LDL-C levels before and after intervention

Group	Before (mg/dL)	After (mg/dL)	Difference (mg/dL)	p
1	138.91±37.23	125.55±40.69	13.36±14.77	0.01
2	127.18±30.70	119.73±33.97	7.46±5.12	0.18
3	114.00±23.18	117.73±23.19	-3.73±7.58	0.13

Discussion

Effect of intervention on total cholesterol level decrease

Low-fat dietary interventions as well as low-carbohydrate diets with aerobic exercise can significantly reduce total cholesterol ($p<0.05$). The mean decrease of total cholesterol with low fat diet was 16.82±12.94 mg/dL greater than low carbohydrate diet: 14.64±14.78 mg/dL, even though it was not significantly different statistically ($p>0.05$). This result is in line with the findings of Tian Hu[5] which suggests that low-carbohydrate diets are as effective as low-fat diets to improve metabolic risk factors.

Cholesterol reduction is caused by increased cholesterol metabolism during diet. In addition there is also a breakdown of triglyceride deposits in adipose tissue. Deposits come from the breakdown of cholesterol in the plasma which is then used as energy. This breakdown is catalyzed by the hormone sensitive lipase (HSL) enzyme present in the adipose tissue. This enzyme is affected by adrenaline. During diet and physical exercise there will be an increase in adrenaline which means there is also an increase in the activity of these enzymes.[6] The type of fat that affects the most increase in cholesterol is saturated fat, while consumption of monounsaturated fats can lower cholesterol levels.[7]

Various hypotheses suggest that physical activity can improve body composition, increase the capacity of mobilization and fat oxidation, control food intake by controlling appetite and high-fat food intake, increasing thermogenesis response, increasing insulin sensitivity and improving blood lipid profile.[8] Total cholesterol levels can be decreased by doing aerobic exercise regularly.[9] Exercise not only has a positive effect on individuals with dyslipidemia, but also can help to improve lipid profile.[10]

Effect of intervention on changes in triglyceride

The average reduction of triglycerides in the low-carbohydrate diet of 27.00 mg/dL is relatively

greater than the low-fat diet of 14.09 ml/dL. This result is in accordance with William S et al.[11] research shows low-carbohydrate diets have a greater decrease in serum triglyceride than a low-fat diet. However, the result of t-paired test showed no significant difference of triglyceride decrease with low fat diet and low carbohydrate diet ($p>0.05$). This may be because the subjects did not adhere to fasting before blood-taking, diet and exercise intervention programs have not managed to control blood triglyceride levels because the intervention was given only 6 weeks. Blood triglyceride levels are strongly influenced by dietary intake consumed by a person and will increase within hours of eating. Similar to this study, previous studies also did not gain significant differences between blood triglycerides before and after diet and exercise interventions.[1]

Effect of intervention on changes in HDL-C

There was no significant difference in HDL-C before and after low-fat dietary interventions as well as low-carbohydrate diets ($p>0.05$). This may occur because the intervention has not managed to control blood levels of HDL because the intervention is given only 6 weeks, so it has not improved physical fitness. According to Cooper,[12] several studies have proven that achieving a high level of fitness with aerobic exercise activities can benefit one of them is improved lipid profile, such as increased HDL-C and lower total cholesterol ratio with HDL-C. The more fit a person aerobically, the more likely that person's HDL-C becomes higher.

In line with the study of Saritas et al.[13] showing a short-term aerobic exercise program (8 weeks) undertaken without diet in active young adolescent males is not enough to make a beneficial effect on blood lipid profiles. In contrast to research results of Augusto et al.[14] showed that after physical exercise intervention, there was an increase in lipid profile (HDL-C) in the experimental group ($p<0.05$).

Effect of intervention on decreased in LDL-C

A low-fat diet significantly decreased LDL-C ($p<0.05$), with a mean reduction of 13.36 ± 14.77 mg / dL. A decrease in LDL-C is achieved when the saturated fat intake is lowered.[15] Regular exercise can also decrease plasma LDL-C, increase HDL-C. Triacylglycerol levels are also reduced, most likely due to increased insulin sensitivity that increases lipoprotein lipase expression.[16] Low-fat and low-carbohydrate diets show a comparable effect on insulin resistance.[17]

While the mean lowering of LDL-C with low carbohydrate diet 7.46 mg/dL, but not statistically significant ($p>0.05$). In line with the William et al [11] study, LDL-C changes did not differ statistically (1.6 mg / dL) with low-carb diets.

Conclusion

Low-fat and low-carb diets, each with aerobic exercise performed for six weeks, can significantly lower total cholesterol and LDL-C ($p<0.05$) and may decrease triglycerides but not statistically significant ($p>0.05$). There was no significant difference in lipid profile changes between low-fat diets compared to low-carbohydrate diets ($p>0.05$). Thus a low-fat diet is as effective as a low-carb diet to improve lipid profile.

Ethical Clearance

Ethical clearance no: 1462/UN.14.2/Litbang/2016, obtained from University Udayana Committee.

Conflict of interest

All authors declare that there is no conflict of interest within this research and publication including the financial agency

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ORIGINAL PAPER

Correlation between Hair Zinc Level and Cognitive Function in Elderly Population

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Abstract

Introduction: Neurodegenerative disease is the most common problem in elderly. Amyloid β (Aβ) accumulation is the major cause of cognitive impairment. Zinc has an important role in antioxidant and Aβ accumulation process. This study aimed to evaluate the correlation between hair zinc level and cognitive function in elderly.

Methods: A cross sectional study was conducted involving 58 subjects of elderly at Kartini Regency, Central Jakarta in January 2019. Hair zinc level was measured by inductively coupled plasma emission spectrometer (ICPS) and cognitive function assessed by abbreviated mental test (AMT). Data analysis was done by spearman rank correlation test and p-value less than 0.05 were considered statistically significant.

Result: The mean of age was 65.4 ± 4.4 years old and 56.9% of subjects were female. The mean of hair zinc level was 123.23 ± 69.71 µg/gram hair and 32.8% subjects had hair zinc deficiency. There was 91.4% subjects had normal cognitive function. The study showed no correlation between hair zinc level and cognitive function in elderly (p=0.871 ; r=-0.022).

Conclusions: There was no correlation between hair zinc level and cognitive function in elderly. Further research is expected to be performed with different level of cognitive function.

Keywords cognitive, elderly, hair zinc level, zinc

Introduction

Raising of elderly population is a global phenomenon, not only in developed country with high income but also in low and medium income.[1] Population survey in 2010 showed that Indonesia is one of the five highest elderly population country in the world.[2] Elderly population have many health problems, mainly neurodegenerative disease.[3] In 2015, there are 9.9 million new case of dementia and 46.8 million people with dementia.[4]

Aging process causes physiological changes in musculoskeletal, sensory, gastrointestinal and nervous system which are related to health problems in the elderly.[1] Cognitive impairment risk factors in elderly include genetic, age, family history, and degenerative diseases.[5] Degenerative diseases such as hypertension, diabetes mellitus and atherosclerosis are related to Aβ accumulation. It is the major cause of cognitive impairment.[6] Cognitive function can be assessed by abbreviated mental test

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(AMT). Abbreviated mental test is a simple assessment which does not need capability of reading, writing or drawing skill and isn't depended to education level.[7]

Oral problem, like loose teeth and dry mouth (xerostomia) are also the most common problem in elderly which can disturb chewing and swallowing process thus cause low nutrient intake.[1] Zinc deficiency is one of nutrient deficiencies in elderly.[8] According to Briefel et al[9] study, only 44% people aged >70 years old had adequate zinc intake. Zinc mineral has many role in more than 2.000 transcription factors and 300 enzymes. Therefore, zinc is important for cellular mechanism such as DNA synthesis, protein synthesis, wound healing, immunity, and cognitive.[10] Zinc also plays an important role in antioxidant and Aβ accumulation process.[11-13]

Zinc level can be assessed by hair sample. Hair sample is a potential biomarker. Hair follicles can reflect zinc intake by 4-8 weeks before sample collection. Some advantages of hair sample are higher zinc concentrations than blood and urine, thus making the measurement easier. Hair sample can be collected, transported, and stored at room temperature. There is no rapid fluctuations seen in serum zinc produced by a recent meal, diurnal and circadian variation, or inflammation. Hair zinc levels are affected by biological factors such as age, sex and hair growth rate.[14]

The association between zinc level and cognitive impairment is a controversial issue. The aim of this study is to determine the correlation between hair zinc level and cognitive function in elderly.

Methods

A cross sectional study was conducted in January 2019 at Kartini Regency, Central Jakarta. Sample size was determined based on the correlation analysis (α=0.05; β=0.20; r=0.38), with estimated 10% drop out. The sum of samples was 60 subjects. Subjects were recruited by consecutive sampling. We disseminate this research information and those who wish to participate in the research can register themselves. If the number of subjects has been met then the recruitment of subjects was stopped.

Inclusion criteria were elderly (aged ≥60 years old), could communicate in Indonesian language (can hear and speak), had hair in the scalp near their necks and willing to participate by signing the informed consent. Exclusion criteria were not willing to participate, suffering from acute disease and was hospitalized, suffering chronic diarrhea and using benzodiazepine drugs in the last 3 months before this study.

Data collection was conducted after obtaining approval from Ethics Committee of the Faculty of Medicine, Universitas Indonesia. Baseline characteristics of subjects, including age, gender, educational level, working status and medical history, were collected by interview. Educational level was categorized into three groups according to Indonesian constitutional law No. 20, 2003.[15] Emotional status was assessed by geriatric depression scale-5 items (GDS-5 items).[7,16,17] Nutritional screening was done by mini nutritional assessment-short form (MNA-SF).[18]

Anthropometric measurements such as height, weight, and calf circumference were performed twice and the average results were used. Measurement of height was done by calculating knee height (0.1 cm accuracy) with Chumlea formulation. Weight measurement was done using the digital scale "SECA" (0.1 kg accuracy). From height and weight measurements body mass index (BMI) were calculated. If BMI could not be assessed, it was then replaced by calf circumference measurements.[19,20] Zinc, protein, and total calorie intakes were obtained from semi-quantitative food frequency questionnaire (SQ-FFQ) and then the data was processed using Nutrisurvey 2007 program. Hair sample as much as 0.5-1 gram of hair was collected for hair zinc level assessment which used inductively coupled plasma spectrometer (ICPS).[21,22] Cognitive functions were assessed by abbreviated mental test (AMT). [23,24]

Data were analyzed by using SPSS version 20.0 program. Normality test was done by Kolmogorov Smirnov. Spearman rank correlation test was used to determine correlation between hair zinc level and cognitive function in elderly.

Results

Subject characteristics

Based on the inclusion and exclusion criteria, 60 subjects were willing to join in this study and signed an informed consent. Subjects who followed this study and the data could be analysed were 58 subjects. Baseline characteristics of the subjects can be seen in Table 1.

Table 1. Characteristic of subjects (n=58)

Variable	Frequency n(%)	Mean ± SD or Median (min-max)
Age (year)		65.36 ± 4.40
60-69	48 (82.8)	
≥ 70	10 (17.2)	
Gender		
Male	25 (43.1)	
Female	33 (56.9)	
Education level		
Low	42 (72.4)	
Moderate	13 (22.4)	
High	3 (5.2)	
Occupation		
Employee	20 (34.5)	
Unemployment	38 (65.5)	
Disease history		
No	32 (55.2)	
Yes	26 (44.8)	
Hypertension history		
No	34 (58.6)	
Yes	24 (41.4)	
Diabetes mellitus history		
No	53 (91.4)	
Yes	5 (8.6)	
Stroke history		
No	58 (100)	
Yes	0 (0)	
Emotional status		
Without depression	58 (100)	
Depression	0 (0)	
Nutritional assessment screening		
Normal	45 (77.6)	
Malnutrition risk	13 (22.4)	
Malnutrition	0 (0)	

The average age was 65.4±4.4 years old. The number of people aged <70 years old (82.8%) was more than those of the elderly ≥70 years. In this study, 56.9% subjects are female, 72.4% had low level education and 65.5% did not work.

A total of 44.8% of subjects had a history of disease. Based on the type of disease, 41.4% of subjects had history of hypertension, 8.6% had history of diabetes mellitus, and none of the subjects had history of stroke. Based on the assessment of mental status, there was no subject suffering from depression, according to GDS-5. Based on nutritional assessment screening with the MNA-SF instrument, 77.6% had normal nutritional status and 22.4% had risk of malnutrition.

Zinc, protein and total calorie intakes

The mean value of zinc intake data was 5.65 (3.2 - 13.3) mg/day. There was 87.9% of subjects who had less zinc intake than *angka kecukupan gizi* (AKG/Indonesian recommended daily intake) 2013. Average value of protein intake per-kg body weight (BW) was 1.09±0.47 gram/kgBW/day. From the analysis of protein intake obtained, as many as 46.6% of subjects had protein intake of less than 1 gram/kg BW/day. The average value of total calorie intake per-kg BW was 29.61±8.86 kcal/kgBW/day. From the analysis of total calorie intake, 56.9% of subjects had a total calorie intake less than 30 kcal/kg BW/day. (Table 2)

Table 2. Characteristic distribution based on zinc, protein, and total calorie intake

Variable	Frequency n(%)	Mean ± SD or Median (min-max)
Zinc intake (mg/day)		5.65 (3.2 – 13.3)
Adequate	7 (12.1)	
Inadequate	51 (87.9)	
Protein intake		1.09 ± 0.47
Adequate	31 (53.4)	
Inadequate	27 (46.6)	
Total calorie intake		29.61 ± 8.86
Adequate	25 (43.1)	
Inadequate	33 (56.9)	

Hair zinc levels

The average hair zinc level was 123.23±69.71 µg/gram of hair (Table 3). There were 34 subjects (58.6%) who had normal zinc levels (80-200 µg/ gram of hair), 19 subjects (32.8%) had zinc hair deficiency, and 5 subjects (8.6%) had high hair zinc levels.

Table 3. Characteristic distribution based on hair zinc level

Variable	Frequency n(%)	Mean ± SD or Median (min-max)
Hair zinc level		123.23 69.71
Deficiency	19 (32.8)	
Normal	34 (58.6)	
High	5 (8.6)	

Cognitive function

The median value of cognitive function was 9 (minimum and maximum value: 3 and 10, respectively) which can be seen in Table 4.

A total of 53 subjects (91.4%) had normal cognitive function, 4 subjects (6.9%) had moderate cognitive impairment (AMT score 4-7) and 1 subject (1.7%) had severe cognitive impairment (AMT sore 0-3).

Correlation between hair zinc level and cognitive function

The correlation between hair zinc level and cognitive function in elderly was assessed by Spearman rank correlation test. The study found that there was no correlation (p=0.871; r=-0.022) between hair zinc levels and cognitive function in the subjects who were assessed by the AMT instrument.

Table 4. Characteristic distribution based on cognitive function

Variable	Frequency n(%)	Mean ± SD or Median (min-max)
Cognitive function		9 (3-10)
Normal	53 (91.4)	
Moderate cognitive impairment	4 (6.9)	
Severe cognitive impairment	1 (1.7)	

Discussion

The average age of this study was 65.4±4.4 years old with 82.8% subject were <70 years old. Rahmawati's research[25] showed that there was more subject (72.8%) less than 70 years old and average age was 66.34±5.34 years. Based on Indonesian population pyramid data in 2016, most of elderly people are ≥70 years old of age. The pyramid shows that the mortality rate is still high in the elderly population, because 70 years old of age is categorized as high-risk elderly.[26] There are various risks of degenerative diseases such as high blood pressure, diabetes mellitus, coronary heart disease, kidney disease and nutritional problems that can affect the elderly.[27]

The average value of hair zinc in this study was 123.23±69.71 µg/gram of hair. The normal zinc level reference in this study was 80-200 µg/gram of hair.[14] Subjects with normal hair zinc levels were 58.6%, subjects with zinc deficiency were 32.8%, and subjects with high hair zinc levels were 8.6%. A research was conducted by Yasuda, et al.[28] in the Japanese population aged 0-100 years old to determine zinc levels through hair specimens using the ICP-MS method. Reference to control of hair zinc levels in the study was 86.6-193 µg/gram hair (ppm). The lowest zinc concentration of 9.69 ppm was found in women aged 51 years old. The prevalence of zinc deficiency in the male group in the 6th decade age was 11.6% and in the 7th decade was 15.1%. However the prevalence of zinc deficiency in the female group in the 6th decade age was 8.5% and in the 7th decade was 15.4%. There is a significant negative correlation ($p<0.001$) between zinc concentration and age ($r=-0.12$ in the male group and $r=-0.14$ in the female group). This study shows that elderly population is susceptible to zinc deficiency. In this study there were 8.6% of subjects who had high hair zinc levels. According to a study by Lee,[29] excess zinc levels can occur due to excess exogenous zinc, excessive oxidants resulting in zinc release from metallothionein (MT), and dysregulation of zinc homeostasis systems related to the expression or function of MT, Zrt- and Irt-like protein (ZIP), and zinc transporter (ZnT). The subjects who had high zinc hair levels in this study had zinc intake pattern that was less than the recommendation. Therefore it is possible that this study subject had high hair zinc levels due to dysregulation of the zinc homeostasis system or the presence of excess oxidant resulting in zinc release from MT.

The median value of cognitive function in this study is 9 (3-10). The number of subjects with normal cognitive function was 91.4%, subjects had moderate cognitive function impairment as much as 6.9% and subjects who experienced severe cognitive impairment were 1.7%. This result is different from Markiewicz-Zukowska's research. The Markiewicz-Zukowska's study was conducted on elderly subjects who lived in the nursing home and it was found that 48% of subjects showed symptoms of depression.[7] While in this study performed on elderly subjects who stayed at home, and did not find subjects who showed symptoms of depression. According to a meta-analysis cohort study shows that depression history increases the risk of dementia.[5] Wherever subjects with dementia often exhibit neuropsychiatric symptoms such as depression, anxiety, agitation, sleep disturbances, and apathy. This increases the risk of progression to dementia in individuals with mild cognitive impairment (MCI).[30]

In this study, there was no correlation between hair zinc level and cognitive function in elderly people. Research on zinc levels with cognitive function is still controversial because it shows different results. The Rabia, et al[21] study showed a significant difference ($p=0.02$) of hair zinc levels between the Alzheimer's group (75 ± 29 µg/gram) compared to the control group (98 ± 54 µg/gram). AMT and GDS-5 items were a simple instrument to screen the cognitive function and mental status. In future study, we recommend to use other examination to diagnose the real of cognitive function and mental status. There are many tools to evaluate the cognitive function and mental status with strengths and weaknesses. We need to consider with the characteristic of the elderly population and collaborate with other professionals like neurologist and psychiatrist doctor.

Zinc has an important role in cellular metabolism such as proliferation, differentiation, and apoptosis. In addition, zinc is an antioxidant element and maintains tissues against oxidative stress. Alzheimer's disease, MCI and the aging process are associated with Aβ deposits and

cognitive decline.[31] Amyloid lesions or senile plaques consist of Aβ peptides originates from the APP proteolytic process. Zinc plays a role in Aβ degradation. In the healthy brain, there was a little production of Aβ and degraded by enzymes which degrades Aβ. The enzymes that play a role in Aβ degradation are also related with zinc.[11]

Zinc is an important micronutrient for various cellular processes especially immune system function. Zinc deficiency may cause a significant decrease of innate and adaptive immune responses which then trigger systemic inflammation.[32] Chronic inflammation is related to oxidative stress.[13] Zinc deficiency increases oxidative stress and resulting in the formation of pro-inflammatory cytokines such as IL-1β, IL-2, IL-6, and tumor necrosis factor-α (TNF-α).[32]

Cognitive function is not only influenced by zinc minerals. There are various kinds of factors that can affect cognitive function. Genetics and family history are unmodifiable risk factors. Modifiable risk factors include sleep patterns, physical activity/exercise, social activities, diets that are not limited to just one micronutrient. Older people also often experience degenerative problems such as hypertension, diabetes and stroke which are risk factors for decreased cognitive function. Psychological conditions and education of elderly people also have a role in cognitive function.[6,33].

In conclusion, there was no correlation between hair zinc level and cognitive function in elderly population. There are many other factors which can influence cognitive function in elderly population that should be assessed e.g. physical and social activity.

This study was the first cross sectional study aiming to find the correlation between hair zinc levels with cognitive function in elderly population who stayed at home. The strong points of this study was the use of hair sample to detect zinc level. In addition, measurement of anthropometric was using calibrated anthropometry tools. The assessment of cognitive function was performed by general physician.

There were several limitation in this study: utilization of SQ-FFQ that relies on the memory and assumptions of the intake portions, frequency, and type of foods by each subject. However, this had been anticipated by trained personnel, food photo book and household utensil to help the subject to remember and estimate the number and type of foods. There were other limitations in this study. Utilization of AMT and GDS-5 items were a simple instrument to screen the cognitive function and mental status however, they could not represent the real cognitive function and mental status. Nonetheless, it was anticipated in this study priory by the instrument's trial tests to some subjects performed by a general physician. We need to consider with the characteristic of the elderly population to choose the appropriate instrument to assess cognitive function and mental status. Besides that, we can collaborate with other professionals like neurologist and psychiatrist doctor.

Further research may be needed using hair sample to assess zinc level for it is simple, stable, and representable method. The researcher should be taking subjects from various cognitive levels and using random sampling method to avoid selection bias. Not only using screening tools but also other examination to diagnose cognitive function and mental status is recommended. Collaboration with other professionals and assessment of other risk factors that influence cognitive function in elderly likes sleep patterns, physical activity/exercise, social activities, diets that influence cognitive function in elderly are also suggested for future studies.

Conflict of Interest

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ORIGINAL PAPER

Is Serum Zinc Level Correlated with Insulin Resistance Among Lactating Mothers in Jakarta?

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Abstract

Introduction: Insulin resistance is a condition that underlies the development of diabetes mellitus. The prevalence of diabetes mellitus keeps rising, including in Indonesia. A higher proportion of diabetes was found in women. Physiological changes during pregnancy can cause insulin resistance that may persist until postpartum period. Lactation and nutrient like zinc may improve insulin resistance. This study aimed to measure the correlation between zinc serum level and insulin resistance of lactating mothers in Jakarta.

Methods: This study used a cross-sectional design, which was conducted in Grogol Petamburan District Community Health Center, West Jakarta and Cilincing District Community Health Center, North Jakarta from February to April 2019. A total of 75 lactating mothers at 3–6 months postpartum were selected using consecutive sampling method. Zinc serum was analyzed using atomic absorption spectrophotometry (AAS) method. Insulin resistance was assessed using the homeostasis model assessment-insulin resistance (HOMA-IR).

Result: Approximately 76% (n = 57) subjects had low serum zinc level. Spearman correlation test between serum zinc level and HOMA-IR was done (r = 0.003, p = 0.977). Also, correlation test between BMI and HOMA-IR (r = 0.563, p <0.001).

Conclusions: No correlation was found between serum zinc level and HOMA-IR however, there was a significant moderate positive correlation between BMI and HOMA-IR.

Keywords lactation, zinc, insulin resistance, HOMA-IR, BMI

Introduction

Rapid advancements of culture, socioeconomic, and technology cause lifestyle changes that come with considerable health consequences like insulin resistance. Insulin resistance is prevalent worldwide, the prevalence of insulin resistance in Venezuela was 46.7% and in Iran was 51%.[1,2] Insulin resistance is the key condition that underlies the development of type 2 diabetes mellitus. Diabetes mellitus is one of the major causes of mortality worldwide. In 2013, 382 million people were affected by diabetes and over 200 million were Asians. Indonesia was included as one of the top ten Asia countries with most diabetes patients.[3] Based on Riskesdas, there was an increase in diabetes patients in Indonesia

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from 2013 to 2018 and the proportion was found higher among women.[4]

In women, physiological changes during pregnancy can cause insulin resistance that may persist until postpartum period.[5] A study by Kirwan et al.[6] showed that by 1 year postpartum, insulin sensitivity only returned to 74% baseline. Lactation can help improve maternal metabolism. A study by Bajaj et al.[7] showed that insulin sensitivity improved significantly in women who were breastfeeding her babies for ≥3 months. However, exclusive breastfeeding rate in Indonesia is still low, below 40%.[8]

Nutrients have also been associated with insulin resistance. Zinc, for instance, has a role in the crystallization and signaling of insulin.[9] A study by Bandeira et al.[9] showed that higher serum zinc level was significantly associated with better insulin sensitivity. Lactating mothers are particularly vulnerable to zinc deficiency because they have relatively greater needs to secrete adequate breastmilk also safeguarding their own healths.[10] A study by Dijkhuizen et al.[11] in 2001, showed that 25% of lactating mothers in Indonesia suffered from zinc deficiency.

Further studies are still needed to assess whether better breastfeeding practice and zinc status can improve insulin resistance, especially in lactating mothers. This study aimed to assess zinc serum level and its correlation with insulin resistance among lactating mothers in Jakarta.

Methods

A cross-sectional study was conducted in Grogol Petamburan District Community Health Center, West Jakarta and Cilincing District Community Health Center, North Jakarta between February and April 2019. This study was part of a larger study on nutritional status, lipid profile, and metabolic status of lactating mothers: specific assessment of zinc, anemia, and insulin resistance with exclusive breastfeeding. This study has been approved by the Committee for Ethics in Research of the Faculty of Medicine Universitas Indonesia (No. 1128/UN2.F1/ETIK/2018 and protocol number 18-10-1241). Subjects were recruited using consecutive sampling method. Both community health centers cover a wide area, so the risk of bias by the sampling method is minimalized. Subjects were included if they were women aged 20–40 years old, at 3–6 months postpartum, were breastfeeding their babies either exclusively or not and gave written consent to participate. Subjects who had diabetes mellitus type 1 or 2, taking diabetes medicine, suffered from a hormonal disease, taking corticosteroid drugs, or smoking were excluded. Subjects with history of gestational diabetes mellitus were not excluded.

Subjects were interviewed for age, number of parity, level of education, occupation, level of physical activity, pregnancy weight gain, postpartum weight changes, and lactation status (exclusive or not). Level of education was classified as low (not graduated or graduated from elementary school and/or not graduated from junior high school), middle (graduated from junior high school and/or not graduated or graduated from senior high school and/or not graduated from college or university), or high (graduated from college or university). Physical activity was assessed using the International Physical Activity Questionnaire (IPAQ) Short Form and classified as light, moderate, or vigorous intensity.[12] Postpartum weight change was defined as the difference between currently measured weight with the weight after giving birth, documented in maternal and child health book. History of gestational diabetes mellitus was assessed from the documentation in maternal and child health book. Intakes of energy, protein, and zinc were assessed using a semi-quantitative food frequency questionnaire (FFQ). Weight and height were measured using a Seca 703s weight scale and stadiometer. Body mass index (BMI) was calculated as weight per height squared (kg/m^2) and then categorized using Asia-Pacific BMI criteria. Blood vein samples were obtained in the morning after 10–12 hours of fasting to measure zinc serum, fasting glucose, and fasting insulin. Zinc serum was analyzed using atomic absorption spectrophotometry (AAS) method, level <70 µg/dL was considered low.[10] Insulin resistance was assessed using the homeostasis model assessment-insulin resistance (HOMA-IR). HOMA-IR was calculated from fasting glucose and insulin using HOMA2 calculator software released by the Diabetes Trials Unit, University of Oxford.
This calculator is available at:
http://www.dtu.ox.ac.uk/homacalculator/index.php.

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20 for Windows. The normality of data distribution was assessed using Kolmogorov-Smirnov test, data were considered normally distributed if p-value >0.05. Normally distributed data were described using mean and standard deviation, otherwise median with minimum-maximum values were used. Correlation between variables was analyzed using Pearson or Spearman correlation test. P-value <0.05 was considered significant.

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Results

A total of 75 subjects were recruited and data were analyzed. The characteristics of the subjects can be seen in Table 1.

Table 1. Baseline characteristic of the subjects

Characteristics	Values
Age (years)	27.53 ± 4.28†
Parity	2 (1–4)‡
First pregnancy, n (%)	31 (41.3)
Multipara, n (%)	44 (58.7)
Education, n (%)	
Low	9 (12.0)
Middle	52 (69.3)
High	14 (18.7)
Occupation, n (%)	
Housewife	70 (93.3)
Working	5 (6.7)
Physical activity, n (%)	
Light intensity	7 (9.3)
Moderate intensity	34 (45.3)
Vigorous intensity	34 (45.3)
Nutritional status based on BMI, n (%)	
Underweight	4 (5.3)
Normal	34 (45.3)
Overweight	15 (20.0)
Obesity	22 (29.3)
Pregnancy weight gain (kg)	12.66 ± 4.41†
Postpartum weight changes (kg)	- 8.45 ± 4.65†
Lactation status, n (%)	
Not exclusive	25 (33.3)
Exclusive	50 (66.7)

†: mean ± standard deviation. ‡: median (minimum–maximum)

The average age of subjects was 27.53 ± 4.28 years old. Most of the subjects had given birth more than once (58.7%), had a middle level of education (69.3%), were a housewife (93.3%), had moderate to vigorous intensity of daily physical activity (90.6%), were overweight and obese (49.3%), also were breastfeeding their babies exclusively (66.7%). The average weight gain during pregnancy was 12.66 ± 4.41 kg and average weight loss during postpartum was 8.45 ± 4.65 kg. All subjects had no history of gestational diabetes mellitus.

Dietary intakes are shown in Table 2. Data were compared to Recommended Dietary Allowances established for Indonesia in 2013.[13] Most of the subjects had low energy intake (52%), adequate dietary protein intakes (66.7%), and low dietary zinc intakes (77.3%).

Serum zinc, BMI, and HOMA-IR values also their correlations were shown in Table 3. Most of the subjects had low serum zinc levels (76%). The median value of HOMA-IR was 0.54 (0.22–2.21) and most subjects had optimal HOMA-IR value (86.7%) compared to cut-off established by Than et al.[14] from a study in Myanmar. Spearman correlation test was conducted between serum zinc and HOMA-IR. No significant correlation was found ($r = 0.003$, $p = 0.977$). Spearman correlation test between BMI and HOMA-IR showed a moderate positive significant result ($r = 0.563$, $p < 0.001$).

Discussion

Evidence shows that lactation has a beneficial effect on insulin sensitivity. Longer duration and higher intensity or exclusive breastfeeding were associated with better maternal metabolism.[7,15,16] Data from Indonesia Demographic and Health Survey in 2017 (IDHS 2017) showed that only 38% of lactating mothers in Indonesia were breastfeeding their babies exclusively at 4–5 months postpartum.[17] Compared to IDHS 2017, in this study, a higher percentage of lactating mothers who were breastfeeding their babies exclusively (66.7%) were found. This discrepancy might be caused by the difference in study areas. More attention is needed to improve exclusive breastfeeding rates. A good nutrition intake and status of lactating mothers is a requirement to ensure an optimal exclusive breastfeeding practice.[18]

In this study, most subjects had adequate dietary protein intakes (75 g/day for lactating women), however dietary zinc intakes of 77.3%

Table 2. Dietary intakes of subjects

FFQ	Range	Values
Energy (kcal/day)		2543.92 ± 745.59†
Low, n (%)	<2500 kcal/day	39 (52.0)
Adequate, n (%)	≥2500 kcal/day	36 (48.0)
Protein (g/day)		87 (41–203) ‡
Low, n (%)	<75 g/day	25 (33.3)
Adequate, n (%)	≥75 g/day	50 (66.7)
Zinc (mg/day)		10.8 (4.4–45.9) ‡
Low, n (%)	<15 mg/day	58 (77.3)
Adequate, n (%)	≥15 mg/day	17 (22.7)

†: mean ± standard deviation. ‡ : median (minimum–maximum)

Table 3. Correlations between serum zinc and BMI with HOMA-IR

Variables	Range	Values	HOMA-IR	
			r	p
HOMA-IR		0.54 (0.22–2.21)‡		
Optimal, n (%)	<1,05	65 (86.7)		
Insulin resistance, n (%)	≥1,05	10 (13.3)		
Serum zinc (µg/dL)		62.33 ± 11.89†	0.003S	0.977
Low, n (%)	<70 µg/dL	57 (76.0)		
Normal, n (%)	≥70 µg/dL	18 (24.0)		
BMI (kg/m^2)		23.56 ± 4.07†	0.563S	<0.001*

†: mean ± standard deviation. ‡: median (minimum-maximum). S: Spearman correlation test. *: statistically significant

subjects did not meet the requirement of Indonesia RDA (15 mg/day for lactating women).[13] This may be caused by different types of protein consumed. A variety of protein foods are also sources of zinc. Animal proteins like oysters, red meat, and poultry are the best sources of zinc compared to plant-based proteins.[10] The majority of subjects in this study fulfill their daily protein needs mostly from plant-based foods like tempeh and tofu. The contents of phytate in plant-based protein foods will inhibit zinc absorption, reducing its bioavailability.[10] A study by Madanijah et al.[19] suggested that lactating women in Bogor purposively doubled their vegetable intakes because they believed it would increase breastmilk quantity and quality. Also, the socioeconomic status of those mothers might influence their choice of foods. Techniques such as milling, soaking, heating, leavening, and fermenting may reduce phytate and increase zinc bioavailability.[20]

Zinc plays an essential role in the storage and secretion of insulin, activation of PI3K/Akt insulin pathway, and induction of the translocation of glucose transporter-4 (GLUT-4). Zinc is also a cofactor for antioxidant enzymes such as superoxide dismutase. Thus, zinc indirectly reduces reactive oxygen species that may damage pancreatic β-cell.[21,22] In this regard, studies have shown the role of zinc in insulin sensitivity.[22-24] However, in this study, there was no significant correlation between serum zinc and HOMA-IR. Capdor et al.[25] conducted a meta-analysis of zinc supplementation effect on glucose tolerance and insulin level. The supplementation of zinc increase zinc blood level thus resulted in significant improvement of glucose tolerance and insulin level on subjects with underlying chronic disease (diabetes mellitus, metabolic syndrome, obesity) compared with those of healthy subjects.[25] This difference implicates that positive effect of zinc on insulin resistance might be significantly found on those with impaired metabolism, whereas in this study most of the subjects had optimal HOMA-IR values.

A study by Ahn et al.[26] in Korea showed a significant inverse correlation between serum zinc and HOMA-IR in non-diabetic subjects after adjusting for cardiometabolic risk factors (waist circumference, HDL cholesterol, triglycerides) statistically.[26] These results suggest that insulin resistance is influenced by other dominant factors that might overshadow zinc status. Subjects of this

study were women of reproductive age whose estrogen level was still high. Estrogen (17B-ethinyl-estradiol) is considered as a protective factor against insulin resistance. By bonding with estrogen receptor-α, estrogen inhibits lipoprotein lipase (an enzyme catalyzing lipogenesis), thus preventing the accumulation of triacylglycerol (TAG) in adipocyte. In liver, estrogen also inhibits the accumulation of TAG, gluconeogenesis, and inflammatory pathways. This will reduce inflammatory process, thus preserving pancreatic cells. Estrogen also has a direct anti-apoptotic effect on pancreatic β-cells that regulate insulin secretion. In skeletal muscle, estrogen modulates expression of insulin-sensitive glucose transporter (GLUT-4), thereby improving glucose disposal.[27,28] This factor may account for the lack of statistically significant results of this study where the subjects were still metabolically protected by estrogen.

Given the strong role of obesity in the development of diabetes mellitus type 2. We also conducted an analysis of BMI and HOMA-IR. There was a significant moderate positive correlation which shows that higher BMI was associated with worse insulin resistance. Studies by Vashum et al.[29] and Islam et al.[30] showed similar results. Release of chemokines and pro-inflammatory cytokines from adipocytes of obese people may cause chronic low-grade systemic inflammation, eventually causing the development of insulin resistance and diabetes.[30] Most subjects in this study were overweight and obese, therefore a lifestyle improvement should be implemented. For instance, by increasing the level of physical activity and diet modification.

This study has several limitations. First, the recruitment of subjects was limited to two administrative cities of Jakarta that did not fully represent the population of Jakarta. Secondly, dietary assessment using FFQ relied on subjects' memory. This might cause a bias, although a food picture book was used to minimalize it.

In conclusion, most of the lactating mothers in Jakarta had low dietary zinc intakes and low serum zinc levels. No correlation was found between serum zinc level and HOMA-IR, however, there was a significant moderate positive correlation between BMI and HOMA-IR.

Further studies relating to other risk factors that may influence insulin resistance should be conducted. Lactating women should improve their dietary zinc intakes by increasing their daily intake of animal proteins also by implementing food processing techniques on plant-based proteins to increase the bioavailability of zinc.

Conflict of Interest

Authors declared no conflict of interest regarding this study. No educational grant is provided to the authors.

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