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EDITORIAL

Breastfeeding is Best. But What After Breastfeeding?

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Long-term exclusive breastfeeding is definitively the best feeding for every infant. Exclusive breast feeding should be for six months. From the age of six months onwards, solid food should be introduced while breast feeding is continued.[1]

There are only very few contra-indications for breast feeding or mother's milk. A maternal severe disease is an example of a contra-indication for breast feeding. If a mother has to take medication or undergo a treatment that may have a deleterious effect on the health of the baby, such as chemotherapy or radiotherapy, breast feeding cannot be recommended.[2]

In such a situation, mother's milk from a different mother or a "milk bank" may offer a solution. If this are not possible, infant formula is indicated. Some seldom metabolic diseases such as galactosemia are also contra-indications for mother's milk, because in such a situation lactose is causing severe damage to the baby. Cow's milk based lactose containing infant formula is then as well contra-indicated, since the baby cannot metabolize lactose. However, it speaks for itself that these situation are exceptional.[3,4]

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Chronic malnutrition and failure to thrive is still an important issue in Indonesia, since recent figures from RISKESDAS 2018 report that around 30.8% of infants and young children up to 5 years old are stunting. Other data showed that the prevalence of stunting in 0.5–1.9 years old in the Indonesian rural and urban areas was 24.3% and 28.9%, respectively.[5,6]

However, introduction of solid food from 6 months onwards, and certainly before the age of 12 months, is recommended by all guidelines. These epidemiological data suggest that diversification of feeding in an infant after the period of exclusive breastfeeding is a problem, and that the nutritional quality of the solid food introduced is insufficient to cover the caloric and nutrient needs of the infants.[6] Looking at these observations from outside, an analysis of the deficiencies and development of adapted guidelines on "how to introduce complementary feeding" seems to a priority topic for research.

The older an infant becomes, the smaller the volume and nutritional impact of mother's milk. However, mother's milk is rich in bioactive proteins and oligosaccharides, which are components improving the protection of the child against infectious disease. The content of these protective components in mother's milk decrease over time: the longer the lactation, the smaller the amount of these protective factors.[7] Since infectious disease and as a consequence death and morbidity such as

failure to thrive and stunting growth are a major health issue in toddlers, the question arises is age-adapted cow milk best formula fortified with some of these protective factor should be recommended or not. Of course, evidence should be obtained before recommendations can be made. Prospective, double blind, randomized trials with normal cow milk in eg 1–3 year old children versus age-adapted special formula should give the answer to this question. The benefit of the addition of probiotics, prebiotic oligosaccharides and other components such as secretory IgA to toddler's formula should be studied. These studies should not only focus on health outcome, but also on the cost/benefit ration.

Specialized formula or solid food will obviously be more expensive than regular cow milk or consumption of unbalanced solid food. However, this extra cost on the short term may result in an economic benefit on the middle or long term. Because if the nutritional status of the toddlers improve, the incidence of failure to thrive will drop down and infectious disease will decrease. And as consequence, health care cost will decrease. Thus, spending some extra money on the short term may safe larger amounts of money later. If this benefit has been clearly demonstrated, government might find it beneficial to support the consumption of age-adapted fortified foods in 1–3 years old toddlers.

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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Reference

1. World Health Organization. Exclusive breastfeeding. E-Library of Evidence for Nutrition Actions (eLENA). Downloaded from: http://www.who.int/elena/titles/exclusive_breastfeeding/en/ [diakses pada 9 Jan 2016]
2. Health Canada; Canadian Paediatric Society; Dietitians of Canada; Breastfeeding Committee for Canada (2012) Nutrition for healthy term infants: recommendations from birth to six months. Can J Diet Pract Res 73:204
3. Martin CR, Ling PR, Blackburn GL (2016) Review of infant feeding: key features of breast milk and infant formula. Nutrients 8:279
4. Kerner JJ. Formula allergy and intolerance. Gastroenterology Clinics of North America 1995;24(1):1-25. [Google Scholar]
5. Badan Penelitian. Riset kesehatan dasar. Jakarta: Kementerian Kesehatan RI (2018)
6. Sandjaja S, Budiman B, Harahap H, Ernawati F, Soekatri M, Widodo Y, et al. Food consumption and nutritional and biochemical status of 0· 5–12-year-old Indonesian children: the SEANUTS study. British Journal of Nutrition 2013;110(S3). [Google Scholar]
7. Nutrition, C.o. (ESPGHAN) . Breast-feeding: A Commentary by the ESPGHAN Committee on Nutrition. J Pediatr Gastroenterol Nutr 2009;49(1):112-25. [Google Scholar]

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ORIGINAL ARTICLE

Serum Lactate Dehydrogenase Activity and Its Correlation with Carbohydrate Intake in Advanced Lung Cancer Patients

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Abstract

Introduction This study aims to determine serum lactate dehydrogenase activity and its correlation with carbohydrate intake in advanced lung cancer patients at Dharmais National Cancer Hospital Jakarta. Anaerobic glycolysis is increased in cancer cells, termed the Warburg effect. This results in lactate as an end product, catalysed by LDH enzyme. Activities of lactate in cancer influence tumor growth initiation, survival, proliferation, angiogenesis and metastasis. Serum LDH activity can be used as a diagnostic, prognostic, and predictive marker for tumor sensitivity and resistance to therapy.

Methods A total of 56 advanced lung cancer patients from Dharmais National Cancer Hospital Jakarta were included in this cross sectional study. Subjects were recruited by consecutive sampling. Food intake of total carbohydrate was obtained using 24 hours food recall method. The activity of serum LDH (IU/L) was measured by using enzymatic spectrophotometry method in automated analyzer.

Results The mean of age subjects was 56.98 ± 10.36 years old and 55.4% were male. Carbohydrate intake based on 24 hours food recall was 57.64 ± 10,85%. The median of LDH activity was 54.5 (164–6539) IU/L, with 60.7% increased. This study showed medium negative significant correlation (p = 0.017, r = -0.317) between total carbohydrate intake per day in grams with LDH serum activity.

Conclusion If carbohydrate source is reduced, the LDH enzyme will increase to keep the glycolysis process going. The results of this study showed adequate carbohydrate is needed in patients with cancer.

Keywords lactate dehydrogenase, lung cancer, carbohydrate intake

Introduction

Cancer is one of the major causes of morbidity and mortality in the world. According to the Global Burden of Cancer (GLOBOCAN) data in 2012, lung cancer has the highest incidence rate and is the leading cause of death in men.[1] Lung cancer is one of the three most common cancer types in Dharmais Cancer Hospital during year 2010–2013.[2] Lung cancer patients have poor prognosis and 85% of patients are diagnosed at an advanced stage.[3]

There is an altered energy metabolism and mitochondrial respiration in cancer cells. Carbohydrate metabolism changes in cancer cells is an increased anaerobic glycolysis rate which

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converts pyruvate to lactate even in oxygenated conditions, known as the Warburg effect. Conversion of pyruvate to lactate in cancer cells is catalyzed by lactate dehydrogenase (LDH) enzyme.[4] This enzyme is scattered in various tissues and its level in the blood increases in several diseases including malignancy.[5] The roles of LDH in cancer cells including the initiation of tumor growth, maintaining cancer cell survival, progression, and metastasis. LDH activities can become a marker to identify different types of malignancy and as a prognostic marker to determine the survival of cancer patients.[6]

The aim of this study was to determine serum lactate dehydrogenase (LDH) activity and its correlation with carbohydrate intake in advanced lung cancer patients. Previous research by Amanda et al.[7] in 49 lung cancer patients at Dharmais Cancer Hospital reported 53.1% of subjects showed total energy intake below ESPEN recommendation, 75.5% of subjects were in sufficient carbohydrate intake with 30.6% subjects were in sufficient simple carbohydrate intake. Yoshimura et al.[8] research in healthy subjects obtained a negative correlation between the percentage of LDH isoenzymes with protein and fat intake. Research by Klement and Swenney in six cancer patients given ketogenic diet (carbohydrate <50 grams per day), get the result of tumor regression and tumor growth deceleration. Thus, modification of carbohydrate intake may affect tumor development associated with patient prognosis and survival.[9]

Research about the effect of nutritional intake with the development of cancer cells is still limited. There has been no research on the correlation between carbohydrate intake to LDH activity. It is expected to know the correlation between serum LDH activity with carbohydrate intake in lung cancer patients to support nutritional management in cancer patients from this research.

Methods

Subjects and study design

A cross sectional study was conducted to patients with advanced lung cancer at Dharmais National Center Hospital Jakarta from March 2018 to May 2018 using consecutive sampling method. The minimal estimation of minimum sample size was calculated using the formula for correlation study by taking α=0.05, β=0.20, and r=0.4 with 20% addition, thus a total number 57 subjects were required. The study was approved by the committee of the Medical Research Ethics of the Dharmais Cancer Hospital. All patients enrollments were voluntary and with informed consent.

Inclusion criteria were men and women age 18 years old, diagnosed with primary lung cancer, any stadium, and currently not receiving any therapy. Subject who had diabetes mellitus, end stage chronic kidney disease, chronic liver disease, cardiovascular disease, tuberculosis, pregnant, any bacterial infection, and trauma were excluded from this study.

Data collection

Interviews were conducted to determine characteristic of the subject. Histopathology and cancer stadium data were determined from the medical record. Food intake of total energy and total carbohydrate were obtained using 24 hours food recall method. Anthropometric measurements including weight, height and body mass index (BMI). Weight was measured using SECA® electrodigital scale, height with Microtoise Stature Meter, and BMI was categorized into five groups according to the Asian Pacific criteria of BMI. Serum activity of LDH (IU/L) were measured with an enzymatic spectrophotometry method in automated analyzer (Roche Cobas 6000 C 501).[10] A high LDH value was defined as ≥480 IU/L.[11]

Statistical analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 20 for Windows. The normality of data distribution was analyzed using Kolmogorov-Smirnov. If $p<0.05$ data were normal distributed and were presented in mean ± standard deviation. If it is not normal, data are presented in median and minimum-maximum range of values. The correlation of carbohydrate intake with LDH activity serum were analyzed by Spearman Rank correlation test.

Results

Subject characteristic

Based on the inclusion and exclusion criteria, 60 subjects were willing to take part in this study and signed an informed consent. In blood sampling collection, there were 4 subjects who refused.

Total subjects who followed this study and whose data could be analyzed was 56 subjects. From this study, the average age of subjects was 56.98 ± 10.36 years. A total of 55.4% subjects were male. From the pathology results, it was revealed that all subjects had non-small cell carcinoma types: 78.6% were adenocarcinoma and 21.4% were squamous carcinoma. Based on cancer stage, 96.4% of subjects were in stage IV and 3.6% were in stage III-B. The average value of subjects' BMI was 20.59 ± 3.86 kg/m^2 and 39.3% were in normal range of BMI. These results are shown in Table 1.

Characteristic distribution based on energy and carbohydrate intake

The median value of total energy intake measured by 24 hours food recall method was 1459.25 (425.9–2205.9) kcal (Table 2). From the analysis, 64.3% of subjects had low level of energy intake. Carbohydrate intake to total energy was in a good amount (64.3%).

Characteristics distribution based on LDH serum activity

The median value of LDH serum activity was 541.5 (164–6539) IU/L. There were 34 subjects (63%) had LDH serum value above 480 IU/L. The

Table 1. Characteristic of subjects (n=56)

Characteristic	Results
Age, (year)	56.98 ± 10.36*
Sex, n (%)	
Men	31 (55.4)
Women	25 (44.6)
Education, n (%)	
Low	17 (30.4)
Middle	28 (50)
High	11 (19.6)
Histopathology, n (%)	
Non small cell lung carcinoma	56 (100)
Adenocarcinoma	44 (78.6)
Squamous cell carcinoma	12 (21.4)
Large cell carcinoma	0 (0)
Small cell lung carcinoma	0 (0)
Stage, n (%)	
Stage III-B	2 (3.6)
Stage IV	54 (96.4)
Anthropometric	
Weight (kg)	50 (35–78)
Height (cm)	160.06 ± 7.54
Body mass index (kg/m^2)	20.59 ± 3.86
Body mass index classification, n (%)	
Underweight	18 (32.1)
Normal	22 (39.3)
Overweight	9 (16.1)
Obese 1	7 (12.5)
Obese 2	0 (0)

Table 2. Characteristics distribution based on energy and carbohydrate intake (n=56)

Variable	Results 24 hours food recall
Total energy intake per day (kcal)	1459.25 (425.9–2205.9)
Low, n (%)	36 (64.3)
Average, n (%)	20 (35.7)
Total carbohydrate intake per day (g)	202.54 ± 91.53
Total carbohydrate of total energy, (%)	57.64 ± 10.85
Low, n (%)	7 (12.5)
Average, n (%)	36 (64.3)
High, n (%)	13 (23.2)

characteristic of subjects based on their LDH serum activity is shown in Table 3.

The correlation between carbohydrate intake and LDH serum activity

This research revealed a medium negative correlation (p = 0.017, r = -0.317) between LDH serum activity and total carbohydrate intake per day (in grams) based on 24 hours food recall (Table 4). No significant correlation was found between LDH serum activity and carbohydrate intake of total energy.

Table 3. Characteristics distribution based on LDH serum activity (n=56)

Variable	Results
LDH serum activity (IU/L)	541.5 (164–6539)*
Normal, n (%)	22 (39.3)
High, n (%)	34 (60.7)
Stage III-B	
Normal, n (%)	2 (100)
High, n (%)	0
Stage IV	
Normal, n (%)	20 (37)
High, n (%)	34 (63)

Discussion

A total of 55.4% of the subjects in this study were male. The results of this study are consistent with GLOBOCAN data in 2012 that lung cancer was the leading cause of death with the highest incidence rate in male.[1] Data from WHO also mentioned that lung cancer is the most common type of cancer affecting males in Indonesia.[12]

This study shows the average age of the subjects was 56.98 ± 10.36 years old. The data is consistent with the *Riskesdas* data in 2013.[13] Previous research conducted by Anwar et al.[13] in lung cancer patients in 2010 – 2011 revealed similar results. Based on the research by Amanda et al.[7] in lung cancer patients stage IIIB and IV in Dharmais Cancer Hospital in 2107, the average age of subjects was 55.83 ± 12.62 years with the majority in the range of 45–65 years, which is also similar to the findings of this research.

Classification of lung cancer can be distinguished into non-small cell lung cancer (NSCLC) and small cell lung cancer (SCLC), with prevalence of 80% for NSCLC.[3] All subjects in this research had NSCLC type.

Table 4. The correlation between carbohydrate intake with LDH serum activity (n=56)

Carbohydrate intake	LDH serum	
	r	P
Carbohydrate intake per day (g) 24 hours food recall	- 0.317+	0.017
Carbohydrate intake of total energy (%) 24 hours food recall	- 0.136+	0.316

There were 78.6% subjects who had adenocarcinoma type. Around 96.4% subjects were in the stage IV. The result is similar with the research conducted by Anwar et al.[13] in *Persahabatan* hospital. Research by Siregar et al.[14] which was related to lung cancer patients showed 66.6% of the subjects had adenocarcinoma, while the rest had small cell carcinoma.

Around 39.3% subjects had normal BMI. Previous research in 2017 at the Dharmais Cancer Hospital showed similar results: 36.7% and 22.5% subjects had normal and low BMI, respectively.[7] Total energy intake based on 24 hours food recall method showed median value of 1425.25 (425.9-2205.9) kcal with as much as 64.3% subjects had low energy intake. Disease and external factors can affect food intake and decreased appetite in cancer patients. Substrates released by cancer cells such as pro-inflammatory cytokines and lactate, metabolic changes, neuro-hormonal changes, cancer types, cancer sites, and cancer pain can affect appetite and food intake.[13] External factors that can affect food intake and appetite including age, psychosocial, economic, and sociocultural factors.[14] Research by Solheim et al.[15] revealed that food intake will decrease along with the increase of age. Family support on assisting patients during treatment as well as motivation from family in nutritional support have impact on appetite and food intake.[16] Dharmais Cancer Hospital is a national referral hospital thus the patients come from diverse sociocultural backgrounds. This will affect eating habit and appetite of the patient. Type of food, cooking method, and taste differ from patient's eating habit can affect appetite and food intake.

Based on 24 hours food recall, total carbohydrate intake on energy requirement was 57.64 ± 10.85%, with most subjects having sufficient total carbohydrate intake. Carbohydrates are the main source of energy for the body with a recommended daily intake of 45-65% of total energy.[17] Research by Caesandri et al.[16] in cancer patients showed 80% of subjects consumed carbohydrates as the main food source.

In this study, 63% of patients had LDH activity >480 IU / L. Research by Lee et al.[18] in NSCLC stage IV patients before therapy revealed similar result. High LDH activity correlates to organ metastatic such as bones, other lung parts, and abdomen. Increased LDH activity in cancer cells correlates with inflammation and tumor necrosis which describe the activity of cancer cells. Various comorbid diseases such as acute heart failure, acute coronary syndrome, severe liver dysfunction, end-stage renal disease, and hemolysis can affect the increase of LDH activity.[19] Study by Wulaningsih et al.[20] revealed there were an increased LDH activity in patients with blood, colorectal, and lung cancer. It was shown that LDH activity was associated with cancer prognosis. Proliferation of cancer cells requires a lot of energy resulting in increased activity of glycolysis. Higher glycolysis results in the increased LDH activity to convert pyruvate into lactate which is the main ATP component in cancer cells. Increased LDH activity reflects increased lactate in cancer cells. Lactate will come out from cancer cells and affect pathways which cause increased angiogenesis, tumor migration and metastasis, increased resistance to therapy, and decreased immunity.[21]

This study found 65.4% of stage IV lung cancer subjects had high LDH values. Stage IV of lung cancer illustrates the presence of distant metastases, either to the contralateral lung, nodules in the pleura, malignant pleural effusions, pericardial effusion (stage 4A), or metastases to other organs such as liver, brain, bones or suprarenal (stage 4B).[2] Research conducted by Hermes et al.[19] in SCLC patients showed LDH activity was found

to increase consistently with the number of organs affected.

Medium negative correlation ($r = -0.317$, $p = 0.017$) was found between total carbohydrate intake, based on 24 hours food recall method, with serum LDH activity. Intake analysis using the 24 hours food recall method is widely used in surveillance studies to determine food intake in a population.[22] Food data from 24 hours recall describes short-term intake. LDH activity increases to supply high glucose needs by catalyzing the change of lactate to pyruvate as gluconeogenesis component. In addition, to supply the need for glucose as the basic ingredient of glycolysis, the intake of external carbohydrates is needed as the main source of glucose. This amount of intake can be analyzed by using 24 hour food recall.

The Warburg effect, which is described as the tendency of cells to get energy in the form of ATP through anaerobic glycolysis process even though in a state of sufficient oxygen, occurs in cancer cells. LDH is an enzyme which converts pyruvate into lactate in the anaerobic glycolysis process.[23] In cancer cells, most of the lactate is exported out of cells by increasing the expression of monocarboxylate transporters (MCT), which acts as facilitator to transport lactate out of the cell. Continuous formation of lactate in order to obtain ATP occurs due to oncogenes and mutations in tumor suppressors in cancer cells. Furthermore, in cancer cells, there is an increased of HIF-Iα transcription factor and c-Myc oncogene, also repressed p53 expression. These increase GLUT (glucose transporter) expression and translocation which then results in increased lactate formation. Expression and activity of glycolytic enzymes, especially LDH isoenzymes LDHA, also escalated due to HIF-Iα, c-MYC, and down regulation of p53. Increased isoenzyme LDHA will convert pyruvate to lactate. Moreover, mitochondrial dysfunction as well as upregulation of MCT1 and MCT4 as lactate transporters also increase lactate production in cancer cells.[24]

Increased glycolysis rate to obtain ATP due to oncogenes and mutations of tumor suppressors in cancer cells also causes NAD+ depletion. To achieve balance between NADH and NAD+, in order to maintain the glycolysis process, pyruvate will be further converted to lactate by the LDH enzyme.[24] If the glucose obtained from carbohydrate source is reduced the LDH enzyme will increase in order for the glycolysis process to obtain ATP and maintain the redox balance by converting pyruvate to lactate. High rates of glycolysis lead to decreased glycogen reserves in the liver resulting in increased proteolysis for gluconeogenesis. Chronic proteolysis is one of cancer cachexia pathophysiology of.[25] If too much glucose is given then it will be used by cancer cells to process anaerobic glycolysis and form ATP by converting pyruvate to lactate.[26] This is supported by the overexpression of GLUT 1 transporters in cancer cells as the main transporters of glucose.[27] The high level of lactate in cells stimulates VEGF production which has a role in cell migration and angiogenesis process. Lactate in cancer cells can act as an antioxidant resulting in resistance to chemotherapy and radiation.[21]

The ESPEN recommendation of total energy intake for cancer patients is 25–30 kcal /bodyweight/day. Inadequate energy intake can cause malnutrition in cancer patients. Adequate energy intake does not affect the growth of cancer cells. Basal energy requirements in patients with lung cancer are higher than other types of cancer.[28] The mechanism of high basal energy demand in lung cancer is unclear. It may be related to systemic inflammation.[29]

In conclusion, if carbohydrate source is reduced, the LDH enzyme will increase to sustain the glycolysis process. The results of this study showed adequate carbohydrate is needed to improve the quality and life expectancy in lung cancer patients.

This study was the first cross sectional study aiming to find the correlation between carbohydrate intake with LDH activity as one of the determinants of prognosis in lung cancer patients. The advantage of this study was using serum LDH activity biomarkers as one of the prognostic markers in lung cancer patients. In addition, calibrated anthropometry tools were used to measure height and weight. The collection of blood specimens and the analysis of laboratory results were performed by well-trained laboratory personnel and analysts.

Limitation in this study was the utilization of 24 hours food recall method to determine the carbohydrate intake. This method relies on the memory and assumptions of the intake portions by each subject. However, this had been anticipated, thus we used trained personnel and food models to help the subject to remember and estimate the number of foods.

Further research may be needed using LDH-A isoenzymes, which is a more specific LDH markers, to assess carbohydrate metabolism in lung cancer patients.

Conflict of Interest

None of the other authors have conflict of interest. No educational grant is provided to the rest of authors.

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References

1. GLOBOCAN. Estimated cancer incidence, mortality dan prevalence worldwide in 2012, International Agency for Research on Cancer, World Health Organization 2012. Available at : http://globocan.iarc.fr/old/FactSheets/cancers/lung-new.asp (accessed 2017 Sept 13)
2. Komite Nasional Penanggulangan Kanker (KPKN). Panduan nasional penanganan kanker paru. Kementrian Kesehatan Republik Indonesia. 2105. Available at : http://kanker.kemkes.go.id/ (accessed 2017 Sept 12)
3. Cruz, C.S. Dela , Tanoue LT, Matthay RA. Lung cancer: epidemiology, etiology, and prevention. Clin Chest Med 2011;32(4):1-61. [Google Scholar]
4. Doherty JR, Cleveland JL. Targeting lactate metabolism for cancer therapeutics. J Clin Invest 2013;123(9):3685-92. [Google Scholar]
5. Agrawal A, Gandhe MB, Gupta D, Reddy MVR. Preliminary Study on Serum Lactate Dehydrogenase (LDH)-Prognostic Biomarker in Carcinoma Breast. J Clin Diagn Res JCDR 2016;10(3). [Google Scholar]
6. Verma A, Phua CK, Sim WY, Algoso RE, Tee KS, Lew SJW, et al. Pleural LDH as a prognostic marker in adenocarcinoma lung with malignant pleural effusion. Medicine. 2016;95(26):e3996.
7. Amanda P, Sunardi D, Sutandyo N. Correlation between carbohydrate, protein and fat intake with serum c-reactive protein level in lung cancer patients stage IIIB-IV. World Nutr J 2018;1(2):31-7. [Google Scholar]
8. Yoshimura T, Miyoshi T, Imaki M, Tamura T, Fujii M, Hori Y, et al. Effect of high carbohydrate diet on serum lactate dehydrogenase isozyme pattern in Japanese young men. Acta Biol Hung 1986;37(3-4):243-8. [Google Scholar]
9. Klement RJ, Sweeney RA. Impact of a ketogenic diet intervention during radiotherapy on body composition: I. Initial clinical experience with six prospectively studied patients. BMC Res Notes 2016;9(143):1-13. [Google Scholar]
10. Groussard C, Morel I, Chevanne M, Monnier M, Cillard J, Delamarche A. Free radical scavenging and antioxidant effects of lactate ion: an in vitro study. J Appl Physiol Bethesda Md 2000;89(1):169-75. [Google Scholar]
11. Zumárraga JP, Am B, Rosa LPDL, Caiero MT, Camargo OPD. Serum values of alkaline phospatase and lactate dehydrogenase in osteosarcoma. Acta Ortop Bras 2016;24(3):142-6. [Google Scholar]
12. WHO. Cancer. February 2017. Available at : http://www.who.int/mediacentre/factsheets/fs297/en/ (accessed 2017 Sept 13)
13. Anwar A, Syahruddin E, Aniwidyaningsih W, Widyahening IS, Susanto AD. The causes of death analysis in lung cancer patient. J Respir Indo 2014;34:11-6. [Google Scholar]
14. Siregar YS, Widyaningsih W, Syahruddin E. Indeks Massa Tubuh, Persentase Otot Rangka dan Albumin pada Pasien Kanker Paru Karsinoma Bukan Sel Kecil Sebelum dan Setelah Kemoterapi. JRI 2016;36(2):73-82. [Google Scholar]
15. Solheim TS, Blum D, Fayers PM, Hjermstad MJ, Stene GB, Strasser F. Weight loss, appetite loss and food intake in cancer patients with cancer cachexia: Three peas in a pod? – analysis from a multicenter cross sectional study. Acta Oncol 2014;53(4):539-46. [Google Scholar]
16. Caesandri SDP, Adiningsih S. Peranan dukungan pendamping dan kebiasaan makan pasien kanker selama menjalani terapi. Media Gizi Indonesia 2015:10(2). Available at :https://e-

journal.unair.ac.id/MGI/article/view/3376 (accessed 2018 May)
17. Ross CA, Caballero B, Cousins RJ, Tucker KL, Zieger TR. Modern Nutrition in health and disease. 7th edition. Wolters Kluwer. Lippincot William&WIlkins; 2014.pg 36-57.
18. Lee DS, Park KR, Kim SJ, Chung MJ, Lee YH, Chang JH. Serum lactate dehydrogenase levels at presentation in stage IV non-small cell lung cancer: predictive value of metastases and relation to survival outcomes. Tumor Biol 2016;37(1):619-25. [Google Scholar]
19. Hermes A, Gatzemeier U, Waschki B, Reck M. Lactate dehydrogenase as prognostic factor in limited and extensive disease stage small cell lung cancer – A retrospective single institution analysis. Respir Med 2010;104(12):1937-42. [Google Scholar]
20. Wulaningsih W, Holmberg L, Garmo H, Malmstrom H, Lambe M, Hammar N. Serum lactate dehydrogenase and survival following cancer diagnosis. Br J Cancer 2015;113(9):1389-96. [Google Scholar]
21. Hirschhaeuser F, Sattler UGA, Mueller-Klieser W. Lactate: A metabolic key player in cancer. Cancer Res 2011;71(22):6921-5. [Google Scholar]
22. Naska A, Lagiou A, Lagiou P. Dietary assessment methods in epidemiological research: current state of the art and future prospects. F1000Research 2017;6:1-8. [Google Scholar]
23. Multhoff G, Molls M, Radons J. Chronic inflammation in cancer development. Front Immunol 2012;2(98):1-17. [Google Scholar]
24. Chaiyasit K, Jularattanaporn V, Muangsri K. Cancer cachexia and metabolism:a challenge in nutrition oncology. JAASP 2012;1(4):187-93. [Google Scholar]
25. San-Millán I, Brooks GA. Reexamining cancer metabolism: lactate production for carcinogenesis could be the purpose and explanation of the Warburg Effect. Carcinogenesis 2017;38(2):119-33. [Google Scholar]
26. Allen BG, Bhatia SK, Anderson CM, Eichenberger-Gilmore JM, Sibenaller ZA, Mapuskar KA. Ketogenic diets as an adjuvant cancer therapy: History and potential mechanism. Redox Biol 2014;2:963-70. [Google Scholar]
27. Tan Z, Yang C, Zhang X, Zheng P, Shen W. Expression of glucose transporter 1 and prognosis in non-small cell lung cancer: a pooled analysis of 1665 patients. Oncotarget 2017;8(37):60954-61. [Google Scholar]
28. Arends J, Bachmann P, Baracos V, Barthelemy N, Bertz H, Bozzetti F. ESPEN guidelines on nutrition in cancer patients. Clin Nutr 2017;36(1):11-48. [Google Scholar]
29. Melkonian SC, Daniel CR, Ye Y, Pierzynski JA, Roth JA, Wu X. Glycemic index, glycemic load, and lung cancer risk in non-hispanic whites. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 2016;25(3):532-9. [Google Scholar]

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ORIGINAL ARTICLE

Correlation between Zinc Intake and Zinc Serum Levels with C-reactive Protein Levels in Head and Neck Cancer Patients

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Abstract

Introduction The inflammatory process of head and neck cancer leads to increased proinflammatory cytokines and the synthesis of c-reactive protein (CRP), which then cause metabolic alteration and anorexia in patients. Zinc is one of nutrients that has an important role in suppressing inflammation, however it is reported that around 65% of head and neck cancer patients had zinc deficiency. The aim of this cross sectional study is to determine the correlation between zinc intake and serum zinc levels with CRP level as an effort in reducing inflammation process in head and neck cancer patients.

Methods and Results Subjects were collected by using consecutive sampling in the Oncology Clinic Dharmais Cancer Hospital. From 49 subjects, 67.3% were men, most subjects were in the age range between 46–65 years old. The most common (65.3%) was nasopharyngeal cancer and 69.4% were already in stage IV. All subjects (100%) in this study had zinc intake below the recommended dietary allowance (RDA) in Indonesia. The mean serum zinc level of the subjects was 9.83±2.62 µmol/L. Most subjects have elevated CRP levels. There was a weak negative correlation between zinc levels and CRP levels (r =-0.292, p =0.042), however there was no correlation between zinc intake and CRP levels of subjects (r =-0.25).

Conclusion There was negative correlation between serum zinc level and CRP levels in the subjects.

Keywords c-reactive protein levels, head and neck cancer, zinc intake, zinc serum levels

Introduction

Head and neck cancer is the seventh most common malignant disease in the world, where the number of new cases each year is increasing and causing many deaths.[1–3] The inflammatory process in cancer leads to increased proinflammatory cytokines such as interleukin (IL)-1, IL-6, tumor necrosis factor-alpha (TNF-α) and interferon-γ (IFN-γ).[4,5] The increase of proinflammatory cytokines will cause metabolic alteration, loss in appetite, induce satiety, resulting in anorexia and weight loss in cancer patients.[6] As response to the inflammatory process, the body will increase acute phase proteins synthesis in the liver as a defense mechanism.[6] C-reactive protein (CRP) is one of the acute phase proteins that are sensitive to acute inflammation, infections, and tissue damage.[7]

Zinc is a nutrient that plays an important role in suppressing inflammation, however it is reported that about 65% of head and neck cancer patients have zinc deficiency.[8] Zinc deficiency in head and

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neck cancer patients is thought to be due to low zinc intake, low bioavailability, high molar ratio of phytate to zinc in food, and increased amount of reactive oxygen species (ROS).[9–11] Zinc deficiency in cancer patients results in decreased appetite and dietary intake, taste and smell disorder, immune system dysfunction, and increased risk of complications.[8,12] Zinc deficiency also affects the formation of cytokines, especially IL-1β, IL-2. IL-6, and TNF-α. The interaction between zinc and inflammatory cytokines is interrelated. Cytokines can increase and decrease the regulation of cellular zinc transporter expression in response to an increased need for zinc in inflammatory conditions.[13] However, zinc also has the ability to decrease the production of inflammatory cytokines through the up regulation of zinc finger protein (A20 protein) which inhibit the activation of NF-κB (nuclear factor kappa B), the major transcription factor in inflammation.[13,14]

The aim of this study is to determine the correlation between zinc intake and serum zinc levels with CRP levels in head neck cancer patients as an effort to reduce inflammation and, therefore, reduce anorexia.

Methods

Subjects and Study Design

This cross sectional study conducted in Oncology Clinic of Dharmais Cancer Hospital, Jakarta. Sample size was determined based on the correlation analysis ($\alpha = 0.05$; $\beta = 0.20$; $r = 0.4$), with estimated 10% of drop out, the sum of samples was 52 subjects. However, the subjects who completed the research were 49 subjects. Inclusion criteria were: patients at the Oncology Clinic of Dharmais Cancer Hospital who were diagnosed with head and neck cancer, stage I-IV, age above 18 years, had not received surgical therapy, radiation, or chemotherapy, willing to participate by signing the informed consent. Exclusion criteria were: had acute or chronic infections, had diarrhea, impaired liver and kidney function.

Data Collection

Data collection was conducted in September 2016 until December 2016 after obtaining approval from the Health Research Ethics Committee of Dharmais Cancer Hospital Number 054 / KEPK / IX / 2016. Subject characteristics including age and sex were collected by interview. Assessment of zinc intake was done by using semi-quantitative FFQ, which was then processed using Nutrisurvey 2007. Anthropometric measurements were performed to obtain data of height and weight. Heights were measured using Microtoise Stature Meter 200 cm (with 0.1 cm accuracy). Weight measurement was done by using Seca electro digital scale 876, Germany. Both anthropometric measurements were performed twice and the average results will be used. Nutritional status assessment were based on body mass index. Type and stage of cancer were obtained from medical records. Three mL of blood samples were taken from the cubital vein, which were then centrifuged at 3000 rpm to obtain the serum. Atomic absorption spectrophotometry method was used for the serum zinc examination using 1 ml of serum which has been transferred to the acid-washed serum cup. Whereas examination of CRP levels used immunoturbidimetry method of COBAS 501.

Statistical Analysis

Data were analyzed by using SPSS version 20.0. Normality test was done by using Kolmogorov Smirnov. Spearman correlation test was used to determine correlation between zinc intake with CRP levels and serum zinc levels with CRP levels.

Results

A total of 49 subjects participated in this study. Most subjects (67.3%) were male, the mean age was 48.33±12.73 years old and most of them (53.1%) were in the age range 46-65 years. Characteristic subjects based on age, gender, type of cancer, stage of cancer, status and nutritional intake, serum zinc levels, and CRP levels are shown in Table 1. Types of cancer consist of nasopharyngeal cancer, larynx, tonsil, sinonasal, and tongue. Nasopharyngeal cancer was the most common (32 people (65.3%)). Most subjects (69.4%) were in stage IV. Mean of body mass index was 22.20±4.2 kg/m^2: 42.9% subjects were overweight, 32.7% were normoweight, and 24.5% were underweight.

Table 1. Characteristics of the subjects

Characteristics	Frequency 47 (%)	Mean±SD or Median (min–max)
Age(year)		48.33±12.73
18 – 25	1 (2)	
26 – 45	19 (38.8)	
46 – 65	26 (53.1)	
>65	3 (6.1)	
Gender		
Male	33 (67.3)	
Female	16 (32.7)	
Type of cancer		
Nasopharynx	32 (65.3)	
Larynx	5 (10.2)	
Sinonasal	4 (8.2)	
Tonsils	4 (8.2)	
Tongue	3 (6.1)	
Stage of cancer		
I	1 (2.0)	
II	7 (14.3)	
III	7 (14.3)	
IV	34 (69.4)	
Body mass index (kg/m^2)		22.20±4.52
Underweight	12 (24.5)	
Normoweight	16 (32.7)	
Overweight	21 (42.9)	
Energy intake		1434.07±558.02
Adequate (≥30 kcal/kg BW/day)	15 (30.6)	
Inadequate (<30 kcal/kg BWday)	34 (69.4)	
Protein intake		46.66±22.96
Adequate (≥1 g/kgBW/day)	16 (32.7)	
Inadequate (<1 g/kgBW/day)	33 (67.3)	
Zinc intake		
Adequate (≥13 mg/day)		3.70 (1.20-11.70)
Inadequate (<13 mg/day)	0 (0)	
	47 (100)	

The mean zinc serum levels were 9.3±2.62 µmol/L and more than half the subjects (59.2%) has low serum zinc level. The median CRP serum of the subjects was at 6.03 (0.33 to 339.29) mg/L and most (51.0%) subjects had levels greater than 5 mg/L (data are shown in Table 2).

Table 2. Zinc serum and CRP levels of the subjects

Variable	Frequency n (%)	Mean±SD or Median (min–max)
Zinc serum (µmol/L)		9.83±2.62
Adequate	20 (40.8)	
Deficiency	29 (59.2)	
CRP serum (mg/L)		6.03 (0.33–339.29)
Adequate	24 (49.0)	
High	25 (51.0)	

This study found a negative weak correlation between serum zinc levels and CRP levels (r = -0.292, p =0.042), but no correlation between zinc intake and CRP levels (r= -0.25, p =0.86). Data are summarized in Table 3.

Table 3. Correlation between zinc intake with CRP levels and zinc serum levels with CRP levels

Variable	CRP serum (mg/L)	
	r	p
Zinc intake (mg/day)	-0.25	0.86
Zinc serum (µmol/L)	-0.292	0.042

Discussion

Dietary zinc intake of all subjects in this study did not meet the Indonesian RDA (13 mg/day for male and 10 mg/day for female).[12] The lowest and highest intake of zinc in male subjects were 1.5 mg/day and 11.7 mg/day, while in female subjects the lowest zinc intake was 1.2 mg/day and the highest was 6.3 mg/day. Similar results were obtained by Westin et al[13] who found the zinc intake in cancer subjects for two days food record was 9±2 mg/day. A cross sectional study by Irene et al[3] in the 2011 found that most of the subjects (80.6%) were included in the inadequate zinc intake group. The lack of zinc intake in this study is thought to be due to various factors including the presence of intake disorders due to tumor sites in the aerodigestive tract and pain that causes the anorexia. Most of the subjects in this study deliberately reduced the portion of food and avoid eating red meat, offal, eggs, milk, and animal-derived food, albeit high protein food are the main source of zinc in the diet. Therefore, the increase of zinc intake depends on increasing protein intake.

The mean serum zinc level in this study was 9.83±2.62 µmol/L and 52% of subjects were in the low serum zinc group. This is similar to study by Irene et al[3] which found serum zinc level median of 7.42 (4.16-14.67) µmol/L and 88.89% of the subjects had low serum zinc level. Sattar et al[14] also revealed that zinc concentrations in lung cancer patients were lower than controls. Based on the theory, low zinc levels in cancer patients can be caused by low intake, inflammatory state, the influence of proinflammatory cytokines, and increased number of ROS.[3–5,8,11] In this study most of the stage IV subjects (61.8%) had low serum zinc levels. This low serum zinc level is thought to be associated with low total zinc intake of subjects and the redistribution to the intracellular compartment as a defense mechanism.

The median of serum CRP level in this study was 6.03 mg/L with a wide range of 0.3 to 339.29 mg/L. A total of 51.0% of subjects had elevated CRP levels above 5 mg/L. Increased levels of CRP may be associated with an increased risk of cancer, proportional to the severity of disease, and increased tumor size.[15,16] Increased levels of CRP is also associated with poor prognosis of cancer.[10]

In this study, there was a statistically significant negative weak correlation between serum zinc level and serum CRP levels in head and neck cancer patients (r =-0.292, p =0.042). No literature mention the correlation between serum zinc levels and serum CRP levels in head and neck cancers yet, however there were reports of zinc levels with CRP levels correlation in lung cancer patients. Study by Sattar et al[14] in lung cancer subjects had significant negative correlation between zinc and CRP concentration (r =-0.66, p <0.05). This is consistent with the theory that zinc has anti-inflammatory properties which can inhibit the formation of

proinflammatory cytokines and then decrease the CRP. Studies of cell cultures in less and enough zinc conditions found that zinc induces upregulation of A20 protein which is one of the inhibitors of NF-κB activation as a major transcription factor of inflammation.[17] However, zinc deficiency condition may also induce the apoptosis and endothelial cell dysfunction due to increased concentrations of proinflammatory cytokines and oxidative stress.[8]

In conclusion, we found negative correlation between serum zinc level and c-reactive protein level in head and neck subject, so it can be used as the basic data for further research development of the possibility of providing supplementation for head and neck cancer patients.

Conflict of Interest

Some of this study funds was supported by the Tulang Bawang district government.

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References

1 Everett EV. Head and Neck Cancer. In: Harrison's Principles of Internal medicine. 18th edition. USA: The Mc-Graw Hill Companies; 2012. [Google Scholar]

2 Argiris A, Eng C. Epidemiology, Staging, and Sreening of Head and Neck Cancer. In: Head and Neck Cancer. USA: Kluwer Academic Publishers; 2004. [Google Scholar]

3 Boyle P, Levin B, editor. World Cancer Report 2008. International Agency for Research on Cancer. World Health Organization; 2008.

4 Muliawati Y, Haroen H, Rotty LWA. Cancer anorexia - cachexia syndrome. Acta Medica Indones 2012;44:154. [Google Scholar]

5 Prasad AS, Bao B, Beck FWJ, Sarkar FH. Zinc-suppressed inflammatory cytokines by induction of A20-mediated inhibition of nuclear factor-κB. Nutrition 2011;27:816. [Google Scholar]

6 Skipworth RJE, Stewart GD, Dejong CHC, Preston T, Fearon KCH. Pathophysiology of cancer cachexia: Much more than host–tumour interaction. Clin Nutr 2007;26:667. [Google Scholar]

7 Allin KH, Nordestgaard BG. Elevated C-reactive protein in the diagnosis, prognosis, and cause of cancer. Crit Rev Clin Lab Sci 2011;48:155. [Google Scholar]

8 Prasad AS, Beck FW, Snell DC, Kucuk O. Zinc in cancer prevention. Nutrition and cancer 2009 Nov;61(6):879-87. [Google Scholar]

9 Irene . Kadar seng serum pada pasien kanker kepala dan leher serta hubungannya dengan status radiasi (tesis. Jakarta: Universitas Indonesia; 2012. [Google Scholar]

10 Garofalo JA, Erlandson E, Strong EW, Lesser M, Gerold F, Spiro R, et al. Serum zinc, serum copper, and the Cu/Zn ratio in patients with epidermoid cancers of the head and neck. J Surg Oncol 1980;15:381. [Google Scholar]

11 Abdulla M, Biörklund A, Mathur A, Wallenius K. Zinc and copper levels in whole blood and plasma from patients with squamous cell carcinomas of head and neck. J Surg Oncol 1979;12:107. [Google Scholar]

12 Mahdavi R, Faramarzi E, Mohammad-Zadeh M, Ghaeammaghami J, Jabbari MV. Consequences of radiotherapy on nutritional status, dietary intake, serum zinc and copper levels in patients with gastrointestinal tract and head and neck cancer. Saudi Med J 2007;28:435. [Google Scholar]

13 Foster M, Samman S. Zinc and regulation of inflammatory cytokines: implications for

cardiometabolic disease. Nutrients 2012;4:676. [Google Scholar]
14 Bao B, Ahmad A, Azmi AS, Wang Z, Banerjee S, Sarkar FH. The Protective Role of Zinc in Cancer: A Potential Chemopreventive Agent. In: Shankar S, Srivastava RK, editors. Nutrition, Diet and Cancer. Springer Netherlands; 2012. [Google Scholar]
15 Permenkes Tentang Angka Kecukupan Gizi [Internet]. Gizinet. [cited 2015 Oct 24]. Available from: http://gizi.depkes.go.id/permenkes-tentang-angka-kecukupan-gizi
16 Westin T, Ahlbom E, Johansson E, Sandström B, Karlberg I, Edström S. Circulating levels of selenium and zinc in relation to nutritional status in patients with head and neck cancer. Arch Otolaryngol Head Neck Surg 1989;115:1079. [Google Scholar]
17 Sattar N, Scott HR, McMillan DC, Talwar D, O'Reilly DS, Fell GS. Acute-phase reactants and plasma trace element concentrations in non-small cell lung cancer patients and controls. Nutr Cancer 1997;28:308. [Google Scholar]
18 Siren PM. Siren MJ. Systemic zinc redistribution and dyshomeostasis in cancer cachexia. J Cachexia Sarcopenia Muscle 2010;1:23. [Google Scholar]
19 Chen HH, Wang HM, Fan KH, Lin CY, Yen TC, Liao CT, Chen IH, Kang CJ, Huang SF. Pre-treatment levels of C-reactive protein and squamous cell carcinoma antigen for predicting the aggressiveness of pharyngolaryngeal carcinoma. PloS one. 2013 Jan 31;8(1):e55327.
20 Aref H, Refaat S. CRP evaluation in non-small cell lung cancer. Egypt J Chest Dis Tuberc 2014;63:717. [Google Scholar]

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ORIGINAL ARTICLE

Nutritional Status Influences High-Molecular Weight (HMW) Adiponectin Levels in Breast Cancer Patients: Comparison with Healthy Controls

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Abstract

Introduction Breast cancer is the leading killer of women in Malaysia. Nutritional status and adiponectin are modifiable risk factors for breast cancer occurrence which can be efficiently targeted. The purpose of this study was to determine the relationship between nutritional status and high molecular weight (HMW) adiponectin levels among breast cancer patients as compared to controls.

Methods This was a case- control study, conducted in Hospital Universiti Sains Malaysia and Universiti Sains Malaysia campus. Newly diagnosed breast cancer cases (n=55) were assigned as cases while healthy controls (n=58) were staff members of HUSM and USM campus. Sociodemographic and reproductive data were obtained with a standard questionnaire while the dietary data was obtained from a validated diet history questionnaire. Anthropometric assessments [weight, height, hip, waist circumference (WC) and body fat composition] were measured while overnight fasting venous blood samples were analysed for lipid profiles, glucose, insulin, high sensitivity C-reactive protein and HMW adiponectin.

Results A significant linear negative relationship exists between WC and HMW adiponectin (β=-0.05; p=0.005) among breast cancer cases. Additionally, HDL cholesterol was positively associated with HMW adiponectin (β=1.83; p=0.010) among the cases. BMI was negatively associated with HMW adiponectin (β=-0.02; p=0.001) among healthy controls.

Conclusion Our findings suggest that WC, BMI and HDL cholesterol had significant relationship with HMW adiponectin. Low levels of HMW adiponectin, low WC and high HDL levels may be protective against breast cancer.

Keywords nutritional status, high-molecular weight adiponectin, waist circumference, body mass index, high density lipoprotein cholesterol, breast cancer

Introduction

Breast cancer is the most common cancer among Malaysian women, where its rates in Malaysia are higher than that reported in Southeast Asian countries. [1] One of the risk factos for breast cancer is obesity[2] where the prevalence of overweight, obesity and abdominal obesity among Malaysian women have been reported to be 28.3%, 20.6% and

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60.2%, respectively. In addition, the National Health and Morbidity Survey (NHMS) 2015 reported that there was an increasing trend in the adiposity prevalence among Malaysian women in 2015 compared with 2011.[3]

Nutritional status is an essential predictor of clinical outcome such as malnutrition. Impaired nutritional status have been linked with inadequate food intake, unsustained hunger and metabolic inefficiency.[4] Several studies modulated nutritional status as the assessment of anthropometry and body composition such as body mass index and body fat distribution.[5] In contrast, nutritional status also has been defined in the scope of dietary intake by considering food intakes and utilisation of nutrients were affecting the consumer‘s health condition.[6]

Two main modifiable risk factors in prevention of cancer are body weight and dietary intake.[7] However, the American Cancer Society provided new nutritional guidelines for prevention of cancer by grouping the recommendations into various categories of weight management, physical activity and dietary intake.[8] This recommendation is useful as nutritional education in promoting good health and optimum nutritional status among public. Moreover, in an effort to increase patient’s quality of life, nutritional status is an important concern. For example, the Subjective Global Assessment (SGA) form has been utilized to screen patients with malnutrition in HUSM. This nutritional assessment tool may guide the incorporation of nutritional intervention in overcoming disease complications.[9]

Previously, adipose tissue was thought to function only for storing fat for energy. However, recently it was recognized that adipose tissue is an endocrine organ that releases large amounts of biochemical modulators, including adipokines.[10] Among these adipokines, adiponectin which abundantly circulates in the plasma at high concentrations (0.5 to 30.0 μg/ml) and accounts for up to 0.01% of total plasma proteins[11] are thought to play a major role in breast cancer development. Adiponectin exists in the plasma as trimer, hexamer or high molecular weight (HMW) adiponectin isoforms. Among these, the HMW isoform is the most biologically active form and is strongly associated with insulin resistance, metabolic syndrome, and cardiovascular disease.[12]
Adiponectin is considered to be a protective hormone because it plays a major role in the regulation of glucose due to its potent insulin-sensitizing activity which affect the uptake of glucose in the muscle. Furthermore, it is involved in lipid homeostasis, and in the pathophysiology of atherosclerosis due to its anti-inflammatory activity.[13] Numerous studies have shown that adiponectin has an inhibitory effect on the proliferation of various cell types, including aortic smooth muscle, endothelial tissue and several types of cancer cells.[14] It has been hypothesized that adiponectin act directly on breast cancer cells by inhibiting proliferation and angiogenesis or by stimulating apoptosis.[15] Serum adiponectin is therefore a potential therapeutic target for breast cancer treatment or protection.[16]

Although adiposity is a well-established health problem related to breast cancer, the data on the association between HMW adiponectin and adiposity obtained from various epidemiological studies has remained elusive in Asian countries, particularly Malaysia. Therefore, the aim of this study was to investigate the relationship between nutritional status and HMW adiponectin levels among breast cancer patients as compared to healthy controls. It is hoped that the data will provide essential information for health professionals planning public health programs for breast cancer prevention in Malaysia with respect to weight and reproductive health management.

Methods

Setting and subjects

This is a case-control study conducted in Kelantan, Malaysia, approved by the Human Research and Ethical Committee of USM. The cases include newly diagnosed women with histologically confirmed malignant breast cancer (stages I to IV) who had not yet undergone any therapies (except for analgesics and/or surgery) while the controls comprised of healthy volunteers with no known history of breast cancer, any other medical illness or medication use. The inclusion criteria for both cases and controls were women aged 20 to 59 years old who were neither pregnant nor lactating during the study periods. Both cases and controls were recruited using a convenience sampling method while the controls were selected to match the cases for age ± 10 years.

Measurements

Written informed consents were obtained and the respondents underwent face-to-face interviews using a set of questionnaires including validated diet history questionnaire (DHQ).[17] The respondents were measured for height using a portable stadiometer, weight and fat composition using a body composition analyzer (TANITA SC-330, Japan), waist circumference (WC) and hip circumference using a non-extendible tape. BMI was calculated by dividing the weight (kg) by the square of the height (m). Fasting blood samples were collected for biochemical test. Serum HMW adiponectin concentrations were measured using a sandwich ELISA kit.

Statistical analyses were performed using SPSS for Windows, version 22.0. Categorical data were presented as frequency (percentage), while chi-squared or Fisher's exact tests were used to determine the association between any categorical variables. Independent samples t-test was used to compare means and multiple linear regression analyses were used to investigate the associations between HMW adiponectin levels and nutritional status. A p value of less than 0.05 was considered as statistically significant.

Results

A total of 55 newly diagnosed breast cancer cases and 58 healthy controls were recruited (Table 1). The mean (SD) age for cases and controls were 46.84 (7.87) years and 40.79 (9.78) years respectively. Education level of the cases mostly from primary or secondary school when compared to controls most of whom graduated from the university. The majority of the respondents were premenopausal women, practiced family planning, breastfed their babies, with no first degree family history of breast cancer. A higher percentage of cases (58.2%) were exposed to second-hand smoke as compared to controls (29.3%).

Multiple linear regression analysis revealed that there was a significant linear negative relationship between WC and HMW adiponectin (p =0.005) where a 10 cm increase in WC lowers HMW adiponectin levels by 0.5 µg/ml (95% CI: -0.8, -0.2 µg/ml) (Table 2). In addition, HDL cholesterol was positively associated with HMW adiponectin (p= 0.006). Furthermore, a 1 mmol/L increase in HDL cholesterol increases HMW adiponectin levels by 1.83 µg/ml (95% CI: 0.47, 3.02 µg/ml).

Table 3 shows the associations of nutritional status with HMW adiponectin among healthy controls. Multiple linear regression analysis revealed that there was a significant (p =0.001) linear negative relationship between BMI and HMW adiponectin where a 1 kg/m2 increase in BMI lowers HMW adiponectin levels by 0.20 µg/ml (95% CI: -0.32, -0.08 µg/ml).

Discussion

Mean age at breast cancer diagnosis showed that mean age breast cancer cases were significantly older than healthy controls. This result is in a good agreement with the previous results reported by Fuhrman et al., who also had frequency matching case control by birth year in 5- year strata in United States.[18] Age matched in this study was quite wide (±10 years) because of the difficulty faced in matching the older cases with older controls free from diseases as older women are synonym with the disease. However, one study from Vietnam found no significant difference in age between case and control groups matched on a single year of age.[19]

According to a study conducted in Malaysia on breast cancer awareness, they concluded that education level emerged to contribute to health behavior and knowledge level, based on an outcome of women had higher education level were significantly more aware of breast cancer.[20] In this present study, breast cancer cases mostly from primary and secondary school compared to healthy controls most of whom graduated from university. Poor education had accounted for late stage at presentation of breast cancer.[21] A qualitative study was conducted by exploring the decision-making experiences of breast cancer women and discovered four phases in the decision-making process (discovery, confirmatory, deliberation and decision). Their knowledge, understanding and experiences affect the final decision for treatment.[22]

Majority of the breast cancer cases were premenopausal women and this may be explained

Table 1 Baseline characteristics of the respondents[a]

Variables	Cases (n=55)	Controls (n=58)	p value[c]
Age (years)[b]	46.84 (7.87)	40.79 (9.78)	0.001
Education level			
Primary/secondary school	35 (63.6)	21 (36.2)	0.004
University	20 (36.4)	37 (63.8)	
Exposure to second-hand smoke			
Yes	32 (58.2)	17 (29.3)	0.002
No	23 (41.8)	41 (70.7)	
Monthly household income (RM)[d,e]			
<RM 2,300	31 (57.4)	4 (7.3)	<0.001
RM 2,300-5,599	13 (24.1)	34 (61.8)	0.403
>RM 5,600	10 (18.5)	17 (30.9)	
Family planning			
Yes	28 (50.9)	37 (63.8)	0.167
No	27 (49.1)	21 (36.2)	
Age during first pregnancy,years[b]	25.75 (5.23)	25.34 (2.66)	0.631
Parity[b]	3.61 (2.03)	3.25 (1.97)	0.335
Breastfeeding			
Yes	50 (90.9)	48 (82.8)	
No	5 (9.1)	10 (17.2)	0.209
Menopausal status			
Premenopause	42 (76.4)	51 (87.9)	
Postmenopause	13 (23.6)	7 (12.1)	0.113
First degree family history with breast cancer			
Yes	6 (10.9)	2 (3.4)	0.142
None	49 (89.1)	56 (96.6)	

Note. SD=Standard deviation; OR= Odds ratio; CI= Confidence interval

[a] Data are presented as frequency (percentage), unless otherwise indicated

[b] Data are presented as mean (SD)

[c] p value based on Independent t- test

[d] Based on the cut-off of the 10th Malaysia Plan

[e] Sample size was not n=113 due to missing values

through breast cancer is typically more aggressive in women under 40 years of age than in older women.[23] This is ordinarily applied to the fact that tumors in premenopausal women bear a higher percentage of biologically negative cellular or histological features which led to a worse prognosis.[24]

In this study, exposure to secondhand smoke was significantly associated with breast cancer. This finding was consistent with recent study on non-smoking breast cancer women with lifetime exposure to passive smoking. Exposure to second-hand smoke had 1.27 (95% CI: 0.97, 1.66) (less than 20 years) and 2.64 (95% CI: 1.87, 3.74) (more than 20 years) times increase risk of breast cancer than unexposed women. Besides that, Caucasian women who experienced second-hand smoke both at work and home had 2.80 (95% CI: 1.84, 4.25) times higher risk of breast cancer compared with women who were never exposed to smoke.[25]

To our knowledge, our study is the first to establish that WC and HDL cholesterol levels are associated with HMW adiponectin among breast cancer cases. In addition, BMI is also associated with HMW adiponectin among healthy controls. Our study successfully determined the association between nutritional status and HMW adiponectin among breast cancer cases and healthy controls.

WC was negatively associated with HMW adiponectin among breast cancer cases which was consistent with another study among obese and non-obese Caucasians indicating that WC is inversely correlated with HMW adiponectin level regardless

Table 2 Associations of nutritional status with HMW adiponectin among breast cancer cases

Variables	Simple linear regression		Multiple linear regression	
	b[a] (95% CI)	p value	Adjusted b[b] (95% CI)	p value
Weight (kg)	-0.05 (-0.08,-0.02)	0.001		
Height (cm)	-0.01 (-0.09,0.07)	0.870		
BMI (kg/m^2)	-0.13 (-0.21,-0.06)	0.001		
WC (cm)	-0.07 (-0.10,-0.03)	<0.001	-0.05 (-0.08,-0.02)	0.005
HC (cm)	-0.06 (-0.10,-0.02)	0.006		
Fat mass (kg)	-0.06 (-0.10,-0.02)	0.007		
Muscle mass (kg)	-0.16 (-0.26,-0.06)	0.003		
Visceral fat rating	-0.24 (-0.37,-0.10)	0.001		
TC (mmol/l)	0.22 (-0.22,0.65)	0.324		
HDL cholesterol (mmol/l)	2.60(1.24,3.97)	<0.001	1.83 (0.47,3.20)	0.010
LDL cholesterol (mmol/l)	0.16 (-0.35,0.66)	0.541		
TG (mmol/l)	-0.30 (-0.67,0.07)	0.108		
Glucose (mmol/l)	0.02 (-0.15,0.19)	0.800		
hs-CRP (mg/ml)	-0.07 (-0.14,0.01)	0.088		
Insulin (μU/ml)	-0.038 (-0.080,-0.004)	0.074		
Energy (kcal/day)	-0.001 (-0.002,0.001)	0.272		
Protein (g/day)	-0.007 (-0.036.0.021)	0.608		
Carbohydrate (g/day)	-0.006 (-0.016,0.003)	0.193		
Fat (g/day)	-0.015 (-0.054,0.024)	0.433		
Saturated fat (g/day)	0.032 (-0.122,0.185)	0.678		
MUFA (g/day)	-0.052 (-0.205,0.102)	0.501		
PUFA (g/day)	-0.107 (-0.251,0.037)	0.140		
Calcium (mg/day)	0.000 (-0.002,0.003)	0.928		
Phosphorus (mg/day)	-0.001 (-0.002,0.001)	0.274		
Iron (mg/day)	-0.070 (-0.155,0.015)	0.105		
Cholesterol (mg/day)	-0.004 (-0.012,0.003)	0.228		
Thiamin (mg/day)	0.020 (-2.251,2.291)	0.986		
Riboflavin (mg/day)	0.225 (-0.992,1.442)	0.711		
Niacin (mg NE/day)	-0.062 (-0.264,0.139)	0.536		
Folate (μg/day)	-0.002 (-0.013,0.009)	0.695		
Vitamin C (mg/day)	0.002 (-0.003,0.007)	0.511		
Vitamin E (mg/day)	-0.047 (-0.237,0.144)	0.624		
Selenium (μg/day)	-0.010 (-0.042,0.021)	0.517		
Fiber (g/day)	-0.087 (-0.369,0.194)	0.534		
Sugar (g/day)	0.003 (-0.025,0.030)	0.857		

Note. BMI=body mass index, WC= Waist circumference; HC=hip circumference; TC=total Cholesterol; HDL=high density lipoprotein cholesterol; LDL=low density lipoprotein cholesterol; TG=triglyceride; hs-CRP=high sensitivity C reactive protein; MUFA=monounsaturated fatty acid; PUFA=polyunsaturated fatty acid

[a]Crude regression coefficient

[b]Adjusted regression coefficient

Stepwise multiple linear regression method applied. Model assumptions were fulfilled.

Interactions amongst independent variables and multicollinearity were not applicable.

Coefficient of determination (R^2) = 0.377

with BMI levels[26] indicating that obese individuals commonly have lower adiponectin levels based on their abdominal adiposity. On the contrary, higher levels of adiponectin were resorted in some obese individuals with higher subcutaneous adipose tissue-to-visceral adipose tissue ratios where the ratios were significantly associated with adiponectin.[27]

Table 3 Associations of nutritional status with HMW adiponectin among healthy controls

Variables	Simple linear regression		Multiple linear regression	
	b[a] (95% CI)	p value	Adjusted b[b] (95% CI)	p value
Weight,kg	-0.08 (-0.13,-0.03)	0.001		
Height,cm	-0.09 (-0.01,-0.19)	0.083		
BMI,kg/m^2	-0.20 (-0.32,-0.08)	0.001	-0.20 (-0.32,-0.08)	0.001
WC,cm	-0.08 (-0.13,-0.03)	0.001		
HC,cm	-0.07 (-0.13,-0,01)	0.018		
Fat mass,kg	-0.11 (-0.19,-0.04)	0.002		
Muscle mass,kg	-0.08 (-0.26,0.10)	0.405		
Visceral fat rating	-0.15 (-0.29,-0.01)	0.035		
TC (mmol/l)	-0.22 (-0.78,0.33)	0.420		
HDL cholesterol (mmol/l)	2.18 (0.26,4.09)	0.027		
LDL cholesterol (mmol/l)	-0.30 (-0.92,0.32)	0.339		
TG (mmol/l)	-1.05 (-2.03,-0.08)	0.035		
Glucose (mmol/l)	-0.10 (-0.44,0.25)	0.565		
hs-CRP[a] (mg/ml)	-0.04 (-0.08,0.01)	0.110		
Insulin[a] (μU/ml)	-0.02 (-0.07,0.03)	0.459		
Energy (kcal/day)	-0.001 (-0.003,0.002)	0.545		
Protein (g/day)	-0.017 (-0.060,0.027)	0.452		
Carbohydrate (g/day)	-0.007 (-0.020,0.005)	0.255		
Fat (g/day)	-0.011 (-0.061,0.039)	0.665		
Saturated fat (g/day)	0.008 (-0.184,0.199)	0.937		
MUFA (g/day)	-0.032 (-0.163,0.100)	0.632		
PUFA (g/day)	-0.051 (-0.208,0.106)	0.518		
Calcium (mg/day)	0.001 (-0.003,0.005)	0.606		
Phosphorus (mg/day)	-0.001 (-0.003,0.001)	0.446		
Iron (mg/day)	-0.003 (-0.105,0.098)	0.946		
Cholesterol (mg/day)	-0.001 (-0.012,0.010)	0.858		
Thiamin (mg/day)	0.986 (-1.680,3.651)	0.462		
Riboflavin (mg/day)	2.114 (0.144,4.083)	0.036		
Niacin (mg NE/day)	0.009 (-0.150,0.168)	0.913		
Folate (μg/day)	0.001 (-0.013,0.015)	0.887		
Vitamin A (μg/day)	0.001 (-0.001,0.003)	0.441		
Vitamin C (mg/day)	0.006 (-0.006,0.018)	0.341		
Vitamin E (mg/day)	-0.007 (-0.362,0.347)	0.968		
Selenium (μg/day)	-0.018 (-0.066,0.031)	0.466		
Dietary fiber (g/day)	0.013 (-0.386,0.411)	0.949		
Sugar (g/day)	0.033 (-0.005,0.070)	0.084		

Note. BMI=body mass index, WC= Waist circumference; HC=hip circumference; TC=total Cholesterol; HDL=high density lipoprotein cholesterol; LDL=low density lipoprotein cholesterol; TG=triglyceride; hs-CRP=high sensitivity C reactive protein; MUFA=monounsaturated fatty acid; PUFA=polyunsaturated fatty acid

[a]Crude regression coefficient

[b]Adjusted regression coefficient

Stepwise multiple linear regression method applied. Model assumptions were fulfilled.

Interactions amongst independent variables and multicollinearity were not applicable.

Coefficient of determination (R^2) = 0.168

Obesity is recognized as risk factor for breast cancer among both post- and pre-menopausal women.[28] Excess adipose tissue significantly increases the risk of breast cancer by 30-50%.[29] Understanding the role of obesity in carcinogenesis is of major importance, especially for obese women with breast

cancer. Recently, it has been proposed that the association between cancer development and adiposity is related to (1) sex hormone metabolism, (2) insulin and insulin-like growth factor (IGF) signaling and (3) the physiology and pathological processes of adipokines.[30]

Our study also indicated that BMI was negatively associated with HMW adiponectin level among healthy controls. Similarly, Nakanishi and colleagues (2016) also who concluded that BMI was significantly lower in increased adiponectin among healthy men.[31] In contrast, a cohort study among healthy males and females showed no significant association in women between BMI and adiponectin but interestingly, positive association of BMI with adiponectin in males possibly is due to significantly higher levels of adiponectin levels in men as compared to that in women.[32] Decreased plasma testosterone in obese male[33] may also explain the higher levels of adiponectin in man since testosterone has been reported to selectively decrease circulating levels of HMW adiponectin by inhibiting its secretion from the adipocytes.[34]

A similar outcome was also be reported in a disease-related group where negative correlation between BMI and adiponectin has been established among breast cancer patients.[35] Moreover, patients with chronic obstructive pulmonary disease had remarkably higher adiponectin levels which are inversely correlated with BMI.[36] The elevation in adiponectin level may be associated with body weight loss among these patients.[37] In fact, adiponectin levels was inversely correlated with BMI and was downregulated with obesity.[38] This is supported by a dietary and exercise intervention study which indicated that weight loss was inversely associated with adiponectin concentrations.[39] However, BMI and adiponectin were positively correlated in patients with multiple sclerosis though the correlation was not significant.[40]

This study demonstrated that HDL cholesterol was significantly associated with HMW adiponectin. The current result support the previous study showing significant positive correlation between adiponectin levels and HDL cholesterol.[41] HDL cholesterol had been proposed to have cardio-protective effect[42] and it is possible that the form of HMW adiponectin may carry a lipid-soluble factor.[43] According to Rothenbacher (2005), high serum concentration may acted as protective effect when mediated by the effects of lipoprotein metabolism remarkably HDL cholesterol. This was concluded based on a study among patients with coronary heart disease presented strong correlation between adiponectin and HDL cholesterol.[44] However, no significant direct effect of HDL cholesterol on adiponectin among type 2 diabetes cases except this relationship was intervened with pre-heparin lipoprotein lipase, a major enzyme in lipoprotein metabolism.[45]

Recent epidemiological study have shown a strong relationship between breast cancer and lipid disorders, including HDL cholesterol.[46] Declined HDL cholesterol contributed to elevated breast cancer risk.[47] A case-control study conducted to determine the correlation of adiponectin with risk factors of breast cancer among premenopause and post menopause women found that HDL cholesterol levels were significantly lower in controls than cases as well as positive correlation between adiponectin and HDL cholesterol.[48]

In conclusion, this study suggests that there is an association between nutritional status and HMW adiponectin. WC, BMI and HDL cholesterol had significant relationship with HMW adiponectin. Breast cancer in Malaysia could be prevented through nutritional education via public health programs.

Conflict of Interest

The authors of this paper declare there is no conflict of interest regarding this research.

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References

1. Forouzanfar MH, Foreman KJ, Delossantos AM, Lozano R, Lopez AD, Murray CJ, et al. Breast and cervical cancer in 187 countries between 1980 and 2010: a systematic analysis. The lancet 2011 Oct;378(9801):1461-84. [Google Scholar]
2. Basen-Engquist K, Chang M. Obesity and cancer risk: recent review and evidence. Current oncology reports 2011 Feb;13(1):71-6. [Google Scholar]
3. Institute for Public Health. (2015). National of Health and Morbidity Survey 2015 Volumn II Non-Communicable Disease, Risk Factors & Other Health Problems. Malaysia: Institute for Public Health, Ministry of Health
4. Shakersain B, Santoni G, Faxen-Irving G, Rizzuto D, Fratiglioni L, Xu W. Nutritional status and survival among old adults: an 11-year population-based longitudinal study. European journal of clinical nutrition 2016;70(3):320. [Google Scholar]
5. Bechard LJ, Duggan C, Touger-Decker R, Parrott JS, Rothpletz-Puglia P, Byham-Gray L, et al. Nutritional status based on body mass index is associated with morbidity and mortality in mechanically ventilated critically ill children in the PICU. Critical care medicine 2016;44(8):1530. [Google Scholar]
6. Jeejeebhoy KN, Detsky AS, Baker JP. Assessment of nutritional status. Journal of Parenteral and Enteral Nutrition 1990;14:193. [Google Scholar]
7. American Cancer Society. (2016). Cancer Prevention & Early Detection, Facts & Figures: 2015-2016. Retrieved from https://www.cancer.org/content/dam/cancer-org/research/cancer-facts-and-statistics/cancer-prevention-and-early-detection-facts-and-figures/cancer-prevention-and-early-detection-facts-and-figures-2015-2016.pdf
8. Bail, J., Meneses, K., & Demark-Wahnefried, W. (2016). Nutritional status and diet in cancer prevention. Paper presented at the Seminars in Oncology Nursing.
9. Sahran, N. F., Harith, S., & Mohamed, R. (2016). Prevalence of geriatric malnutrition and its associated factors at the Hospital Universiti Sains Malaysia, Kelantan. Malaysian journal of nutrition, 22(1), 41-53.
10. Coelho M, Oliveira T, Fernandes R. State of the art paper Biochemistry of adipose tissue: an endocrine organ. Archives of Medical Science 2013 Mar;9(2):191-200. [Google Scholar]
11. Ronti T, Lupattelli G, Mannarino E. The endocrine function of adipose tissue: an update. Clinical endocrinology 2006;64(4):355-65. [Google Scholar]
12. Zhu N, Pankow JS, Ballantyne CM, Couper D, Hoogeveen RC, Pereira M, et al. High-molecular-weight adiponectin and the risk of type 2 diabetes in the ARIC study. The Journal of Clinical Endocrinology & Metabolism 2010 Nov;95(11):5097-104. [Google Scholar]
13. Waki H, Yamauchi T, Kamon J, Kita S, Ito Y, Hada Y, et al. Generation of globular fragment of adiponectin by leukocyte elastase secreted by monocytic cell line THP-1. Endocrinology 2005 Feb;146(2):790-6. [Google Scholar]
14. Arita Y, Kihara S, Ouchi N, Maeda K, Kuriyama H, Okamoto Y, et al. Adipocyte-derived plasma protein adiponectin acts as a platelet-derived growth factor-BB–binding protein and regulates growth factor–induced common postreceptor signal in vascular smooth muscle cell. Circulation 2002 Jun;105(24):2893-8. [Google Scholar]
15. Ye R, Scherer PE. Adiponectin, driver or passenger on the road to insulin sensitivity. Molecular metabolism 2013 Aug;2(3):133-41. [Google Scholar]
16. Katira A, Tan PH. Adiponectin and its receptor signaling: an anti-cancer therapeutic target and its implications for anti-tumor immunity. Expert opinion on therapeutic targets 2015 Aug;19(8):1105-25. [Google Scholar]
17. Shahar S, Salleh RM, Ghazali AR, Koon PB, Mohamud WN. Roles of adiposity, lifetime physical activity and serum adiponectin in occurrence of breast cancer among Malaysian women in Klang Valley. Asian Pac J Cancer Prev 2010 Jan;11(1):61. [Google Scholar]
18. Fuhrman BJ, Freedman DM, Bhatti P, Doody MM, Fu YP, Chang SC, et al. Sunlight,

polymorphisms of vitamin D-related genes and risk of breast cancer. Anticancer research 2013 Feb;33(2):543-51. [Google Scholar]
19. Trieu PD, Mello-Thoms C, Peat JK, Do TD, Brennan PC. Risk Factors of Female Breast Cancer in Vietnam: A Case-Control Study. Cancer research and treatment: Official journal of Korean Cancer Association 2017;49(4):990. [Google Scholar]
20. Norlaili AA, Fatihah MA, Daliana NF, Maznah D. Breast Cancer Awareness of Rural Women in Malaysia: is it the Same as in the Cities. Asian Pacific Journal of Cancer Prevention 2013;14(12):7161-4. [Google Scholar]
21. Yip CH, Bhoo PN, Teo S. A review of breast cancer research in Malaysia. Med J Malaysia 2014;69(suppl A):8-22. [Google Scholar]
22. Abdullah A, Abdullah KL, Yip CH, Teo SH, Taib NA, Ng CJ. The decision-making journey of Malaysian women with early breast cancer: A qualitative study. Asian Pacific Journal of Cancer Prevention 2013;14(12):7143-7. [Google Scholar]
23. Boucher BA, Wanigaratne S, Harris SA, Cotterchio M. Postdiagnosis Isoflavone and Lignan Intake in Newly Diagnosed Breast Cancer Patients: Cross-Sectional Survey Shows Considerable Intake from Previously Unassessed High-Lignan Foods. Current Developments in Nutrition 2017 Dec;2(3). [Google Scholar]
24. Vetto JT, Luoh SW, Naik A. Breast cancer in premenopausal women. Current problems in surgery 2009 Dec;46(12):944-1004. [Google Scholar]
25. Strumylaite, L., Kregzdyte, R., Poskiene, L., Bogusevicius, A., Pranys, D., & Norkute, R. (2017). Association between lifetime exposure to passive smoking and risk of breast cancer subtypes defined by hormone receptor status among non-smoking Caucasian women. PLoS ONE, 12(2), e0171198. doi:10.1371/journal.pone.0171198
26. Ahl S, Guenther M, Zhao S, James R, Marks J, Szabo A, et al. Adiponectin levels differentiate metabolically healthy vs unhealthy among obese and nonobese white individuals. The Journal of Clinical Endocrinology & Metabolism 2015 Nov;100(11):4172-80. [Google Scholar]
27. Guenther M, James R, Marks J, Zhao S, Szabo A, Kidambi S. Adiposity distribution influences circulating adiponectin levels. Translational Research 2014 Oct;164(4):270-7. [Google Scholar]
28. Amadou A, Ferrari P, Muwonge R, Moskal A, Biessy C, Romieu I, et al. Overweight, obesity and risk of premenopausal breast cancer according to ethnicity: a systematic review and dose-response meta-analysis. Obesity Reviews 2013;14(8):665-78. [Google Scholar]
29. Huang Z, Hankinson SE, Colditz GA, Stampfer MJ, Hunter DJ, Manson JE, et al. Dual effects of weight and weight gain on breast cancer risk. Jama 1997 Nov;278(17):1407-11. [Google Scholar]
30. Booth A, Magnuson A, Fouts J, Foster M. Adipose tissue, obesity and adipokines: role in cancer promotion. Hormone molecular biology and clinical investigation 2015 Jan;21(1):57-74. [Google Scholar]
31. Nakanishi K, Nishida M, Yamamoto R, Koseki M, Moriyama T, Yamauchi-Takihara K. Association between N-terminal pro-brain natriuretic peptide and adiponectin in healthy Japanese men. Clinica Chimica Acta 2016 Sep;460:138-41. [Google Scholar]
32. Pointer, M. A., Bridges, L., Wells, C., Bolin, D., & Greene, N. (2015). Abstract P240: Gender Differences in the Association of Adiponectin and BMI in a Rural Cohort of African Americans. Hypertension, 66(Suppl 1), AP240-AP240.
33. Botella-Carretero JI, Balsa JA, Gomez-Martin JM, Peromingo R, Huerta L, Carrasco M, et al. Circulating free testosterone in obese men after bariatric surgery increases in parallel with insulin sensitivity. Journal of endocrinological investigation 2013 Apr;36(4):227-32. [Google Scholar]
34. Xu A, Chan KW, Hoo RL, Wang Y, Tan KC, Zhang J, et al. Testosterone selectively reduces the high molecular weight form of adiponectin by inhibiting its secretion from adipocytes. Journal of Biological Chemistry 2005 May;280(18):18073-80. [Google Scholar]
35. Duggan C, Irwin ML, Xiao L, Henderson KD, Smith AW, Baumgartner RN, et al. Associations of insulin resistance and adiponectin with mortality in women with

breast cancer. Journal of Clinical Oncology 2011 Jan;29(1):32. [Google Scholar]
36. Bianco A, Nigro E, Monaco ML, Matera MG, Scudiero O, Mazzarella G, et al. The burden of obesity in asthma and COPD: Role of adiponectin. Pulmonary pharmacology & therapeutics 2017 Apr;43:20-5. [Google Scholar]
37. Tomoda K, Yoshikawa M, Itoh T, Tamaki S, Fukuoka A, Komeda K, et al. Elevated circulating plasma adiponectin in underweight patients with COPD. Chest 2007 Jul;132(1):135-40. [Google Scholar]
38. Wei EK, Giovannucci E, Fuchs CS, Willett WC, Mantzoros CS. Low plasma adiponectin levels and risk of colorectal cancer in men: a prospective study. Journal of the National Cancer Institute 2005 Nov;97(22):1688-94. [Google Scholar]
39. Abbenhardt C, McTiernan A, Alfano CM, Wener MH, Campbell KL, Duggan C, et al. Effects of individual and combined dietary weight loss and exercise interventions in postmenopausal women on adiponectin and leptin levels. Journal of internal medicine 2013;274(2):163-75. [Google Scholar]
40. Winsz-Szczotka K, Kuźnik-Trocha K, Komosińska-Vassev K, Kucharz E, Kotulska A, Olczyk K. Relationship between adiponectin, leptin, IGF-1 and total lipid peroxides plasma concentrations in patients with systemic sclerosis: possible role in disease development. International journal of rheumatic diseases 2016;19(7):706-14. [Google Scholar]
41. Falahi E, Rad AH, Roosta S. What is the best biomarker for metabolic syndrome diagnosis. Diabetes & Metabolic Syndrome: Clinical Research & Reviews 2015 Oct;9(4):366-72. [Google Scholar]
42. Wen, S.-Y., Tamilselvi, S., Shen, C.-Y., Day, C. H., Chun, L.-C., Cheng, L.-Y., Ou, H.-C., Chen, R.-J., Viswanadha, V. P., Kuo, W.-W. (2017). Protective effect of HDL on NADPH oxidase-derived super oxide anion mediates hypoxia-induced cardiomyocyte apoptosis. PLoS ONE, 12(6), e0179492.
43. Hao G, Li W, Guo R, Yang JG, Wang Y, Tian Y, et al. Serum total adiponectin level and the risk of cardiovascular disease in general population: A meta-analysis of 17 prospective studies. Atherosclerosis 2013 May;228(1):29-35. [Google Scholar]
44. Rothenbacher D, Brenner H, März W, Koenig W. Adiponectin, risk of coronary heart disease and correlations with cardiovascular risk markers. European Heart Journal 2005 Jun;26(16):1640-6. [Google Scholar]
45. Maser RE, Lenhard MJ, Pohlig RT, Balagopal PB. Pre-heparin lipoprotein lipase mass as a potential mediator in the association between adiponectin and HDL-cholesterol in type 2 diabetes. Journal of clinical & translational endocrinology 2017 Mar;7:7-11. [Google Scholar]
46. Lu CW, Yh, Lo , Chen CH, Lin CY, Tsai CH, Chen PJ, et al. VLDL and LDL, but not HDL, promote breast cancer cell proliferation, metastasis and angiogenesis. Cancer letters 2017 Mar;388:130-8. [Google Scholar]
47. Furberg AS, Veierød MB, Wilsgaard T, Bernstein L, Thune I. Serum high-density lipoprotein cholesterol, metabolic profile, and breast cancer risk. Journal of the National Cancer Institute 2004 Aug;96(15):1152-60. [Google Scholar]
48. Assiri A, Kamel HF, Hassanien MF. . Resistin, visfatin, adiponectin, and leptin: risk of breast cancer in pre-and postmenopausal saudi females and their possible diagnostic and predictive implications as novel biomarkers. Disease markers. 2015; 2015. [Google Scholar]

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ORIGINAL ARTICLE

Prediction of Post-operative Survival of Colorectal Cancer Patient by Using the Prognostic Nutritional Index: An Evidence-based Case Report

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Abstract

Introduction Colorectal cancer patients may be treated with several modalities and one of them is surgical treatment. Surgery in cancer patients is a risky procedure and may not always result in prolonged survival. Therefore, before receiving any recommended treatment, the patient's prognosis has to be assessed and defined properly. Several methods are available to assess the prognosis of cancer patients; one of them is the prognostic nutritional index (PNI).
Objective This study aimed to predict the survival of a colorectal cancer patient postoperatively by calculating the preoperative PNI score.
Method Literature searching was done using inclusion and exclusion criteria on two databases, i.e. the PubMed and the Cochrane Library. The outcome was survival (disease-free survival, relapse-free survival, or overall survival).
Results Five articles that address the clinical question were retrieved. All indicated that a patient with low PNI score (<44.5) had a shorter overall survival (HR between 1.92 and 3.98 with all *p* values were <0.05).
Conclusion Pre-operative PNI score can be used to assess the overall survival of a colorectal cancer patient who underwent surgical resection. Patients with a PNI score ≥ 44.5 had better survival than lower PNI score.

Keywords prognostic nutritional index, post-operative colorectal cancer, survival

Clinical Scenario

Mr. MR, aged 67 years old, was complaining to have bloating and incomplete bowel emptying in the last 8 months. He might have 1-2 defecations per day but the consistency was soft or liquid for about ½ glass each stool; the color is pale yellow and might be accompanied by dark red blood. He denied having nausea or vomitus and no black stool. During this time, his food intake was unchanged but he felt that his clothing was getting looser. His family also told him that he was getting thinner. Mr. MR visited a doctor in Hospital K and underwent a complete laboratory check-up. The results at 2 weeks before coming to our clinic was as follows: Hb 9.6 g/dL, leukocyte count 8000/mm^3, platelet count: 200.000/uL, lymphocyte count 2000/m^3, and albumin 2.8 g/dL. A tumor was found and a biopsy confirmed that it was ascending colon cancer T3N0M0. The doctor recommended complete surgical resection of the tumor, followed by chemotherapy if needed. The patient asked more time to think and to discuss with his family. His

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family suggested him to find another doctor for another opinion. Therefore, Mr. MR came to this clinic to find a second opinion for the recommended surgical treatment. He asked how long his chance to live if he takes the procedure.

Introduction

Colorectal cancer is the third most common malignancies worldwide with mortality rate rank the second after lung cancer.[1] According to GLOBOCAN 2018 database, over 1.8 million new colorectal cancer cases are estimated to occur in 2018, with 1 mortality in 10 cases. The incidence of colorectal cancer in south-eastern Asia is 5-9% of all cancers,[2] otherwise the incidence rate of colorectal cancer per 100.000 population in Indonesia is 19.1 (men) and 15.6 (female).[3] Colorectal cancer in Indonesia has increased sharply due to the changing pattern of eating habit towards a high fat-low fiber diet or a diet high in processed meat consumption. Surgical management is offered to the patient whenever feasible and may be followed by chemotherapy.[4] Colorectal cancer has a high recurrence rate after surgery; this is an important consideration for clinicians when choosing the best treatment for the patient. Assessment of prognostic factor is needed to assist clinicians in selecting the right treatment and education for the patient.[5] One of the prognostic factors that can be used is the prognostic nutritional index (PNI). It is calculated pre-operatively as follows: PNI = 10 x serum albumin (g/dL) + 0.005 x total lymphocyte count (per mm^3). Assessment of PNI was first done by Onodera *et al* to predict patients who underwent gastrointestinal surgery (colorectal, gastric, hepatocelullar, pancreatic cancer).[6] The PNI is a method to objectively assess the patient's prognosis, which is relatively cheap and easy to use by the clinicians.

Clinical Question

P: Post-operative adult patient with colorectal cancer
I: The Prognostic Nutritional Index (PNI) score
C: -
O: Post-operative survival

Clinical question: How does the prognostic nutritional index predict the postoperative survival of colorectal cancer patients?

Methods

Strategy of Article Searching

Literature searching was done on PubMed and Cochrane Library on October 9, 2018 (Table 1).

Strategy of 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 adult patients (aged ≥ 18 years); 2) subjects were diagnosed as colorectal cancer of various stages and underwent surgical treatment; 3) the PNI calculation was done pre-operatively; 4) the study population was originated from Asia and 5) the cutoff PNI score was set between 44 and 46. The exclusion criteria were 1) non-English journal and 2) no available full text.

Method of Critical Appraisal

Critical appraisal was done by all authors and by using the method of critical appraisal according to the Center of Evidence Based Medicine (www.cebm.net) for prognostic studies that has been modified in Indonesian language.

Results

Based on the results from the two databases and by assessing the inclusion and exclusion criteria, we obtained 5 eligible articles to be included as references for a critical appraisal (Figure 1).

Selected articles were studies with cohort design, either prospective or retrospective. The number of study subjects should be more than 200 patients in the adult group. Patients should be followed-up at least for 60 months. Study characteristics is shown in Table 2. All studies had a level of evidence of 2 that were individual cohort studies. All their results showed that low PNI score indicated a shorter overall survival. The validity criteria are given in Table 3. There was a report that did not meet the criteria of applicability and importance, i.e. the study by Park *et al*.

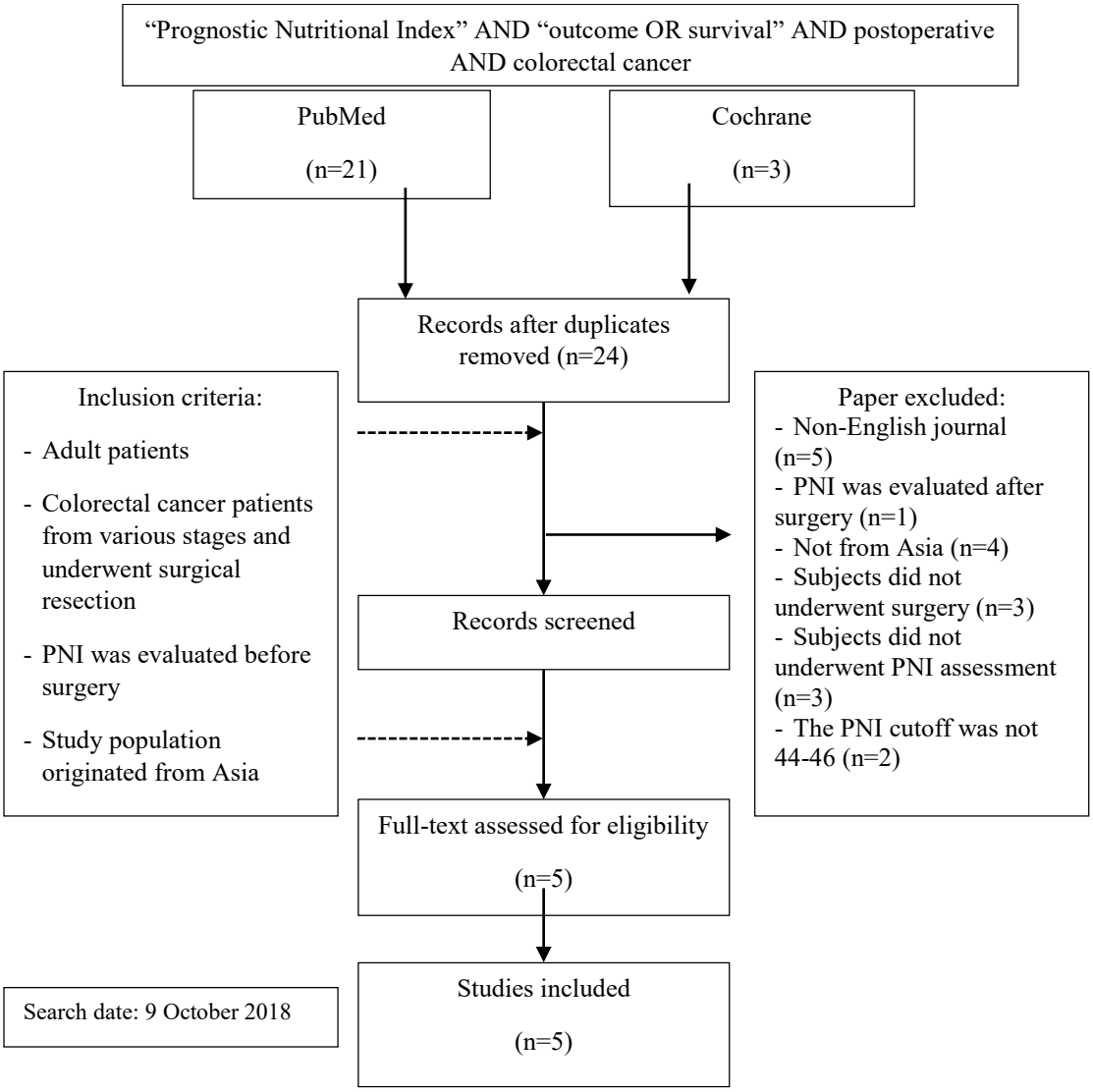

Figure 1. PRISMA Flowchart

Discussion

Mohri *et al* did a retrospective study by assessing patients who underwent colorectal cancer resection between January 2001 and December 2016 in the Department of Gastrointestinal Surgery at Mie University Hospital, Japan. The study involved 365 subjects with colorectal cancer from stage I to IV. Blood test was done before surgery and was used to count PNI; the score was low if PNI <45. The study results showed that PNI score can be a good predictor of postoperative complication (OR = 1.58 [95% CI 1.03 to 2.42]; $p = 0.04$) and overall survival (OR = 2.25 [95% CI 1.42 to 3.59]; $p < 0.0001$) of patients with colorectal cancer.[5]

Cao *et al* did a retrospective study in an institution in China under the National Health and Family Planning Commission. The study was held between January 2009 and January 2012 involving 228 study subjects who underwent laparoscopic surgery in Beijing Hospital. Patients' age ranged from 27 to 92 years old and was followed-up every 3 months up to 2 years, then every 6 months up to 5 years and annually afterwards until they died. The median follow-up was 47 months (ranging from 3 to 82 months); the last follow-up was in December 2015. Blood specimen for laboratory test was withdrawn just before surgery was performed. The median overall survival of patients with high PNI score (≥ 44.55) was 70.2 months (95% CI: 66.1 to 74.2 months), whereas the median OS of patients with low PNI score (<44.55) was 47.1 months (95%

CI: 42.9 to 51.2 months). Multivariate analysis on postoperative severe complications resulted in an OR of 4.03 (95% CI 1.10 to 14.71]; $p = 0.035$.[7]

Jian Hui et al[6] and most of studies set the optimal cut off value of PNI at 45, according to receiver operating characteristic (ROC) analysis for 5-year overall analysis. Patients in the low PNI consider to have a greater aggressive histological features of cancer.

Tokunaga *et al* did a retrospective study in 2017. The study enrolled 468 patients aged more than 18 years with primary colorectal cancer and underwent colectomy in Kumamoto University Hospital, Japan between March 2005 and August 2014. Patients were then followed-up till July 31, 2016, or death with a mean follow-up of 48.5 months (ranged from 2 to 124 months). Blood test was done two weeks before surgery. The study results showed that PNI and modified Glasgow prognostic score (mGPS) were associated with overall survival and relapse-free survival (RFS). PNI score was low if <45. Multivariate analyses showed that PNI score on overall survival was HR = 2.89 [95% CI 1.81 to 4.64]; $p < 0.001$; while PNI analysis on RFS was HR = 2.31 [95% CI 1.53 to 3.48]; $p < 0.001$.[8]

Park *et al* did a retrospective study on 1035 patients with a median age of 65 years old (ranging from 56 to 71 years old) in National University Hospital Seoul. Subjects were patients who underwent surgery for primary colorectal cancer between January 2002 and December 2010. Blood test was done 4 weeks before surgery. Follow-up was done every three months in the first two years, every 6 months for the next three years and then annually afterward. The median time of follow-up was 66 years (2 to 140 months). The study results show that the American Society of Anesthesiologists (ASA) score, age, tumor location, the number of lymph node involvement, vein invasion, perineural invasion, adjuvant therapy, and PNI were significant prognostic factors. The PNI score of <45.5 was predictive for disease-free survival (DFS) (HR = 1.534; 95% CI 1.065 to 2.211; $p = 0.022$) and overall survival (HR = 1.915; 95% CI 1.286 to 2.852]; $p = 0.001$.[9]

Tokunaga *et al* in 2015 did a retrospective study on 556 patients with primary colorectal cancer underwent a colectomy at Kumamoto University Hospital, Japan, between March 2005 and August 2014. Patients' age ranged from 63 to 83 years. Laboratory test was done two weeks before surgery. Patients were followed-up till death or till November 20, 2014, with a mean follow-up of 31.8 months (1 to 104 months). The study results indicated that PNI score of <45.5 was an independent risk factor of postoperative complication (OR = 2.06; 95% CI 1.22 to 3.50; $p = 0.007$) and overall survival (HR = 3.98; 95% CI 2.38 to 6.89]; $p < 0.001$).[10]

Predictor of survival is also determined by systemic inflammatory responses, reflected by lymphocyte-to-monocyte ratio (LMR), neutrophil-to-monocyte ratio (NMR), platelet-to-lymphocyte ratio (PLR), and C-reactive protein (CRP). PNI had positive correlation with LMR (r= 0,483, p < 0,001), but negative correlation with NLR (r=-0,441, p < 0,001), PLR (r= -0,607, p < 0,001), and CRP level (r=-0,333, p < 0,001). A low PNI was associated with short overall survival and disease free survival in patients with stage III C colon cancer but not in patients with stage III A or III B. Patients with stage III C may have a higher tumor burden with more complex systemic pro inflammatory cytokines than those are with lower stage. Therefore, preoperative PNI has significantly correlated with immunological status.[11]

In conclusion, based on the publications appraised in this evidence-based case reports, pre-operative PNI score can assess the overall survival of postoperative patients with colorectal cancer of various stages, either laparoscopically or conventionally. The overall survival of colorectal cancer patients with PNI $\geq$ 44.5 showed an HR between 1.92 and 3.98. The PNI score can also be used to assess DFS and postoperative complication. Thus, PNI should be evaluated before surgical treatment to predict the patient's postoperative prognosis. If the PNI score is low (P< 44.5), the nutritional status should be improved (in terms of serum albumin level and lymphocyte count) before surgical treatment to prolong the patient's survival.

Table 1. Terminology

Database	Terminology	Hits	Eligible
PubMed	(((((((prognostic nutritional index[MeSH Terms]) OR prognostic nutritional index[Title/Abstract])) AND ((colorectal cancer[MeSH Terms]) OR colorectal cancer[Title/Abstract])) AND ((postoperative[MeSH Terms]) OR postoperative[Title/Abstract])) AND ((((survival[Title/Abstract]) OR survival[MeSH Terms]) OR outcome[MeSH Terms]) OR outcome[Title/Abstract]))	21	5
Cochrane	#1 (pni):ti,ab,kw OR (prognostic nutritional index):ti,ab,kw (Word variations have been searched) #2 MeSH descriptor: [Nutrition Assessment] explode all trees #3 #1 or #2 #4 (outcome):ti,ab,kw OR (survival):ti,ab,kw (Word variations have been searched) # MeSH descriptor: [Colorectal Neoplasms] explode all trees #6 (colorectal cancer):ti,ab,kw #7 #5 or #6 #8 (postoperative):ti,ab,kw OR (surgery):ti,ab,kw (Word variations have been searched) #9 #3 and #4 and #7 and #8	3	0

Table 2. Study characteristics

Article by	Study design	Characteristics of the population	Number of subjects	Age group (years)	Prognostic Factor	Control	Outcome	Follow up Period (months)
Mohri Y, *et al* (2013)[3]	Retrospetive Cohort	Postoperative colorectal cancer patients	365	n/a	PNI Score	-	Overall survival	>16
Cao X, e*t al* (2017)[5]	Retrospetive Cohort	Post-laparoscopic surgical colorectal cancer patients	228	>18	PNI Score	-	Overall survival and complications	47 (3-82)
Tokunaga R, *et a*l (2017)[6]	Retrospetive Cohort	Colorectal cancer patients who underwent surgical treatment	468	>18	Systemic inflammation scores and nutrition (NLR, *prognostic index* (PI), PLR, PNI)	modified Glasgow prognostic score (mGPS) and TNM	Overall survival	48.5 (2-124)
Park BK, *et al* (2016)[7]	Retrospetive Cohort	Stage II A Colorectal cancer patients	1035	56-71	Systemic inflammation score (NLR, dNL PLR, PNI, and serum fibrinogen)	-	Overall survival	66 (2 - 140)
Tokunaga R, *et al* (2015)[8]	Retrospective Cohort	Postoperative colorectal cancer patients	556	63-83	PNI Score	-	Severe complications, recurrence, and overall survival	31.8 (1-104)

Table 3. Validity criteria

Validity				**Relevance**						
Authors	Common point	Follow up	Blind fashion	Sub-group analysis	Outcome	Precise	Apply	Important	**Result**	**Level of Evidence**
Mohri Y, *et al* (2013)[3]	+	+	-	+	+	+	+	+	**A**	**2**
Cao X, *et al* (2017)[5]	+	+	-	+	+	+	+	+	**B**	**2**
Tokunaga R, *et al* (2017)[6]	+/-	+	-	+	+	+	+	+	**C**	**2**
Park BK, *et al* (2016)[7]	+	+	-	+	+	+	-	-	**D**	**2**
Tokunaga R, *et al* (2015)[8]	+	+	-	+	+	+	+	+	**E**	**2**

A. Subjects with low PNI was associated with low **postoperative** survival ($p < 0{,}0001$);
B. Low PNI score is an independent factor associated with **postoperative** complication and overall survival of colorectal cancer patient ($p < 0.001$).
C. PNI score and mGPS are independent prognostic factors for overall survival and relapse-free survival of postoperative colorectal cancer patients ($p<0.001$). The PNI score can predict the patient's survival more clearly than the mGPS combined with TNM staging.
D. PNI score can be used for overall survival of stage II colorectal cancer patients **postoperatively** ($p = 0.001$).
E. Subjects with PNI score $\leq$ 45.5 had shorter overall survival ($p < 0.001$).

Table 4. Relevance criteria

Article	Similarity Population	Similarity determinant/ intervention/ indicators	Similarity Outcome
Mohri Y, *et al* (2013)[3]	+	+	+
Cao X, *et al* (2017)[5]	+	+	+
Tokunaga R, *et al* (2017)[6]	+	+	+
Park BK, *et al* (2016)[7]	-	+	+
Tokunaga R, *et al* (2015)[8]	+	+	+

Table 5. Results from critical appraisal

Study	**Outcome**	**n**	**HR**	**95% CI**
Mohri Y, *et al* (2013)[3]	Overall survival	365	2.29*	1.42 to 3.59
Cao X, *et al* (2017)[5]	Overall survival and complications	228	70.2**	66.1 to 74.2
Tokunaga R, *et al* (2017)[6]	Overall survival	468	2.89	1.81 to 4.64
Park BK, *et al* (2016)[7]	Overall survival	1035	1.92	1.29 to 2.85
Tokunaga R, *et al* (2015)[8]	Severe complications, recurrence and overall survival	556	3.98	2.38 to 6.89

* Odds ratio; ** months; HR = hazard ratio; CI = confidence interval

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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Reference

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A cancer journal for clinicians 2018;68(6):394-424. [Google Scholar]

2 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A cancer journal for clinicians 2018;68(6):394-424. [Google Scholar]

3 Abdullah M, Sudoyo AW, Utomo AR, Fauzi A, Rani AA. Molecular profile of colorectal cancer in Indonesia; is there another pathway. Gastroenterol Hepatol Bed Bench 2012;5(2):71-78. [Google Scholar]

4 Basir I, Rudiman R, Lusikoy R, Lukman K, Jeo WS, AH R, et al. Pedoman Nasional Pelayanan Kedokteran Kolorektal. In: Indonesia KKR, editor. Jakarta 2017.

5 Mohri Y, Inoue Y, Tanaka K, Hiro J, Uchida K, Kusunoki M. Prognostic nutritional index predicts postoperative outcome in colorectal cancer. World J Surg 2013;37:2688-92. [Google Scholar]

6 Jian-hui C, Iskandar EA, Cai SI, Chen CQ, Wu H, Xu JB, et al. Significance of Onodera's prognostic nutritional index in patients with colorectal cancer: a large cohort study in a single Chinese institution. Tumor Biology 2016 Mar;37(3):3277-83. [Google Scholar]

7 Cao X, Zhao G, Yu T, An Q, Yang H, Xiao G. Preoperative Prognostic Nutritional Index Correlates with Severe Complications and Poor Survival in Patients with Colorectal Cancer Undergoing Curative Laparoscopic Surgery: A Retrospective Study in a Single Chinese Institution. Nutr Cancer 2017;69:454-63. [Google Scholar]

8 Tokunaga R, Sakamoto Y, Nakagawa S, Izumi D, Kosumi K, Taki K, et al. Comparison of systemic inflammatory and nutritional scores in colorectal cancer patients who underwent potentially curative resection. Int J Clin Oncol 2017;22:740-8. [Google Scholar]

9 Park BK, Park JW, Han EC, Ryoo SB, Han SW, Kim TY, et al. Systemic inflammatory markers as prognostic factors in stage IIA colorectal cancer. J Surg Oncol 2016;114:216-21. [Google Scholar]

10 Tokunaga R, Sakamoto Y, Nakagawa S, Izumi D, Kosumi K, Taki K, et al. Comparison of systemic inflammatory and nutritional scores in colorectal cancer patients who underwent potentially curative resection. Int J Clin Oncol 2017;22:740-8. [Google Scholar]

11 Park BK, Park JW, Han EC, Ryoo SB, Han SW, Kim TY, et al. Systemic inflammatory markers as prognostic factors in stage IIA colorectal cancer. J Surg Oncol 2016;114:216-21. [Google Scholar]

12 Tokunaga R, Sakamoto Y, Nakagawa S, Miyamoto Y, Yoshida N, Oki E, et al. Prognostic Nutritional Index Predicts Severe Complications, Recurrence, and Poor Prognosis in Patients With Colorectal Cancer Undergoing Primary Tumor Resection. Dis Colon Rectum 2015;58:1048-57. [Google Scholar]

13 Peng J, Zhang R, Zhao Y, Wu X, Chen G, Wan D, et al. Prognostic value of preoperative prognostic nutritional index and its associations with systemic inflammatory response markers in patients with stage III colon cancer. Chin J Cancer 2017;36:96. [Google Scholar]

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ORIGINAL ARTICLE

Higher Nutritional Status of Lung Cancer Cachexia Patients is Associated with Higher Functional Capacity and Appetite

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Abstract

Introduction Lung cancer is highly prevalent and is the major cause of cancer-related deaths worldwide. Severity of weight loss has been shown to have a negative impact on patients' performance and quality of life. Early detection of anorexia and decline of functional capacity will be very useful to prevent severe weight loss and for better prognosis. This study aims to find relationship between nutritional status with functional capacity and appetite in lung cancer cachexia patients

Methods A cross sectional study was conducted in Dharmais Cancer Hospital. Subjects were adult patients over 18 years old with newly diagnosed lung cancer or a minimal of 2 months post chemotherapy or radiotherapy, taken consecutively from inpatients and outpatients. Patients with hepatic cirrhosis and end stage kidney disease were excluded. Parameters of functional capacity (ECOG) and appetite (VAS and SNAQ) were the dependent variables, while nutritional status were the independent.

Results Subjects eligible for the study were 47 patients: 55.3% men and 44.7% women with the age range from 36–79 years old. There were significant relationship between body weight and BMI with ECOG score (p=0.038; p=0.016). Body weight, BMI and weight loss related significantly with VAS appetite (p=0.016; p=0.006; p=0.028) and SNAQ score (p=0.005; p=0.009; p=0.028; p=0.014). These result indicate that subjects with a higher BMI and a lower weight loss have a better physical performance and appetite. There were significant relation between hemoglobin level, anemia status and serum albumin level with VAS appetite (p=0.004; p=0.004; p=0031) and risk for anorexia (p=0.038; p=0.004). This result indicate that subjects with normal hemoglobin and albumin have good appetite and lower risk for anorexia.

Conclusion higher nutritional status, including body weight, BMI, hemoglobin and albumin positively affect functional capacity and appetite.

Keywords lung cancer, albumin, hemoglobin, appetite, functional capacity

Introduction

The incidence of cancer is increasing worldwide and with it the prevalence of malnutrition, which may vary between 40 and 80%. The etiology of malnutrition in cancer patients is complex, multifactorial and may be influenced by the location and type of tumor, stage of the disease, side effects of the treatment, socioeconomic status, functional performance, symptoms of nutritional impact, need for fasting and inadequate nutritional therapy, as well as medical staff awareness about the importance of nutritional status for the prognosis and quality of life of hospitalized patients.[1,2] Weight loss is the primary defining feature of the wasting syndrome, cancer cachexia.[3] Cachexia is a condition where skeletal muscle mass and adipose tissue are

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progressively wasted. Incidence of cancer cachexia in patients with a cancer is more than 50%. The presence of some degree of weight loss in 60% of some gastrointestinal tumors and 80% of lung cancers upon diagnosis suggest that cancer cachexia should be considered as an "early event". Lung cancer is highly prevalent and the major cause of cancer-related deaths worldwide. Severity of weight loss has been shown to have a negative impact on patients' performance and quality of life.[4,5]

The prominent clinical feature of cachexia is weight loss, anorexia, inflammation, insulin resistance, and increased muscle protein breakdown.[6] Patients with cancer cachexia frequently report reduced appetite and have reduced food intake. Paradoxically, it is still unclear what proportion of cancer related weight loss can be attributed to reduced dietary intake and how much cancer-related weight loss could be prevented or reversed by increasing nutritional intake.[7] Normal appetite involves peripheral and central pathways. Peripheral appetite control has four phases of normal hunger and satiety cycles. The four phases are gastric motility phase, post absorptive phase, metabolic phase and ileal phase. Central appetite control depends on the balance between energy inputs and resting energy expenditure governed by a parallel system of NPY and pro-opiomelanocortin (POMC). NPY and POMC are regulated primarily by leptin and serotonin. NPY and agouti-gene related transcript (AGRP) is the main appetite stimulating central neurotransmitters with separate but synergistic appetite response. POMC reduces appetite by opposing the actions of NPY. Leptin is the dominant negative peripheral NPY regulator secreted by white adipocytes. Serotonin inhibits NPY neuron activity cause satiety.[8]

Cachexia contributes substantially to morbidity in cancer patients. It is associated with symptoms such as fatigue, weakness, poor physical performance, and thus leads to a lower self-rated quality of life. Patients who continue to lose weight while receiving palliative chemotherapy have reduced global quality of life and performance scores when compared to those whose weight loss stabilises.[6]

The assessment of the body weight change, nutritional status, and non-obvious symptoms that affect nutrition tend to be relatively low on the priority list.[9] The identification of factors that can be assessed during the hospital admission can alert the medical and healthcare staff about the need for evaluation and early nutritional intervention to avoid further complications, an increase in length of hospital stay and costs.[10]

The above description shows that functional capacity and appetite are prognostic factors for cancer patients. Then lead us to questions, are there relation between nutritional status with functional capacity and appetite. The aim of the study was to find relation between nutritional status with functional capacity and appetite.

Methods

A cross sectional study was conducted in Dharmais Cancer Hospital, as part of a larger study on the association between cytokines pro and anti-inflammatory. The study was approved by the Committee for Ethics in Research of the Dharmais Cancer Hospital. Patient recruitment took place from September 2017 to May 2018. Subjects were lung cancer patients newly diagnosed or a minimal of 2 months post chemotherapy or radiotherapy, taken consecutively from outward and inward. Sixty patients agree to take part of the study by signing written informed consent, 47 were eligible to take part in this study.

The anthropometric variables, body height and weight, was measured twice and then calculated the average by medical doctor with SECA portable stadiometer and SECA body weight scale with a variation of 0.01 cm and 0.1 kg precision. BMI was calculated as weight (kg)/height squared (m2). The performance status was obtained from the scale developed by the Eastern Cooperative Oncology Group (ECOG), which ranks the functional capacity in five levels. Level zero indicates the individual is fully active, and level four indicates the bedridden and unable to perform self care activities. Appetite was measured with VAS, and the risk for anorexia was measured using SNAQ. Serum albumin and hemoglobin, obtained from blood vein analysis, were measured as parameters of nutritional status. All laboratory values were determined using routine automated analyzers at the Department of Clinical Pathology of Dharmais Cancer Hospital.

The database was structured using the Microsoft Excel 2013 software, and the analyses were done using the Statistical Package for Social Sciences (SPSS) software version 20 for Windows.

The numeric variables were described with mean (standard deviation) for normal distributed data or median (minimal–maximal) value for otherwise. Comparison between patient groups was assessed using T-test or Mann-Whitney, according to data distribution. The Chi Squared or Mann-Whitney U test were utilized to associate clinical and biochemical parameters, and malnutrition. Statistical significance was determined as $p < 0.05$ with a two-sided test.

Results

Sixty patients agreed to take part of the study, 47 of them fulfilled the study subject criteria. Subjects of the study composed of 55.3% men and 44.7% women, with the age range from 36–79 years old. The highest age range was between 51–65 years old (40.4%).

Table 1. Subject characteristics

Characteristics		Percentage (%)
Sex		
male	26	55.3
female	21	44.7
Age, year		
36 – 50	14	29.8
51 – 65	19	40.4
>65	14	29.8

The median body weight was 49.2 (35 – 78) kg, with average BMI 20.4 ± 4.0 kg/m^2. The average weight loss in 6 months was 14.9 ± 7.8, while the median in 12 months was 14.7 (0–32.6) kg. The average albumin level was 3.2 ± 0,6 g/dL, hypoalbuminemia occurred in 48.9. The average hemoglobin level was 11.3 ± 1.7 g/dL, anemia was found in 63.8%.

There were significant relationship between body weight and ECOG score, VAS appetite and SNAQ score. Body mass index was significantly related to ECOG score. Weight loss in six months was related with SNAQ score, while weight loss in twelve months were related with VAS appetite and SNAQ score. There were significant relation between hemoglobin level and VAS appetite, and anemia status was related significantly with appetite status. This result indicates that subjects with normal hemoglobin have a good appetite. Anemia status was related significantly with anorexia risk status, which indicates that subjects with anemia have a higher risk for anorexia. We found that there were significant relation between albumin level and VAS appetite and SNAQ score (Table 2).

Discussion

Nutritional and functional deterioration are so frequently encountered in cancer patients that they are often accepted as part of the disease. The majority of patients with advanced lung cancer also present with malnourishment and, subsequently, with hypoalbuminemia and anemia.[11] There were significant relationship between body weight and ECOG score, VAS appetite and SNAQ score. Body mass index (BMI) was significantly related to ECOG score. ECOG score is the picture of one functional capacity, this result shows us that body weight and BMI significantly affected functional capacity. A Greek prospective study conducted with lung cancer showed an association between the performance status and the weight loss of more than 5% in the last 3 months, percent weight loss is as an indicative of a considerable deterioration of the nutritional status.[10]

This study found that weight loss in six months was related with SNAQ score, while weight loss in twelve months was related with VAS appetite and SNAQ score. Nasrah et al,[7] did not found a correlation between weight loss and appetite. Anorexia or loss of appetite was the symptom most closely linked to both reduced dietary intake and weight loss, as well as being an independent explanatory variable for weight change in multivariate analysis. This is consistent with the concept that the symptom of anorexia can promote weight loss through reduced food intake, but also that anorexia can be an indicator of cancer- related changes in central nervous system signaling that promote tissue loss independent of food intake.

Table 2. Nutritional status related to ECOG score, VAS appetite and SNAQ score

Nutritional status	ECOG score			VAS appetite			Risk of anorexia		
	Low N=21	Good N=26	p	Low n=15	Good n=32	p	Risk n=26	Not at Risk n=21	p
Body weight, Kg	48.9±9.1	54.7±9.4	**p=0.038**	47.2±7.5	54.4±9.8	**p=0.016**	48 (35-75)	55.8±9.4	**p=0.005**
Height, Kg	161.6±8.0	159.2±7.5	p=0.289	162.2±9.2	159.3±6.9	p=0.244	160.8±8.1	159.5±7.3	p=0.583
BMI, Kg/m^2	18.9±3.8	21.6±3.7	**p=0.016**	18.1±3.7	21.5±3.7	p=0.006	18.5(13.1-27.1)	22.0±3.7	p=0.009
Weight loss:									
6 months	14.9±8.3	12.6(5,1-32.6)*	p=0.923	18.0±8.0	11.8(0-32.0)	p=0.055	17.2±7.7	12.2±7.1	**p=0.028**
12 months	16.7±9.4	15.3±7.6	p=0.588	19.8±8.8	14.1±7.7	**p=0.028**	18.6±8.3	12.7±7.5	**p=0.014**
Hemoglobin, mg/dL	10.8±1.7	11.7±1.7	p=0.070	10.2±1.5	11.8±1.6	**P=0.004**	10.9±1.7	11.8±1.7	p=0.070
Anemia	15	15	p=0.330	14	16	**P=0.004**	20	10	**p=0.038**
Normal	6	11		1	16		6	11	
Albumin, g/dL	3.0±0.5	3.3±0.6	p=0.089	2.9±0.5	3.3±0.6	**P=0.031**	3.0±0.5	3.4±0.6	**p=0.004**
Hypoalbuminemia	12	11	p=0.312	10	13	P=0.096	16	7	p=0.054
Normal	9	15		5	19		10	14	

Studies in cancer-bearing rodents have shown elevated levels of inflammatory cytokines in the hypothalamus which can induce anorexia. The anorexia induced by hypothalamic inflammatory mediators can be reversed by melanocortin type-4 receptor blockade, but centrally acting cytokines such as IL-1b can also trigger muscle wasting, independent of central melanocortin signaling. We hypothesize that for some patients with cancer cachexia and anorexia, the presence of anorexia is a marker for cancer-related hypothalamic inflammatory cytokine signaling. If this central signaling also directly triggers tissue catabolism and weight loss in humans, its effects would likely not be reversed by increased nutritional intake alone. This in turn would explain the independent explanatory power of anorexia for weight change, even when dietary intake is taken into account.[12,13,14]

There was a significant relation between hemoglobin level and VAS appetite, and anemia status was related significantly with Appetite status. This result indicate that subjects with normal hemoglobin have a good appetite. Anemia status was related significantly with anorexia risk status, this result indicate that subjects with anemia have a higher risk for anorexia. Kalantar Zadeh et al, on their study in hemodialysis patients found a similar trend was also found for blood hemoglobin, patients with a diminished appetite had a slightly lower hemoglobin concentration.[15] This result shows us that to maintain good appetite we must maintain our cancer patient's hemoglobin. We found that there was a significant relation between Albumin level and VAS appetite and SNAQ score (Table 1). Arrieta et all,[11] found the same result: hypoalbuminemia was associated with loss of appetite in cancer patients. A need for normal albumin level, by this result, is needed for a good appetite.

Our results in this study shows that maintaining body weight is very important for cancer patients in order to have a good physical performance, which will also affect their prognosis. This study give an evidence that cancer patients appetite affected by many factors. Those factors were body weight, BMI, weight loss, hemoglobin and albumin level.

In conclusion, this study shows that nutritional status, including body weight, BMI, hemoglobin and albumin are related with functional capacity and appetite. Maintaining body weight, BMI, normal hemoglobin and albumin are keys factors of functional capacity and appetite. Serum Albumin and hemoglobin are simple and cheap tests, clinical markers that may be used to assess the risk of anorexia in cancer patients objectively. Screening for nutritional status, including body weight, BMI, history of weight loss and biochemical markers are very important to do in cancer patients.

Conflict of Interest

None of the other authors have conflict of interest. No educational grant is provided to the rest of authors.

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References

1. Pressoir M, Desné S, Berchery D, et al. Prevalence, risk factors and clinical implications of malnutrition in french comprehensive cancer centres. Br J Cancer 2010;102(6):966-971. [Google Scholar]
2. Wu BW, Yin T, Cao WX, et al. Clinical application of subjective global assessment in Chinese patients with gastrointestinal cancer. World J Gastroenterol 2009;15(28):3542-3549. [Google Scholar]
3. Fearon K, Strasser F, Anker SD, et al. Definition and classification of cancer cachexia: An international consensus. Lancet Oncol 2011;12(5):489-495. [Google Scholar]

4. Inui A. Cancer anorexia-cachexia syndrome: current issues in research and management. CA Cancer J Clin 2002;52(2):72-91. [Google Scholar]
5. Topkan E, Yavuz AA, Ozyilkan O. Cancer cachexia: Pathophysiologic aspects and treatment options. Asian Pacific J Cancer Prev 2007;8(3):445-451. [Google Scholar]
6. Donohoe CL, Ryan AM, Reynolds JV. . Cancer cachexia: mechanisms and clinical implications. Gastroenterol Res Pract. 2011; 2011. [Google Scholar]
7. Nasrah R, Kanbalian M, Borch, C. Van Der , Swinton N, Wing S, Jagoe RT. Defining the role of dietary intake in determining weight change in patients with cancer cachexia. Clinical Nutrition 2018 Feb;37(1):235-41. [Google Scholar]
8. Davis MP, Dreicer R, Walsh D, Lagman R, LeGrand SB. Appetite and cancer-associated anorexia: A review. J Clin Oncol 2004;22(8):1510-1517. [Google Scholar]
9. Mariani L, Vullo, S. Lo , Bozzetti F. Weight loss in cancer patients: A plea for a better awareness of the issue. Support Care Cancer 2012;20(2):301-309. [Google Scholar]
10. Silva FR de M, , Oliveira, M.G.O.A. de , Souza ASR, Figueroa JN, Santos CS. Factors associated with malnutrition in hospitalized cancer patients: a croos-sectional study. Nutr J 2015;14(1):123. [Google Scholar]
11. Arrieta O, Rm MO, Villanueva-Rodríguez G, et al. Association of nutritional status and serum albumin levels with development of toxicity in patients with advanced non-small cell lung cancer treated with paclitaxel-cisplatin chemotherapy: A prospective study. BMC Cancer 2010;10(22):1-7. [Google Scholar]
12. Ropelle ER, Pauli JR, Zecchin KG, et al. A central role for neuronal adenosine 5′-monophosphate-activated protein kinase in cancer-induced anorexia. Endocrinology 2007;148(11):5220-5229. [Google Scholar]
13. Grossberg AJ, Scarlett JM, Marks DL. Hypothalamic mechanisms in cachexia. Physiol Behav 2010;100(5):478-489. [Google Scholar]
14. Braun TP, Zhu X, Szumowski M, et al. Central nervous system inflammation induces muscle atrophy via activation of the hypothalamic–pituitary–adrenal axis. J Exp Med 2011;208(12):2449-2463. [Google Scholar]
15. Kalantar-Zadeh K, Block G, McAllister CJ, Humphreys MH, Kopple JD. Appetite and inflammation, nutrition, anemia, and clinical outcome in hemodialysis patients. Am J Clin Nutr 2004;80(2):299-307. [Google Scholar]

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ORIGINAL ARTICLE

Correlation between the Consumption Frequency of Sugar Sweetened Beverages with Serum Triglyceride Levels in Female Adolescents

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Abstract

Introduction The prevalence of overweight and obesity in adolescence increases significantly from year to year particularly in Depok City, Indonesia. Consumption of sugar-sweetened beverages is one of the causes. Excess triglyceride levels are one of the risk factor for metabolic syndrome and cardiovascular disease. Consumption frequency of sugar-sweetened beverages is associated with increased serum triglyceride levels.

Methods This study used a cross-sectional design involving 47 subjects recruited through the consecutive sampling method. The consumption frequency of sugar-sweetened beverages is taken by the semi quantitative FFQ method. Samples of serum triglyceride levels were taken from venous blood and measured using enzymatic methods.

Results Forty-seven female adolescence subjects, age ranged 15-17 years old, finished the study protocol. The result showed that there is a significant positive correlation with very strong degrees (p=<0.001, r=0.88) between the consumption frequency of sugar-sweetened beverages with serum triglyceride levels.

Conclusion There is a significant positive correlation with very strong degrees between the consumption frequencies of sugar-sweetened beverages with serum triglyceride levels in our subject.

Keywords overweight, female adolescence, sugar-sweetened beverages, triglyceride

Introduction

The prevalence of overweight and obesity in adolescence increases significantly from year to year. According to *Riset Kesehatan Dasar* (Riskesdas) Indonesia 2013 shows nationally that the problem of overweight in adolescents aged 13-15 years in Indonesia is 10.8%, which consists of 8.3% overweight, and 2.5% obesity.[1] In addition, in Indonesia it was also found an increase in the

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incidence of overweight from 1.4% in 2007 to 7.3% in 2013 in adolescents over the age of 15 years. Based on the 2013 Riskesdas data for the city of Depok, the prevalence of adolescents aged 13–15 years who are overweight is 12.1% while those who are obese are 1.5%. For adolescents aged 16–18 years, the prevalence of obesity is 17.0% and obesity is 3.8%.[1]

The trend of increasing prevalence of overweight and obesity is one of which can be caused by ignorance in the selection of drinks. Sugar-sweetened beverages are beverages that are given simple sugar additions during the production process that can add energy content, but have a small amount of other nutrients.[2] Among all age groups, the age group of teens is the one who consumes the most sugar-sweetened beverages. In adolescents aged 12–19 years in America as many as 65.4% consume soft drinks, sweetened at least 1 time per day.[3] Additional sugars from sugar-sweetened beverages also contribute significantly to the total energy. From a study conducted by Sanchez-Pimienta stated that sugar-sweetened beverages contribute 13.5% to total energy in adolescents.[4]

Female adolescence need special attention because they will become mothers who will conceive and give birth and it has been known that an abnormal increase in triglyceride levels in the first trimester has a significant correlation with gestational hypertension, preeclampsia, induction of preterm birth, and fetal weight greater than gestational age.[5]

Triglycerides are one form of fat deposits in the body and are used as an energy source for various metabolic processes and constituents of cell membranes. The recommended triglyceride level for adolescents is <130 mg / dL.[6] Frequent consumption of sweetened soft drinks can increase triglyceride levels through increased of de novo lipogenesis.[7]

Sugar-sweetened beverages contain a high amount of calories. Calories that are high enough from sweeteners with a low nutrient content can result in individuals at high risk for body fat accumulation.[8] This increase in body fat mass can occur in two ways, namely an increase in the size of mature adipocytes (hypertrophy) as a result of accumulation excessive triglycerides during periods of energy imbalance and the addition of adipocyte cell counts (hyperplasia) as a result of immature adipocyte cells into more cells.[9,10]

The study conducted by Maria et al 2015 in children aged 8-15 years in America found high triglyceride levels in children who often consume sugar-sweetened beverages.[11] On the other hand A study conducted by Kosova et al in 2013 in America stated that there was no significant relationship between the consumption of sugar-sweetened beverages and triglyceride levels in children aged 3-11 years.[12] Thus, the purpose of the current study is to researchers to conduct research on the frequency of consumption of sugar-sweetened beverages with serum triglyceride levels in female adolescents.

Methods

Subjects

Forty seven female students, age ranged between 15-17 years old, in some high school in Depok City, Indonesia were recruited. Subjects and subject's parents who were willing to take part in the study were asked to sign an informed consent. In subjects and parents of research subjects who signed an informed consent, interviews were conducted to obtain characteristic data, weight and height to obtain body mass index (BMI) and nutritional status, interview using semi-quantitative food frequency questionnaire (FFQ) for consumption frequency of sugar-sweetened beverages and repeated 24 hour recall 3x24 hours to get data on carbohydrate, fat and protein intake. Then a blood sample is taken to obtain serum triglyceride levels. Medical Ethics Committee of Universitas Indonesia has approved the study protocol, and 47 subjects as the minimal sample size for a correlation study with an assumption of 0.4 as correlation coefficient value, had finished the study protocol.

Measurements

Data collection was carried out from April 2018 to May 2018. The data collected consisted of subject characteristics, weight, height, macro nutrient intake, consumption frequency of sugar-sweetened beverages and blood samples for examination of serum triglyceride levels. Body weight is measured by SECA 875 electrodigital scale. Height was measured by ShorrBoard from USA. From measurements of body weight and height then the body mass index is calculated then plotted in the BMI-for-age WHO curve to obtain nutritional

status. Intake of macro nutrients was measured using food recall and then analyzed with Nutrisurvey software 2007 with an additional database of Indonesian food and then converted as carbohydrate, protein and fat intake. Serum triglyceride levels were measured using enzymatic colorimetric with glycerol-3-phosphate-oxidase (GPO) method.

Statistical

Data were analyzed with Shapiro-Wilk test to check the normality distribution of each data. Pearson correlation test was used to analyze the correlations between consumption frequency of sugar-sweetened beverages and serum triglyceride levels variables by using SPSS statistical software version 20 for Windows operating system.

Results

The result of this study showed the middle value age of the subjects are 16 years. BMI data were obtained through measurement of body weight and height. BMI measurements were used to determine the nutritional status of the subject. The nutritional status of the subjects was determined using the BMI-for-age curve from WHO 2005. Through normality tests on BMI it was found that BMI data were not normally distributed and presented in the form of middle values, minimum values and maximum values. In this study, the median of the subject BMI was at 20.9 kg / m2 and for nutritional status around 1.4% of subjects were obese, 16.4% were overweight, 61.7% were normal, 4.3% were lean, and 6.4% were very thin (Table 1).

Table 1. Characteristics of subjects based on age, BMI, and nutritional status (n=47)

Characteristics	Results
Age (years)	16 (15–17)**
BMI (kg/m^2)	20.9 (13.8–41.5)**
Nutritional status n(%)	
Very thin	3 (6.4)
Lean	2 (4.3)
Normal	29 (61.7)
Overweight	12 (26.2)
Obese	1 (1.4)

*mean ± standart deviation; **median (minimum–maximum)

Table 2 shows the middle value for carbohydrate intake for the total study subjects was 155.4 grams per day and 87.2% of subjects have a carbohydrate intake below than 80% of the Recommended Dietary Allowance (RDA). In this study the total protein intake was 38.9 grams per day and 76.6% of the subjects had a protein intake below than 80% of the RDA. From the results of fat intake, it was found that the middle value of total fat intake was 45.5 grams per day, and 85.1% of subjects with fat intake below than 80% RDA. The average consumption frequency of sugar-sweetened beverages was 8.91 times per week and triglyceride levels was 110.49 mg/dL.

The results of the Pearson correlation test showed a significant positive correlation with very strong degrees ($p = <0.001$, $r = 0.88$) between the consumption frequency of sugar-sweetened beverages and serum triglyceride levels. Figure 1 shows the scatter plot for correlation between consumption frequency of sugar-sweetened beverages an triglyceride levels. The regression equation is $Y = 41{,}236 + 7{,}768X$

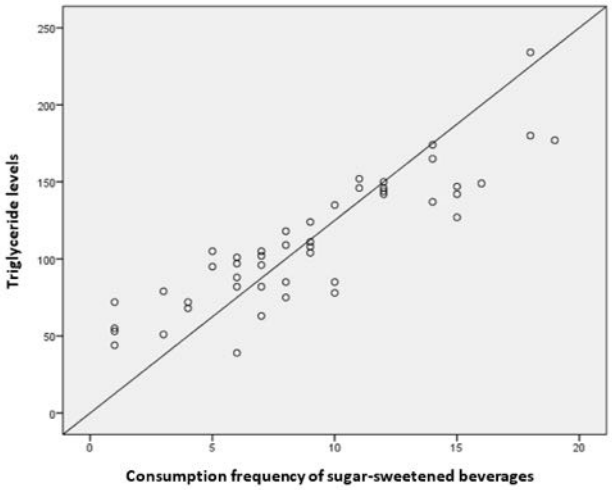

Figure 1 Scatter plot for correlation between consumption frequency of sugar-sweetened beverages an triglyceride levels

Discussion

To our knowledge, this is the first study in Indonesia to investigate the correlation between consumption frequency of sugar-sweetened beverages and serum triglyceride levels in female adolescence. The age

range and sex of the subjects in this study are in line with the results of a study from Guelinckx et al, in which groups groups of female adolescence who consumed more soft drinks compared to male adolescence groups.[13] In this study we found that 16.7% of subjects were overweight. This result is in line with data in Depok, namely adolescents aged 13-15 years who are overweight at 12.1% and for the age group adolescents 16-18 years of age who are overweight are 17.0%.[1] The macro nutrient intake of the subjects in this study was less than the RDA because the subjects reported less than what was actually consumed

the rare group and those who did not consume sugar-sweetened beverages at all.[12]

There are some limitations in this study: this study is a cross-sectional study where it cannot infer the temporal association between a risk factor and the outcome and the researchers did not analyze additional sugar levels in sugar-sweetened beverages consumed. This additional sugar level can illustrate how much extra sugar from soft drinks that contribute to the daily intake of individuals. In conclusion there was a significant positive correlation with very strong degrees between the consumption frequency of sugar-sweetened

Table 2 Characteristic of subjects based on intake of carbohydrates, fats, proteins, consumption frequency of sugar-sweetened beverages, and serum triglyceride levels (n=47)

Characteristics	Results
Carbohydrates intake per day (g)	155.4 (60.8–342.7)**
Carbohydrates intake to RDA (%)	53.2 (20.8–117.4) **
Low (<80% RDA), n(%)	41 (87.2)
Adequate (80–120% RDA), n(%)	6 (12.8)
High (>120% RDA), n(%)	0 (0)
Protein intake per day (g)	38.9 (16.6–140.2)**
Protein intake to RDA (%)	60.7 (28–237)**
Low (<80% RDA), n(%)	36 (76.6)
Adequate (80–120% RDA), n(%)	9 (19.1)
High (>120% RDA), n(%)	2 (4.3)
Fat intake per day (g)	45.5 (13.5–133.6)**
Fat intake to RDA (%)	64.1 (19–188)**
Low (<80% RDA), n(%)	40 (85.1)
Adequate (80–120% RDA), n(%)	5 (10.6)
High (>120% RDA), n(%)	2 (4.3)
Consumption frequency of sugar-sweetened beverages (times/week)	8.91 ± 4.71*
Serum triglyceride levels (mg/dL)	110.49 ± 41.49 *

*mean ± standart deviation; **median (minimum–maximum)

This study found a significant positive correlation with very strong degrees (p=<0.001, r=0.88) between the consumption frequency of sugar-sweetened beverages and serum triglyceride levels. The results of this study are in line with Van Rompay et al study which states that in children and adolescents who consumed sweetened soft drinks more than once a week increased their triglyceride levels higher about 7.9 mg/dL compared to those who consumed less frequently.[11] Other studies that conducted by Kosova et al. in children aged 9-11 years also stated the same thing, namely the female sex group that often consumed sugar-sweetened beverages had higher triglyceride levels compared to

beverages and serum triglyceride levels. Thus, the present findings can be regarded as a small step forward for other researchers to research further, for example, doing an intervention study about sugar-sweetened beverages.

Conflict of Interest

None of the other authors have conflict of interest. No educational grant is provided to the rest of authors.

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References

1. Kementerian Kesehatan RI. Badan Penelitian Dan Pengembangan Kesehatan Kementerian RI Riset Kesehatan Dasar 2013. Jakarta; 2013.
2. Preedy V. Dietery Sugars; Chemistry, Analysis, Function, and Effect. Cambridge: Royal Society of Chemistry; 2012. [Google Scholar]
3. Bleich SN, Vercammen KA. The negative impact of sugar-sweetened beverages on children's health: An update of the literature. BMC obesity 2018;5(1):6. [Google Scholar]
4. Sánchez-Pimienta TG, Batis C, Lutter CK, Rivera JA. Sugar-Sweetened Beverages Are the Main Sources of Added Sugar Intake in the Mexican Population–5. The Journal of nutrition. 2016 Aug 10;146(9):1888S-96S.
5. Bel-Serrat S, Mouratidou T, Huybrechts I, et al. Associations between macronutrient intake and serum lipid profile depend on body fat in European adolescents: The Healthy Lifestyle in Europe by Nutrition in Adolescence (HELENA) study. Br J Nutr 2014;112(12):2049-2059. doi: 10.1017/S0007114514003183. [Google Scholar]
6. Magnussen CG, Raitakari OT, Thomson R, et al. Utility of currently recommended pediatric dyslipidemia classifications in predicting dyslipidemia in adulthood: Evidence from the childhood determinants of adult health (CDAH) study, cardiovascular risk in Young Finns study, and Bogalusa heart study. Circulation 2008;117(1):32-42. doi: 10.1161/CIRCULATIONAHA.107.718981. [Google Scholar]
7. Harrington S. The role of sugar-sweetened beverage consumption in adolescent obesity: a review of the literature. J Sch Nurs 2008;24(1):3-12. doi: 10.1622/1059-8405(2008)024[0003:TROSBC]2.0.CO;2. [Google Scholar]
8. Malik VS, Schulze MB, Hu FB. Intake of sugar-sweetened beverages and weight gain: A systematic review. Am J Clin Nutr 2006;84(2):274-288. doi: 84/2/274. [Google Scholar]
9. McGregor RA, Choi MS. microRNAs in the Regulation of Adipogenesis and Obesity. Curr Mol Med 2011;11(4):304-316. doi: 10.2174/156652411795677990. [Google Scholar]
10. Nelms M, Sucher K, Lacey K, Roth S. Nutrition Therapy & Pathophysiology. J Chem Inf Model. 2013;53.
11. Rompay, M. Van , McKeown N, Eliasziw M, et al. Intakes of sugar-sweetened beverages and total sugars are associated with higher triglycerides in a multi-ethnic sample of children. Circulation 2015;145:2389. [Google Scholar]
12. Kosova EC, Auinger P, Bremer AA. The Relationships between Sugar-Sweetened Beverage Intake and Cardiometabolic Markers in Young Children. J Acad Nutr Diet 2013;113(2):219-227. doi: 10.1016/j.jand.2012.10.020. [Google Scholar]
13. Guelinckx I, Iglesia I, Bottin JH, et al. Intake of water and beverages of children and adolescents in 13 countries. Eur J Nutr 2015;54:69-79. doi: 10.1007/s00394-015-0955-5. [Google Scholar]

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ORIGINAL ARTICLE

Economic Value of Atopic Dermatitis Prevention via Partially-hydrolyzed Whey-based Infant Formula (PHF-W) Use in High-risk, Non-exclusively Breastfed, Indonesian Urban Infants: Results of a Cost-effectiveness Model

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Abstract

Introduction Early nutritional intervention with partially-hydrolyzed whey-based formula (PHF-W) instead of standard cow's milk formula (CMF) has been found to reduce the risk of atopic dermatitis (AD) development in non-exclusively breastfed infants with familial heredity of AD.
Objective To estimate the 6-year economic impact of this nutritional intervention in non-exclusively breastfed Indonesian urban infants with family history of AD.
Methods A mathematical model simulated AD incidence and burden of using PHF-W vs. CMF in the target population from birth to age 6. The model integrated literature, current cost and market catalogues, and expert clinician opinion. Modelled outcomes included AD risk, time spent post-AD diagnosis, days without flare, quality-adjusted life-years, and costs.
Results Using PHF-W instead of CMF resulted in an estimated absolute 14% (95% CI: 4%, 23%) AD risk reduction, a 0.69 year (95% CI: 0.26, 1.13) per-child reduction in time spent post-AD diagnosis, a 38 (95% CI: 12, 67) increase in days without AD flare, and a 0.046 gain in quality-adjusted life-years. The AD-related 6-year cost estimates when feeding high-risk urban infants with PHF-W were Indonesian Rupiah (IDR) 8,695,057 (95% CI: IDR 4,519,447, IDR13,995,605) and IDR13,139,569 (95% CI: IDR 7,098,794, IDR 19,216,068) per child, respectively, resulting in a net per-child difference of IDR 4,444,512 (95% CI: IDR1,893,080, IDR 8,557,946) favoring PHF-W.
Conclusion PHF-W for the first 17 weeks of non-exclusively breastfed Indonesian urban infants with a hereditary risk of AD demonstrated a reduction in AD incidence, increased days without flare, and increased quality-adjusted life-years and net cost reductions.

Keywords cost effectiveness; atopic dermatitis; infant formula; hydrolyzed formula; Indonesia

Introduction

Atopic dermatitis (AD) is a common inflammatory skin disorder that most commonly occurs during infancy.[1,2] Often a chronic disorder, AD imposes a substantial economic and quality of life (QoL) burden on children, caregivers, and society.[3-7]

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In Indonesia, AD incidence was 11% among infants aged 0-4 months.[8] Available estimates of the annual cost of AD per child in Asia range from $199 in Thailand[9] to USD3,522 (direct cost only: USD1,253) in patients receiving care at allergy clinic in South Korea[10] (all figures inflated to 2012-2013 and converted to USD).

AD is affected by various genetic, immunologic, and environmental factors. For example, in Indonesia, infants with family atopy were over 22 times as likely of developing AD compared to infants with no family history.[8] Exposure to allergens, such as proteins within standard cow's milk formula (CMF), can increase the risk of AD in infants. Despite recommendations to exclusively breastfeed infants in the first 6 months of life,[11-13] formula feeding with CMF is often used as a nutritional supplement or replacement for breast milk. In high-risk infants with first degree heredity of AD (i.e., those with ≥1 parent or sibling with history of allergic disease[14-16]), such exposure to cow's milk may result in a greater risk of AD development.

Partially or extensively hydrolyzed formulas are two alternative protein sources that have been shown to reduce the risk of AD and other allergies[17,18] compared to CMF in these high-risk infants.[14,19,20] In particular, the German Infant Nutritional Intervention (GINI) trial found that non-exclusively breastfed infants with atopic heredity randomized to whey-based partially hydrolyzed formulas (PHF-W) for their first 4 months experienced a lower cumulative incidence of AD relative to CMF 6 years following birth (27.4% vs. 39.1%, adjusted RR=0.64; 95% CI: 0.48-0.86).[14] On the basis of such data, several national and international allergy organizations have suggested hydrolyzed formulas as an allergy risk reduction strategy for these high-risk infants.[16,21-23] As demonstrated previously, the potentially higher costs of PHF-W relative to CMF during the 17-week interventional period should be partially offset by the direct and indirect cost savings and QoL improvements associated with the reduction in AD incidence in this high-risk population.[24-31]

Using health economic modeling techniques that combine data from the GINI study (the largest comparative trial of infant formula in high risk infants),[14] experts opinions, and local cost data, this study estimated the clinical and economic impact of an intervention consisting in feeding high-risk urban Indonesian infants with PHF-W instead of CMF for the first 17 weeks of life. The analysis was limited to the urban population because it is considered most likely to be consuming the infant formula evaluated herein.

Methods

Overview

Mathematical modeling (i.e., Markov cohort techniques—an extension of life table analysis)[32,33] were used to compare costs and outcomes associated with AD development over time among those using PHF-W vs. CMF from birth to 17 weeks of life in non-exclusively breastfed urban Indonesian infants with first degree atopic hereditary risk. The experiences of the cohorts were simulated from birth to age six. The target population, risk reduction, formula feeding and duration, and age-specific AD incidence were selected on the basis of the GINI.[14,19]

The analysis adopted a societal perspective and included direct medical, indirect (time loss), and out of pocket (transportation) costs associated with the prevention and treatment of AD. The primary outcomes for each treatment arm included the proportion of patients developing AD, the number of days with AD flare, the time spent post-AD diagnosis, quality adjusted life years (QALYs), and costs.

The simplified model structure is presented in Figure 1; urban infant cohorts entered the model at birth and were followed in bi-weekly cycles until age 6. Infants were initiated on CMF or PHF-W for the first 17 weeks of life (as in GINI) until 12 months of age or the development of AD. Similar to previous published models on this topic[24-26,28,30,31,34], three treatment approaches were possible after initial development of AD, as confirmed by Indonesian pediatricians with AD treatment experience (authors AS and ZM). The first approach involved a switch in feeding formula, including a switch to extensively hydrolyzed formula (EHF), soy or amino acid. This approach was used among infants ≤ 12 months presenting with mild AD (in 100% of cases) or moderate AD (in 50% of cases). The second approach included pharmacological therapies and

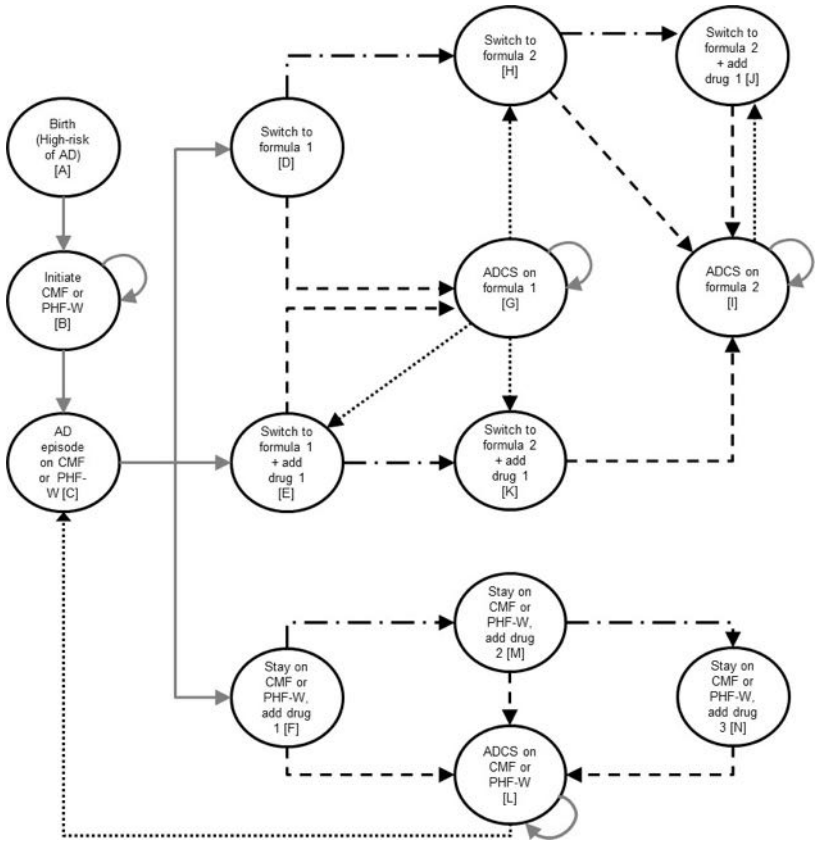

Figure 1. Simplified Presentation of the Model Structure

Arrow key: Dash is response; Dot is flare; Dash/Dot combination is no response.

Abbreviations: AD, atopic dermatitis; ADCS, atopic dermatitis controlled state; CMF, standard cow's milk formula; PHF-W, partially hydrolyzed whey formula.

Schematic diagram of the Markov decision model for healthy children at high risk for AD. Children not exclusively breastfed with a family history of allergy enter into the model at birth [A] and initiate a 4-month course of PHF-W or CMF [B]. Children who develop AD [C] are treated by 1 of 3 approaches: formula change only [D], formula change combined with first-line pharmacotherapy [E], or first-line pharmacotherapy only [F]. After first-line treatment, children either enter into the ADCS or, if no response is seen, have a change in treatment regimen [G-N].

was used among all children > 12 months regardless of severity at presentation. The third approach combined both changes in formula and pharmacological therapies and was used in 50% of infants ≤ 12 months presenting with mild AD and in all infants ≤ 12 months presenting with severe AD. Any infant formula use was assumed to end at 12 months of age as nutrient requirements shift to solid foods by this age; hence, the pharmacological treatment is the only treatment pathway available post 12 months of age. If a child was treated with a formula switch and responded favorably, she/he was assumed to continue on that new formula until (a) reaching 12 months of age, (b) the next AD episode (i.e., flare), or (c) death. If a child was treated with pharmacotherapy, she/he was assumed to continue treatment until completion of the recommended course and remain on his/her initial formula.

Treatment success was assessed every two weeks and was defined by a resolution of AD symptoms. Response rates determined the distribution of children who experience AD symptom resolution and hence the proportion of children transitioning to from the initial AD episode into a so-called "AD-controlled state" (ADCS). Response rates varied according to AD severity, treatment approach, and the line of treatment.

Finally, a child could experience subsequent relapse(s) (i.e., flare[s]) following period(s) of ADCS as determined based upon age and AD severity.

Inputs

Epidemiologic inputs are provided in Table 1. Probability of initial AD development and subsequent flares obtained from the GINI study[14] were stratified by severity (i.e., mild, moderate, and severe) and age (i.e., 0-1 years; >1-6 years). The biweekly probabilities of AD for PHF-W and CMF were obtained using linear interpolation of the 1, 3, and 6 year cumulative incidence data from the GINI study.[14] Table 2 provides the clinical management and treatment effectiveness inputs, including AD management modalities and response rates by AD severity, treatment line, and age group.

Daily formula intake was age adjusted for nutrient needs from birth to 12 months by means of a previously-reported method[25] that accounted for partial breast feeding. Formula acquisition costs (IDR 129,000 for a 400g can of PHF-W; IDR 91,800 for a 650g can of CMF; IDR 167,139 for a 400g can of soy; 417,000 for 400g of EHF; and 490,000 for 400g of amino acid) were based on the price and market share in Indonesia (Source: Packaged Food: Euromonitor from trade sources/national statistics, February 2013). Recommended quantities from the package inserts were used to determine quantity of formula for daily consumption. The analysis took into account the additional, incremental cost that

Table 1. Epidemiologic Inputs

	Base Case	Value in uSA		PSA Distribution
		Low	High	
Probability of AD: CMF‡				
0 to 1 year	16.80%	6.96%	29.85%	Beta
1 to 3 years	20.07%	9.00%	34.19%	Beta
3 to 6 years	8.42%	0.18%	29.66%	Beta
RR of AD (cumulative) (PHF-W vs. CMF) ‡				
0 to 1 year	0.54	0.33	0.89	Lognormal
1 to 3 year	0.57	0.36	0.90	Lognormal
3 to 6 year	0.82	0.40	1.70	Lognormal
Distribution of cases by severity at initial presentation: 0-1 years§				
Mild AD	50.00%	46.20%	53.80%	Beta
Moderate AD	40.00%	46.67%	32.91%	Beta
Severe AD	10.00%	7.13%	13.28%	Beta
Distribution of cases by severity at initial presentation: >1 years§				
Mild AD	60.00%	56.05%	63.88%	Beta
Moderate AD	30.00%	36.81%	22.83%	Beta
Severe AD	10.00%	7.13%	13.28%	Beta
Probability of flare recurrence over 12 weeks: 0-1 years§				
Mild AD	30.00%	24.83%	35.44%	Beta
Moderate AD	50.00%	39.99%	60.01%	Beta
Severe AD	75.00%	33.41%	98.53%	Beta
Probability of flare recurrence over 12 weeks: >1 years§				
Mild AD	10.00%	8.39%	11.74%	Beta
Moderate AD	30.00%	24.83%	35.44%	Beta
Severe AD	50.00%	39.99%	60.01%	Beta
Mortality ‖	0.0310%			

Abbreviations: AD, atopic dermatitis; CMF, standard cow's milk formula; PHF-W, partially-hydrolyzed whey-based formula; PSA, probabilistic sensitivity analysis; RR, relative risk; uSA, univariate sensitivity analyses.
‡ Source: von Berg et al. 2008 for PHF-W vs. CMF[14]
§ Source: Expert panel

‖ Source: Mortality data for children under 5 (Source: World Bank data)

Table 2. Clinical Management and Effectiveness Inputs

Variable	Base Case	Value in uSA		PSA Distribution
		Low	High	
Response rate to change of formula in PHF-W cohort	50%	40%	60%	Beta
Response rate to change of formula in CMF cohort	80%	18%	100%	Beta
Response rate to combination treatment				
1st-line Moderate AD	70%	19%	99%	Beta
2rd-line Moderate AD	70%	19%	99%	Beta
3rd-line Moderate AD	70%	19%	99%	Beta
1st-line Severe AD	55%	43%	67%	Beta
2nd-line Severe AD	55%	43%	67%	Beta
3rd-line Severe AD	55%	43%	67%	Beta
Response rate to 1st-line pharmacotherapy				
Mild AD	100%	100%	100%	NA
Moderate AD	50%	40%	60%	Beta
Severe AD	50%	40%	60%	Beta
Response rate to 2nd-line pharmacotherapy				
Mild AD	85%	51%	100%	NA
Moderate AD	90%	66%	100%	Beta
Severe AD	90%	66%	100%	Beta

Abbreviations: AD, atopic dermatitis; CMF, standard cow's milk formula; PHF-W, partially-hydrolyzed whey-based formula; PSA, probabilistic sensitivity analysis; uSA, univariate sensitivity analyses.

Source: Expert panel

would be incurred as a result of feeding with alternative infant formula (such as PHF-W, soy-based formula, and EHF).

The two experts (authors AS and ZM) provided assumptions on the type and amount of resources used with each treatment modality based on severity of AD (Table 3). Table 3 also provides costs information. For inpatient/outpatient visits and diagnostic tests, average fees charged in Indonesian hospitals or laboratories where information was available were used. Emollients and or moisturizer creams were utilized by all AD patients both during and between flares. Pharmacotherapies acquisition costs were obtained from an online drug information tool (http://www.mims.com/Indonesia) commonly used in Indonesia. To be conservative, the lowest available drug price was used if more than one option was available. Reduced productivity (i.e., indirect costs) included lost time to care of AD children following the initial physician visit (4 hours) and 2 hours per visit thereafter. Transportation costs to and from each physician visits were also included in the analysis.

Based on previously published data, young children who do not have AD were assumed to experience a utility of 1.000, but that those in ADCS after an episode had a utility of 0.980 to recognize that mild, subclinical episodes could permanently reduce QoL.[35,36] The utilities associated for a mild, moderate, and severe AD episodes were 0.863, 0.690, and 0.450, respectively. Death was associated with a utility of zero.

Analysis

Using the model structure and inputs as detailed, several incremental cost effectiveness ratios (ICERs) were computed to estimate the economic value of PHF-W vs. CMF. These outcomes included the incremental costs per AD case avoided, per day(s) with flare avoided, and QALY gained. In addition, the cost of AD per patient with AD (overall and per year) and the number of annual AD visits per patient with AD were also derived from the model to allow comparisons of these values with previous published estimates, as a way to validate the present analysis.

Table 3. Price and Quantities of Resources Used Treat AD by Severity at Presentation

	Cost per unit†	Use per AD patient		
		Mild	Moderate	Severe
Number of physician visits§				
At diagnosis	150,000	1.00 visit, regardless of severity		
Follow up				
<12 months of age	150,000	1.00 visit / month until month 6, 1.00 visit / 2 months from month 6 to month 12, all regardless of severity		
≥12 months of age	150,000	1.00 visit / 3 months, regardless of severity		
Number of hospitalizations (at initial diagnosis)§				
Any age	500,000	0.00	0.00	0.10
Number of diagnostic tests (at initial diagnosis)§				
Specific IgE test (≤3 years)	259,000	1.00	1.00	1.00
Skin prick test (>3 years)	425,000	1.00	1.00	1.00
Pharmacotherapy units per child with AD (at initial diagnosis and in case of flare or non-response)‡				
Emollient cream (40 g/unit)	80,000	3.00	3.00	3.00
Antibiotic oral 50 mL (<12 months of age)	50,000	0.00	0.00	0.50
Antibiotic oral 300 mg x 30's (≥12 months of age)	326,345	0.00	0.00	0.50
Antibiotic Topical 2% x 10g x 1's	54,000	0.00	1.50	2.25
Antihistamines 5 mg x 30's	110,000	0.00	0.50	0.75
Corticosteroid - oral 16 mg x 5 x 6's	162,000	0.00	0.00	0.12
Corticosteroid - topical 10g x 1's (tube)	54,500	0.00	1.00	1.50
Immunosuppressants 25 mg x 5 x 10's	763,665	0.00	0.00	0.60
Pimecrolimus 1g x 1's (tube)	139,125	0.00	0.00	1.00
Special wash care 100g bar of soap (per flare)	31,000	2.00	2.00	2.00
Other costs‖				
Hours lost to attend initial care	714.15	4.00	4.00	4.00
Hours lost per physician visit	714.15	2.00	2.00	2.00
Trip per physician visit	35,880	1.00	1.00	1.00

Abbreviations: AD, atopic dermatitis; IDR, Indonesian Rupiah; IgE, immunoglobulin E
Source: Expert opinion.
† Varied by ±25% in univariate and multivariate sensitivity analyses (via uniform distributions).
‡ Costs obtained from MIMS (http://www.mims.com/Indonesia/home/Index).
§ Costs are based on average fees charged in Indonesia.
‖ Costs associated with the time loss were estimated using average hourly wages in Indonesia, labor force participation, and hours spent was obtained from the expert panel and is based on their experience of treating AD patients.

Sensitivity analyses evaluated the robustness of the results. Univariate sensitivity analyses (uSA) varied individual model parameters while keeping other base-case values unchanged (see Tables 1-3 for ranges). Scenario analyses were conducted to test the impact of changing key model assumptions either alone or in combination. These included omitting any flares from the analysis and restricting the analysis to 1 year (as opposed to the 6-year time frame). Multivariate, probabilistic sensitivity analysis (PSA) was conducted whereby the models were run 5,000 times via the Monte Carlo simulation to estimate so-called bootstrapped 95% "credible intervals" (95% CIs).

In accordance with common health economics research guidelines, clinical and economic outcomes occurring after the first year were discounted at 3% per annum to estimate the net

present value of the different strategies, to reflect society's preference for the present. All costs reported in this study represent 2013 values, expressed in Indonesian Rupiah (IDR) (IDR100,000=USD7.58 as of May 12, 2015).

Results

CMF was associated with higher AD incidence (+14%) compared to PHF-W (CMF 39% vs. PHF-W 25%), less AD days (58 vs. 96), and fewer years (-0.69) in a post-AD diagnosis state (1.69 vs. 1.00). Discounted QALYs were 5.454 with PHF-W versus 5.500 for CMF, for a net difference of 0.046 (Table 4). All differences were predicted to be significant on the basis of the PSA, as indicated by the 95% CI (Table 4).

The total discounted costs (direct and indirect) among the non-exclusively breastfed infants with atopic heredity were lower among those fed with PHF-W formula (IDR 8,695,057; or USD659) compared to those in the CMF group (IDR 13,139,569; or USD996). Primary drivers of total costs were those associated with pharmacological treatments followed by indirect costs and physician visits. The resulting 6-year net savings due to risk reduction of AD with PHF-W was IDR 4,445,512 (USD337) (Table 4). Comparison of PHF-W versus CMF using ICER values showed PHF-W to be a net cost saving strategy that also resulted in reductions of AD cases and gains in AD-free days and QALYs. Thus, PHF-W was the "dominant" strategy (i.e., more effective and less expensive) relative to CMF (Table 4).

Table 4. Results

	PHF-W arm	CMF arm	Difference
Discounted Costs (IDR)			
Formula prevention	783,291	--	783,291
Formula treatment	495,843	674,119	-178,276
Physician visits	334,329	563,353	-229,025
Pharmacotherapy	6,928,005	11,655,352	-4,727,347
Diagnostic testing	68,903	104,210	-35,307
Hospitalization	1,196	1,886	-690
Indirect costs	83,491	140,649	-57,158
Total costs (95% CI)‡	8,695,057 (4,519,447, 13,995,605)	13,139,569 (7,098,794, 19,216,068)	-4,444,512 (-8,557,946, -893,080)
Discounted Costs (in USD)	USD 659	USD 996	-USD 337
Clinical effects			
Proportion of children developing AD (95% CI) ‡	25% (0.13, 0.43)	39% (0.23, 0.54)	-14% (-0.23, -0.04)
Years of life post AD diagnosis (95% CI)‡	1.00 (0.56, 1.67)	1.69 (1.04, 2.43)	-0.69 (-1.13, -0.26)
Days with AD symptoms (95% CI)‡	58 (29, 95)	96 (53, 142)	-38 (-67, -12)
Discounted QALYs (95% CI)‡	5.500 (5.418, 5.537)	5.454 (5.332, 5.514)	0.046 (0.014, 0.103)
ICER (Discounted)			
Cost per AD-case avoided			Dominant §
Cost per AD-free day gained			Dominant §
Cost per QALY gained			Dominant §

Abbreviations: AD, atopic dermatitis; IDR, Indonesian Rupiah; CMF, standard cow's milk formula; PHF-W, partially-hydrolyzed whey-based formula; QALY, quality adjusted life-year.

Base-case results are presented in the table above for an average healthy formula-fed infant with a positive family history of allergy (high-risk of developing AD).

‡Percentile distributions (2.5^{th} and 97.5^{th}) for the parameters selected to represent the uncertainty surrounding the mean value of the parameter.

§ Dominance refers to a situation where one intervention (PHF-W in this study) is said to dominate another (CMF in this study) when its effectiveness is found to be higher and the costs lower.

PSA also indicated that PHF-W was dominant in almost all 5,000 model runs (Figure 2).In uSA, the relative risk of AD between PHF-W and CMF, and the probability of AD with CMF, had the largest

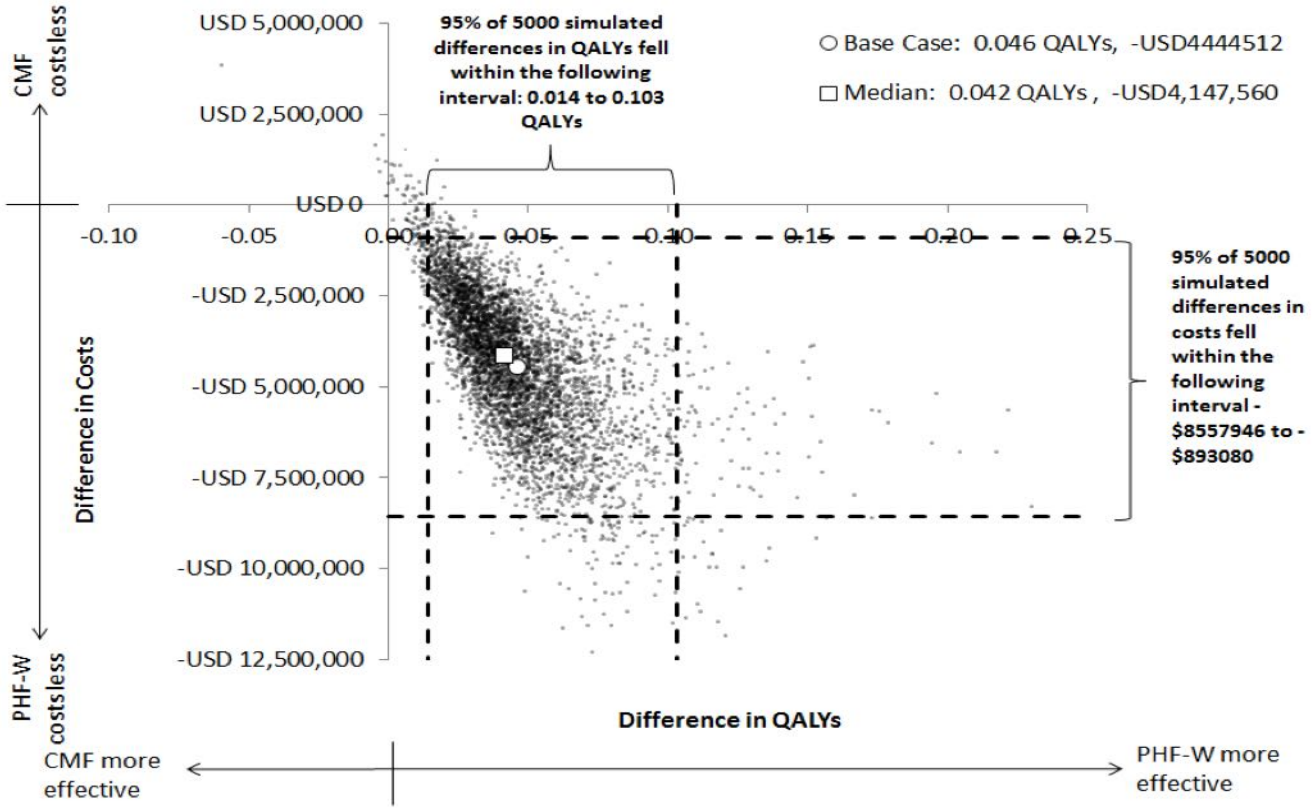

Figure 2. Scatterplot of Difference in Costs and QALYs Resulting from Multivariate PSA
Each black dot represents 1 of the 5000 multivariate PSA simulations.

direct costs alone). The total annual number of visits per AD case was estimated to be approximately 2.47 (across all severity levels).

influence on the difference in cost between PHF-W and CMF. Other variables with potentially minor effect on net cost savings were the costs of PHF-W, CMF, and emollients. Finally, in one scenario analysis, it was conservatively assumed that no AD patient would experience a recurrence. In that case, PHF-W remained cost dominant (i.e., resulting in a net discounted cost saving of IDR 3,545,058, 3 additional AD-symptom-free days, and discounted QALY gains of 0.014).

Finally, AD development at any time within the first 6 years of life was predicted to result in an undiscounted total (direct and indirect) AD cost of approximately IDR 35,600,000 (i.e., USD2,700) over this period. The estimated average annualized undiscounted total (direct and indirect) cost for an infant developing AD at any time within the first 6 years of life was approximately IDR 8,500,000 (i.e., USD645) (including IDR 8,443,175 [USD640] in

Discussion

This model shows that an early nutritional intervention with PHF-W in urban and non-exclusively breastfed Indonesian infants with first-degree atopic heredity offers favorable AD risk reduction, fewer AD days with flare, and more QALYs compared to CMF while reducing costs. The robustness of these results was confirmed via sensitivity analyses.

The cost differential between the two formulas was driven by the incidence of AD in each arm and the costs associated with pharmacotherapy. Other variables and costs had minimal impact. The cost of pharmacotherapy was high because it was the most common and expensive treatment method. In a study reviewing awareness and practice of AD management among 255 dermatologists in Southeast Asian countries, pharmacotherapy had a

high rate of use in all countries (i.e., Philippines, Vietnam, Thailand, Malaysia, Singapore, and Indonesia) reviewed.[37] Moisturizers were used frequently, with over 79% of respondents in Indonesia having used moisturizers in any given phase of treatment,[37] consistent with the use of emollients assumed in this analysis.

This analysis was limited by a lack of published data on Indonesia AD epidemiology and treatment patterns in at risk urban infants with first degree AD heredity. The impact of PHF-W and CMF on AD incidence has also not been specifically studied in urban Indonesian infants. Consequently, we relied on the results of GINI[14] as the best source of data given its standing as the largest and longest intervention trial on PHF-W and CMF to date.[20,38] The cumulative AD incidence rates observed in GINI for PHF-W and CMF are also consistent with, if not perhaps more conservative than, those observed in a smaller Southeast Asian study by Chan et al, 2002 (N=110) in genetically predisposed Singaporean infants.[39] Specifically, cumulative AD incidence in the CMF and PHF-W arms at 24 months of age in this Southeastern Asian study was 43.9% and 22.6%, respectively (an absolute difference of 21.3 percentage points; odds ratio=0.37, P=0.019).[39] Corresponding rates in GINI were 33.5% and 19.4%, respectively (an absolute difference of 14 percentage points; adjusted RR=0.57, 95% CI: 0.36-0.90).[14]

Little evidence is available regarding the severity of AD in Indonesia and elsewhere. In the present analysis, it was assumed that AD would be moderate and severe in 40% and 10% of cases in children aged <1 year, respectively, and in 30% and 10% of cases in children aged 1-6 years, respectively. In the International Study of Asthma and Allergies in Childhood (ISAAC),[40] severe AD (defined as current eczema associated with sleep disturbance 1 or more nights per week) accounted for 11% of AD cases in those aged 6 to 7 years old. In a survey of knowledge, attitudes, and practices of Southeast Asian dermatologists in the management of AD,[37] mild and moderate cases accounted for 65% and 35% of patients, respectively. Thus, the assumptions used herein may be considered reasonable given the population considered (i.e., high-risk urban infants - defined as those having ≥1 parent or sibling with history of allergic disease/first degree atopic heredity). At the same time, it should be noted that the assumptions regarding both the severity and prevalence of AD may reflect the perspective adopted herein, which focuses on the urban, affluent population, which was expected to be most prone to use hydrolyzed infant formula. Thus, the outcomes of this analysis could have been substantially different had we adopted a rural or government practice perspective.

Treatment patterns and assumptions regarding AD treatment effectiveness once a child developed AD were derived largely from the clinical opinion of three Indonesian physicians, reflecting the relative lack of Indonesian data on AD severity. This reliance on expert opinion is an important limitation of--but is not unique to--the present analysis. For instance, other cost-effectiveness analyses of hydrolyzed formula in Western countries[24-30] have relied upon similar data collection methods and evidence standards adopted herein. In part, the reliance on expert opinion is dictated by the clinical diagnosis of AD and its subjective assessment of severity. Furthermore, AD diagnosis and management are not routinely recorded administratively for reimbursement purposes. Hence many AD treatments require out-of-pocket expenditure borne by families. These may be under-recorded and are difficult to estimate.

Despite these important limitations, it should be noted that the annual costs of AD IDR 8,500,000 (i.e., USD645) are within a comparable range of estimates found in other developing Asian countries such as Thailand (USD199 for direct cost),[9] Malaysia (USD584 overall and USD398 in direct costs),[41] the Philippines (USD359),[31] or a recent estimate of annual treatment costs in patients aged 7 years in low-income Asian countries including Indonesia (ranging from USD640 to USD929 depending on the emollient used).[42] While not directly comparable due to difference in income per capita, it is worth noting that the present estimates are not surprisingly much lower than estimates from higher income countries such as Singapore (USD1,212 including USD1,007 in direct costs alone),[43] Australia (total costs: USD6,187, direct cost: USD4,842; AD patients from a dermatology clinic),[6] or South Korea (total cost: USD3,522, direct cost: USD1,253; patients from an allergy clinic)[10] (all figures inflated to 2012-2013 and converted to USD). These differences reflect variations in study design and methods, target patient populations, treatment patterns and per-capita income.

The average number of physician visits per year needed for AD management (2.47) appears conservative compared with data from Thailand (approximately 4 to 5 visits overall)[9] and in analyses similar to this one conducted for Singapore (3.51)[43] and Malaysia (6.88).[41]

The relative consistency of present study's estimates of both the annual cost of, and number of visits associated with, AD with previous research in lower income Asian countries as described above provide some reassurance that our estimates of the benefits of preventing AD with hydrolyzed infant formula are likely relatively robust despite uncertainty regarding AD treatment patterns in Indonesia.

In some ways, one might consider that the present study is conservative in a number of aspects. First, incidence and effects of AD were exclusive within to the first 6 years of life only; given the chronic nature of AD, further burden is possible. Secondly, PHF-W could also have a protective effect to other allergic manifestations; impact of which is not captured here. Lastly, details on the impact on parents' productivity and quality of life (as a result of poor night sleep to attend a crying child, etc.) was not captured in its entirety due to lack of data; compounded with the potential impact of AD of QoL could result in further additional cost savings to be realized.

In conclusion, this model showed the long-term cost-effectiveness of PHF-W nutritional intervention versus CMF in healthy urban infants with atopic heredity (high-risk) who are not exclusively breastfed from an Indonesian perspective. Results suggests that the use of PHF-W is superior to CMF as it reduces the clinical and QoL burden of AD while decreasing overall costs, even after the inclusion of formula costs. These results will be important to note by key payers in making decisions regarding reimbursement/coverage policies for formulas among at-risk urban infants.

Abbreviations

AD, atopic dermatitis; ADCS, AD-controlled state; CMF, standard cow's milk formula; CI, credible interval; EHF, extensively hydrolyzed formula; GINI, German Infant Nutritional Intervention; IDR, Indonesian Rupiah; ICER, incremental cost effectiveness ratio; ISAAC, International Study of Asthma and Allergies in Childhood; PHF-W, partially-hydrolyzed whey-based formula; PSA, probabilistic sensitivity analysis; QALY, quality adjusted life year; QoL, quality of life; RR, relative risk; uSA, univariate sensitivity analyses; USD, United States dollars

Conflict of Interest

Pharmerit International ("Pharmerit") received partial research funding from the Nestlé Nutrition Institute in Vevey, Switzerland to conduct this study. Abhijeet J. Bhanegaonkar, Xiang Ji, and Wing Yu Tang were employees of Pharmerit. Erica G. Horodniceanu is an employee of Pharmerit. Marc F. Botteman is co-founder and managing partner of Pharmerit. Nestlé Research Center in Lausanne, Switzerland, funded this study. Ray Wagiu Basrowi is an employee of Nestlé Nutrition Institute, Indonesia and PT Nestlé Indonesia. Patrick Detzel is an employee of Nestlé Research Center. The Nestlé Research Center in Lausanne is part of Nestlé. Nestlé NAN HA®, one of the products evaluated in this study, is manufactured and commercialized by Nestlé. Pharmerit retained independent control of the methodology and presentation of results for this study.

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Author contributions

All authors contributed to this research and manuscript and provided final approval for publication. MF led the study design, model design, determination of model inputs, data analysis, interpretation of results and findings, and the writing of the manuscript. ZM and AWS provided clinical input, validated model assumptions, and were involved in the review and revision of the manuscript. EH and WT contributed to the literature review, data collection, identification of model inputs, and writing and finalizing of the manuscript.

AB and XJ contributed to the model design, data analysis, and the reporting of results. RWB contribute in local market and healthcare data and was involved in review and revision of the manuscript. PD initiated the study and provided oversight and guidance on the model design, inputs, and analysis, and was involved in review and revision of the manuscript.

References

1. Spergel JM, Paller AS. Atopic dermatitis and the atopic march. The Journal of allergy and clinical immunology 2003;112. [Google Scholar]
2. Catherine Mack Correa M, , Nebus J. . Management of patients with atopic dermatitis: the role of emollient therapy. Dermatology research and practice 2012; 2012. [Google Scholar]
3. Lewis-Jones S. Quality of life and childhood atopic dermatitis: the misery of living with childhood eczema. International journal of clinical practice 2006;60:984-92. [Google Scholar]
4. Asher MI, Montefort S, Bjorksten B, Lai CK, Strachan DP, Weiland SK, et al. Worldwide time trends in the prevalence of symptoms of asthma, allergic rhinoconjunctivitis, and eczema in childhood: ISAAC Phases One and Three repeat multicountry cross-sectional surveys. Lancet 2006;368:733-43. [Google Scholar]
5. Aziah MS, Rosnah T, Mardziah A, Norzila MZ. Childhood atopic dermatitis: a measurement of quality of life and family impact. The Medical journal of Malaysia 2002;57:329-39. [Google Scholar]
6. Su JC, Kemp AS, Varigos GA, Nolan TM. Atopic eczema: its impact on the family and financial cost. Archives of disease in childhood 1997;76:159-62. [Google Scholar]
7. Williams H, Stewart A, Mutius, E. von , Cookson W, Anderson HR. International Study of Asthma and Allergies in Childhood (ISAAC) Phase One and Three Study Groups. Is eczema really on the increase worldwide. The Journal of allergy and clinical immunology 2008;121:947-54. [Google Scholar]
8. Anggraeni M, Wati KDK, Tangking K. Using family atopy scores to identify the risk of atopic dermatitis in infants. Paediatr Indones 2014;54:331. [Google Scholar]
9. Ngamphaiboon J, Kongnakorn T, Detzel P, Sirisomboonwong K, Wasiak R. Direct medical costs associated with atopic diseases among young children in Thailand. Journal of medical economics 2012;15:1025-35. [Google Scholar]
10. Kang KH, Kim KW, Kim DH. Utilization Pattern and Cost of Medical Treatment and Complementary Alternative Therapy in Children with Atopic Dermatitis. Pediatric Allergy and Respiratory Disease 2012;22:27-36. [Google Scholar]
11. Halken S, Host A, Hansen LG, Osterballe O. Effect of an allergy prevention programme on incidence of atopic symptoms in infancy. A prospective study of 159 "high-risk" infants. Allergy 1992;47:545-53. [Google Scholar]
12. Host A, Halken S, Muraro A, Dreborg S, Niggemann B, Aalberse R, et al. Dietary prevention of allergic diseases in infants and small children. Pediatr Allergy Immunol 2008;19:1-4. [Google Scholar]
13. World Health Organization. Infant and young child nutrition. Global strategy on infant and young child feeding. Report by the Secretariat. Fifty-fifth World Health Assembly2002 April 16. Report No.: A55/15. Provisional agenda item 13.10.
14. Berg, A. von , Filipiak-Pittroff B, Kramer U, Link E, Bollrath C, Brockow I, et al. Preventive effect of hydrolyzed infant formulas persists until age 6 years: long-term results from the German Infant Nutritional Intervention Study (GINI. The Journal of allergy and clinical immunology 2008;121:1442-7. [Google Scholar]
15. Berg, A. von , Filipiak-Pittroff B, Kramer U, Hoffmann B, Link E, Beckmann C, et al. Allergies in high-risk schoolchildren after early intervention with cow's milk protein hydrolysates: 10-year results from the German Infant Nutritional Intervention (GINI) study. The Journal of allergy and clinical immunology 2013;131:1565-73. [Google Scholar]

16. Greer FR, Sicherer SH, Burks AW, Immunology, o.N.a.S.o.A.a. (Committee) . Effects of early nutritional interventions on the development of atopic disease in infants and children: the role of maternal dietary restriction, breastfeeding, timing of introduction of complementary foods, and hydrolyzed formulas. Pediatrics 2008;121:183-91. [Google Scholar]
17. Hays T, Wood RA. A systematic review of the role of hydrolyzed infant formulas in allergy prevention. Archives of pediatrics & adolescent medicine 2005;159:810-6. [Google Scholar]
18. Jin YY, Cao RM, Chen J, Kaku Y, Wu J, Cheng Y, et al. Partially hydrolyzed cow's milk formula has a therapeutic effect on the infants with mild to moderate atopic dermatitis: a randomized, double-blind study. Pediatr Allergy Immunol 2011;22:688-94. [Google Scholar]
19. Berg, A. von , Koletzko S, Grubl A, Filipiak-Pittroff B, Wichmann HE, Bauer CP, et al. The effect of hydrolyzed cow's milk formula for allergy prevention in the first year of life: the German Infant Nutritional Intervention Study, a randomized double-blind trial. The Journal of allergy and clinical immunology 2003;111:533-40. [Google Scholar]
20. Alexander DD, Cabana MD. Partially hydrolyzed 100% whey protein infant formula and reduced risk of atopic dermatitis: a meta-analysis. Journal of pediatric gastroenterology and nutrition 2010;50:422-30. [Google Scholar]
21. Host A, Koletzko B, Dreborg S, Muraro A, Wahn U, Aggett P, et al. Dietary products used in infants for treatment and prevention of food allergy. Joint Statement of the European Society for Paediatric Allergology and Clinical Immunology (ESPACI) Committee on Hypoallergenic Formulas and the European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN) Committee on Nutrition. Archives of disease in childhood 1999;81:80-4. [Google Scholar]
22. Boyce JA, Assa'ad A, Burks AW, Jones SM, Sampson HA, Wood RA, et al. Guidelines for the diagnosis and management of food allergy in the United States: report of the NIAID-sponsored expert panel. The Journal of allergy and clinical immunology 2010;126. [Google Scholar]
23. Fleischer DM, Spergel JM, Assa'ad AH, Pongracic JA. Primary prevention of allergic disease through nutritional interventions. J Allergy Clin Immunol: In Practice 2013;1:29-36. [Google Scholar]
24. Iskedjian M, Belli D, Farah B, Navarro V, Detzel P. Economic evaluation of a 100% whey-based partially hydrolyzed infant formula in the prevention of atopic dermatitis among Swiss children. Journal of medical economics 2012;15:378-93. [Google Scholar]
25. Iskedjian M, Dupont C, Spieldenner J, Kanny G, Raynaud F, Farah B, et al. Economic evaluation of a 100% whey-based, partially hydrolysed formula in the prevention of atopic dermatitis among French children. Current medical research and opinion 2010;26:2607-26. [Google Scholar]
26. Iskedjian M, Haschke F, Farah B, Odijk, J. van , Berbari J, Spieldenner J. Economic evaluation of a 100% whey-based partially hydrolyzed infant formula in the prevention of atopic dermatitis among Danish children. Journal of medical economics 2012;15:394-408. [Google Scholar]
27. Iskedjian M, Szajewska H, Spieldenner J, Farah B, Berbari J. Meta-analysis of a partially hydrolysed 100%-whey infant formula vs. extensively hydrolysed infant formulas in the prevention of atopic dermatitis. Current medical research and opinion 2010;26:2599-606. [Google Scholar]
28. Su J, Prescott S, Sinn J, Tang M, Smith P, Heine RG, et al. Cost-effectiveness of partially-hydrolyzed formula for prevention of atopic dermatitis in Australia. Journal of medical economics 2012;15:1064-77. [Google Scholar]
29. Mertens J, Stock S, Lungen M, Berg, A. von , Kramer U, Filipiak-Pittroff B, et al. Is prevention of atopic eczema with hydrolyzed formulas cost-effective? A health economic evaluation from Germany. Pediatr Allergy Immunol 2012;23:597-604. [Google Scholar]

30. Spieldenner J, Belli D, Dupont C, Haschke F, Iskedjian M, Nevot Falco S , et al. Partially hydrolysed 100% whey-based infant formula and the prevention of atopic dermatitis: comparative pharmacoeconomic analyses. Annals of nutrition & metabolism 2011;59 Suppl 1:44-52. [Google Scholar]
31. Bhanegaonkar AJ, Horodniceanu EG, Gonzalez RRH, Mv CD, Detzel P, Erdogan-Ciftci E, et al. Cost-Effectiveness of Partially Hydrolyzed Whey Protein Formula in the Primary Prevention of Atopic Dermatitis in At-Risk Urban Filipino Infants. Value in Health Regional Issues 2014;3:124-35. [Google Scholar]
32. Beck JR, Pauker SG. The Markov process in medical prognosis. Medical decision making : An international journal of the Society for Medical Decision Making 1983;3:419-58. [Google Scholar]
33. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. Medical decision making : An international journal of the Society for Medical Decision Making 1993;13:322-38. [Google Scholar]
34. He ECE, Botteman MF, Detzel P, Verheggen BG. Cost-effectiveness analysis of 100% whey-based partially hydrolyzed infant formula used for prevention of atopic dermatitis in Germany [abstr. Value in Health 2012;15(7). [Google Scholar]
35. Pitt M, Garside R, Stein K. A cost-utility analysis of pimecrolimus vs. topical corticosteroids and emollients for the treatment of mild and moderate atopic eczema. The British journal of dermatology 2006;154:1137-46. [Google Scholar]
36. Stevens KJ, Brazier JE, McKenna SP, Doward LC, Cork MJ. The development of a preference-based measure of health in children with atopic dermatitis. The British journal of dermatology 2005;153:372-7. [Google Scholar]
37. Chan YC, Tay YK, Sugito TL, Boediardja SA, Chau DD, Nguyen KV, et al. A study on the knowledge, attitudes and practices of Southeast Asian dermatologists in the management of atopic dermatitis. Annals of the Academy of Medicine, Singapore 2006;35:794-803. [Google Scholar]
38. Szajewska H, Horvath A. Meta-analysis of the evidence for a partially hydrolyzed 100% whey formula for the prevention of allergic diseases. Current medical research and opinion 2010;26:423-37. [Google Scholar]
39. Chan YH, Shek LP, Aw M, Quak SH, Lee BW. Use of hypoallergenic formula in the prevention of atopic disease among Asian children. Journal of paediatrics and child health 2002;38:84-8. [Google Scholar]
40. Odhiambo JA, Williams HC, Clayton TO, Robertson CF, Asher MI. Global variations in prevalence of eczema symptoms in children from ISAAC Phase Three. The Journal of allergy and clinical immunology 2009;124:1251-8. [Google Scholar]
41. Bhanegaonkar AJ, Horodniceanu EG, Ah AL, Woodhull S, Khoo PC, Detzel P, et al. Economic value of atopic dermatitis prevention via infant formula use in high-risk Malaysian infants. Asia Pac Allergy 2015;5:84-97. [Google Scholar]
42. Tang M, Leong K, Ou LS, Munasir Z, Parekh PR, Azmi S, et al. Cost-Effectiveness Study of Pediatric Atopic Dermatitis in Asia: Atopiclair vs. Regular Emollient (AD-ATOP. Journal of drugs in dermatology: JDD 2015;14:169-75. [Google Scholar]
43. Botteman MF, Bhanegaonkar AJ, Horodniceanu EG, Ji X, Lee BW, Shek LP, et al. Economic value of using partially hydrolysed infant formula for risk reduction of atopic dermatitis in high-risk, not exclusively breastfed infants in Singapore. Singapore medical journal 2018;59(8):439. [Google Scholar]

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ORIGINAL PAPER

Plasma Folate, Vitamin B6 and B12 in Their Relationship to the Presence of Probiotic Strain *Bifidobacterium animalis* subsp. *Lactis* HNO19 (DR10™) Among Indonesian Pregnant Women in Their Third Semester

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Abstract

Introduction Vitamin B12 plays a role during pregnancy in maintaining folate metabolism. Together with folate and vitamin B6, B12 is involved as a coenzyme in DNA synthesis and various methylation reactions in developing embryos. This study aims to compare plasma folate, vitamin B6 and B12 blood levels with respect to the presence of probiotic strain *Bifidobacterium animalis* subsp. *lactis* HNO19 (DR10™) among pregnant women in Indonesia. **Methods:** This study is part of a larger study entitled "Effects of *Bifidobacterium animalis* subsp. *lactis* HNO19 (DR10™), inulin, and micronutrient fortified milk on fecal DR10™, immune markers, and maternal micronutrients among Indonesian pregnant women." Further analyses were performed using independent-t test or Mann Whitney test, GLM-repeated measures and chi-square test, to compare folate, vitamin B6 and B12 intake and blood concentration during pregnancy with presence (n=22) and absence (n=55) subjects of fecal DR10™ at third trimester. **Results:** At the first trimesters there was no difference in plasma vitamin B6 and vitamin B12 levels between the two groups, based on the presence or absence of fecal DR10™. However, at the second and third trimester, vitamin B6 blood concentration (p=0.034 and p=0.001) and vitamin B12 blood concentrations at the third trimester (p=0.035) were significantly higher in the fecal DR10™ positive group, while having a similar vitamin B6 and B12 intake. **Conclusion:** Consumption of pre- and probiotics during the periconceptional period may be a useful strategy for improving maternal vitamin B's vitamins, especially vitamin B6 and B12 status and therefore provide benefits for the offspring's quality of life.

Keywords Folate, Indonesia, pregnancy, probiotic DR10™, vitamin B6, vitamin B12

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Introduction

Until recently, attentions are given more to several important nutrients for maternal nutrition, which play roles for fetal growth and development, i.e. iron and folic acid, but less for other vitamin B's, i.e. vitamin B6 and B12. Vitamin B12 also has a

potential role during pregnancy, to maintain folate metabolism, and preventing the production of homocystein, which otherwise increases the risk for cardiovascular diseases. While together with folate and vitamin B6, it plays role as coenzyme in DNA synthesis and many methylation reactions in developing embryos.[1] Study done in the UK found that maternal B12 levels are associated with BMI, risk of GDM, and additionally may have an independent effect on macrosomia.[2]

Folate rich foods are frequently consumed as it derives from variety of green leafy and colorful vegetables (i.e. broccoli, tomato, etc) and fortified staple foods (i.e. bread). Dietary folate is absorbed in the intestine and/or liver and metabolized primarily to 5-methyl tetrahydrofolate (THF) and subsequently gets polyglutamated for cellular retention. THF is then converted to 5,10-methyleneTHF by vitamin B6 dependent serine hydroxymethyltransferase and will be reduced irreversibly to 5-methyl-THF by methylene-THF reductase. 5-Methyl-THF acts as a primary methyl donor for the remethylation of homocystein to methionine, thus preventing homocysteinemia.[3]

The richest sources of vitamin B6 include fish, beef liver and other organ meats, potatoes and other starchy vegetables, and fruit (other than citrus). Maternal B6 adequacy is crucial at conception and throughout pregnancy to ensure healthy pregnancy outcomes. Although there is a crucial role of B6 in health, however, while it was reported that some women did not meet the estimated average requirement, there was no biochemical measurement of B6 status. Based on the US National Health and Nutrition Examination Survey (NHANES), over 40% of adult women (21–44 years) had B6 deficiency (defined as having plasma PLP concentration of<20nmol/L).[4]

Vitamin B12-rich foods are derived only from animals, i.e. meat, fish, and dairy. Although the body storage of vitamin B12 is relatively high (i.e. approximately for 1–5 mg), however vitamin B12 deficiency is emerging as a growing public health problem, which is commonly seen in pregnancy.[1] There are several common causes of vitamin B12 deficiency. Besides of the increased requirements, such as in pregnancy, impaired intestinal absorption is also one of the causes.[5] Noroyono et al. shows that there are decreasing of serum B12 levels by trimesters during pregnancy regardless to the prebiotic and probiotic supplementation provided during the pregnancy.[6] However, it has been known that commensal bacteria produce vitamins, particularly B vitamins, thus it plays a major role in meeting the needs, as some studies have documented that some probiotic strains can synthesize vitamin K, folate, vitamin B2 and B12.[7] This study aims to compare plasma folate, vitamin B6 and B12 levels in relation to the existence of fecal probiotic strain *Bifidobacterium animalis* subsp. *lactis* HNO19 (DR10™) among pregnant women in Indonesia.

Methods

Study design

This study is part of a main study entitled "Effects of *Bifidobacterium animalis* subsp. *lactis* HNO19 (DR10™), inulin, and micronutrient fortified milk on fecal DR10™, immune markers, and maternal micronutrients among Indonesian pregnant women" by Noroyono et al.[4] We applied a repeated cross-sectional study design (i.e. at first, second and third trimester) among two comparative population (i.e. those having positive fecal DR10™ as compared to those with negative fecal DR10™). From the total population of the previous study, we purposively selected the subjects, i.e. pregnant women aged 18–35 years, were residents of Jakarta and likely to remain in the city for one year, had singleton pregnancy at 8–12 weeks of gestation, were apparently healthy, had uncomplicated pregnancy, provided written informed consent, and who had fecal DR10™ at their third trimester of pregnancy. The eligible subjects were allocated into those having positive or negative result as the comparative groups. Exclusion criteria were those subjects with incomplete data on dietary and plasma folate, vitamin B6 and B12.

From the previous study, we only had 22 subjects and 55 subjects of pregnant women with positive and negative fecal DR10™, respectively in their third trimester, as our quota sampling. This limited sample size might be a limitation of this study, because we should calculate minimal sample size for the equal number of each group to detect differences between two means. All the subjects were requested to undergo several measurements, including baseline weight and height measures, energy and nutrient intake by using repeated 24-hour food recall (i.e. at first, second and third trimester), which were then converted to folate, vitamin B6 and

B12 intake, by using the free Nutrisurvey 2007 food-processor software. The Indonesian RDA for dietary intake of folate is 600 μg, vitamin B6 is 1.7 mg, and vitamin B12 during pregnancy is 2.6 mcg.

Study overview

As mentioned in the main study, this study was done at Cipto-Mangunkusumo and Budi Kemuliaan hospital in Jakarta during 2013 until 2014. The study protocol was approved by the Ethics Committee of the University of Indonesia (71/H2.F1/ETIK/2013) and registered at clinicaltrials.gov. Written informed consent were provided from the subjects before doing subjects recruitment.

Data collection

Plasma folate, vitamin B6 and B12 was collected from the whole blood sample and analysed by using reversed-phase high-performance liquid chromatographic tandem mass spectrometry (RP-HPLC-MS/MS) procedure. Data collection was done at first, second and third trimester. The reference range for plasma folate level is 4.5–45.3 nmol/L (2–20 ng/mL), and its insufficiency is defined as <4.5 pmol/L (2.0 pg/mL). The reference range for serum B6 (pyridoxal phosphate) is 5–50 mcg/L), and its insufficiency is defined as <5 mcg/L). The reference range for serum B12 is 150–489 pmol/L (203.3–662.8 pg/mL), and its insufficiency is defined as <150 pmol/L (203.3 pg/mL).

Statistical analyses

All data was presented accordingly based on its normality distribution. Statistical analyses were done by using independent-t test or Mann Whitney test and chi-square (Fisher-exact) test, to compare dietary and blood folate, vitamin B_6 and B_{12} by pregnancy trimester among the two groups, i.e. having fecal DR10^{TM} positive versus having fecal DR10^{TM} negative at third trimester, respectively.

Results

Table 1 shows that during baseline, at the first trimester, there is no difference in general characteristics of the two comparison groups based on the existence of fecal probiotic (DR10^{TM}), except for having daily food supplement in the form of prebiotic (FOS/inulin 2.5g) and probiotic (*Bifidobacteria animalis* subsp. *lactis* 5x10^{6}cfu) enriched-milk, consumed twice a day, as the intervention product as compared to the placebo, in the main study. Among the 36 subjects supplemented, 22 subjects (61.1%) revealed having

Table 1. Baseline characteristics of the subjects at first semester

Variables	Fecal DR10^{TM} 3rd Trimester		P-value
	Positive (n=22)	Negative (n=55)	
Socio-demographic:			
Age, y	31 (4)^	28 (7)*	0.157 ^{MW}
Gestational age, week by USG	10.6 (2.5)*	10.7 (2.8)*	0.897^{T}
Nutritional status:			
Height, cm	155.1 (4.7)*	157.3 (5.1)*	0.084^{T}
Weight, kg	58.6 (9.8)*	60.4 (11.6)*	0.514^{T}
BMI, kg/m^2	24.3 (3.9)*	24.3 (4.2)*	0.998^{T}
Haemoglobin, mg/dL	12.3 (0.8)*	12.4 (1.0)*	0.613^{T}
Total energy intake, kcal	1308 (418)*	1353 (317)*	0.611^{T}
Protein intake, g	48 (16)^	51 (14)*	0.710 ^{MW}
Iron intake, mg	10.7 (5.3)^	10.3 (10.3)^	0.946^{MW}
Folate intake, mcg	284 (418)^	422 (363)^	0.189^{MW}
Supplemented with pre- and probiotic enriched-milk, n(%)	22 (100)	14 (25.5)	**<0.001^{chi}**

^in median and interquartile range; *in mean and standard deviation, ^{MW}Mann-Whitney U test; ^{T}independent-t test; ^{chi}Pearson chi-square test

positive fecal DR10™, while none of the non-supplemented subjects had a positive result.

Focusing on folate, vitamin B_6 and B_{12} status during the pregnancy, Table 2 shows that during the pregnancy there were no significant differences in the folate and vitamin B_6 intake, while there was a significant difference in vitamin B_{12} intake (p=0.048) at first trimester. There was no difference in folate blood concentrations throughout the pregnancy. For vitamin B_6 blood concentration, there were significant higher concentrations in the presence of fecal DR10™ at first and second trimesters (P=0.035 and P=0.001, respectively). It was similar with vitamin B_{12}, in which there were higher vitamin B_{12} blood concentrations in the presence of fecal DR10 ™ at third trimesters (P=0.035), and by the third trimester the blood concentration changes were different between

Table 2. Folate, vitamin B_6 and B_{12} status during pregnancy by the existence of fecal DR10™ at the third trimester

Variables	Fecal DR10™ 3rd Trimester		P-value
	Positive (n=22)	Negative (n=55)	
Folate:			
Dietary intake, in mcg			
Trimester-1	284.2 (417.9)^	419.9 (366.2)^	0.189[MW]
Trimester-2	470.3 (68.5)^	470.6 (97.7)^	0.577 [MW]
Trimester-3	449.2 (39.7)^	471.1 (185.2)^	0.311 [MW]
Blood concentration, ng/mL			
Trimester-1	25.6 (11.5)^	19.6 (10.8)^	0.410 [MW]
Trimester-2	22.8 (5.9)*	25.8 (11.8)^	0.391 [MW]
Trimester-3	23.8 (8.8)*	19.5 (12.7)^	0.814 [MW]
Changes at trimester-3	-0.04 (9.16)*	1.04 (8.79)*	0.643[T]
Vitamin B_6:			
Dietary intake, in mg			
Trimester-1	0.3 (0.5)^	0.34 (0.3)^	0.450 [MW]
Trimester-2	0.5 (0.3)*	0.3 (0.6)^	0.168 [MW]
Trimester-3	0.4 (0.3)^	0.4 (0.4)^	0.819 [MW]
Blood concentration, mcg/mL			
Trimester-1	30.0 (39.7)^	22.6 (24.5)^	0.051 [MW]
Trimester-2	25.8 (12.1)^	20.1 (12.5)^	**0.035 [MW]**
Trimester-3	28.9 (25.1)^	19.7 (12.6)^	**0.001 [MW]**
Changes at trimester-3	-9.66 (35.04)*	-4.2 (20.9)^	0.527 [MW]
Vitamin B_{12}:			
Dietary intake, in mcg			
Trimester-1	0.8 (2.2)^	1.8 (1.9)^	**0.048[MW]**
Trimester-2	3.8 (14.4)^	3.6 (2.5)^	0.661[MW]
Trimester-3	3.8 (2.4)^	4.8 (3.2)^	0.855[MW]
Blood concentration, pg/mL			
Trimester-1	466.3 (189.8)*	489.3 (154.8)*	0.605[T]
Trimester-2	362.2 (95.4)*	312.5 (126.2)^	0.467[MW]
Trimester-3	326.3 (83.5)*	275.5 (112.5)^	**0.035[MW]**
Changes at trimester-3	-140.05 (149.66)*	-196 (164)^	**0.046 [MW]**

^in median and interquartile range; *in mean and standard deviation, [MW]mann-whitney U test; [T]independent-t test

groups based on the presence of fecal DR10^{TM} (P=0.046).

Furthermore, to see the insufficiency status of folate, vitamin B_6 and B_{12}, Figure 1 clearly shows the increasing proportions of serum B_{12} insufficiency by trimesters among subjects having negative fecal DR10^{TM}, although they are not statistically significant by Fisher's exact test. While all subjects had no insufficiency for blood folate and vitamin B_6.

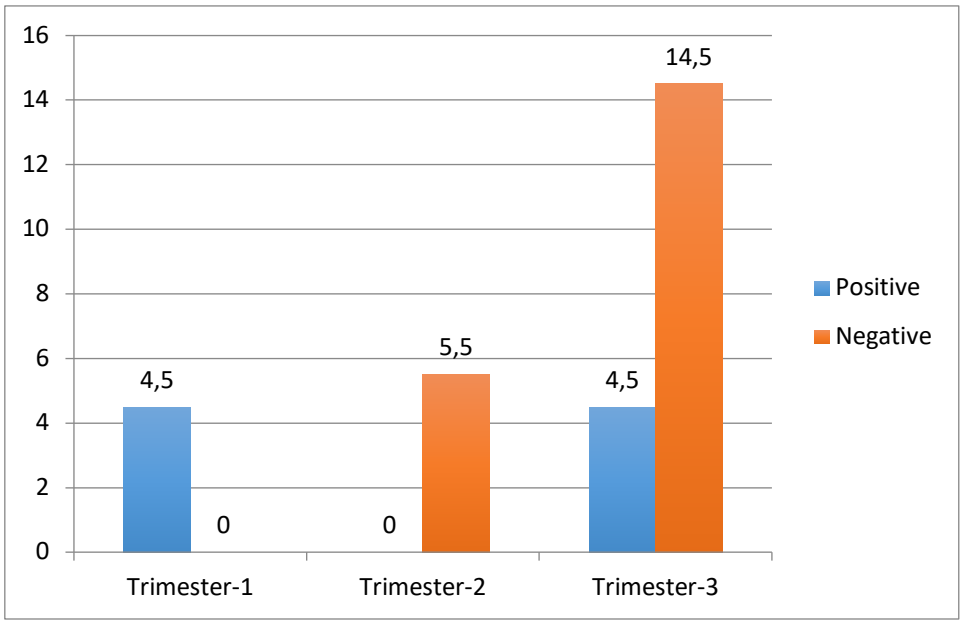

Figure 1
Proportions (%) of serum B_{12} insufficiency during pregnancy between groups by trimester and the presence of fecal DR10^{TM}
(no insufficiency status for folate and vitamin B_6 levels)

Discussion

This study found that there were no significant differences in the folate and vitamin B_6 intake during pregnancy, while there was a significant difference in vitamin B_{12} intake at first trimester only. The vitamin B's deficiency occurs primarily as a result of insufficient dietary intake and poor absorption. Folate is present in high concentrations in legumes, leafy vegetables and some fruits, and fortified wheat, maize or rice.[8] Indonesian pregnant mothers as part of Indonesian populations, commonly consume unfortified rice, however high consumption of leafy vegetables and folic acid supplementation program, would prevent them from having insufficient blood folate concentration. This was confirmed in this study in that no insufficiency for blood folate concentration was observed throughout the pregnancy.

Meanwhile, it is also revealed in this study that there was no difference in folate blood concentrations in relation to the existence of fecal DR10^{TM}. This shows that there was no effect of *Bifidobacterium animalis* subsp. *lactis* in producing/release and/or increase folate in foods. Actually, probiotics have the ability to synthesize folate in fermented foods, however the ability varies considerably being a strain-dependent trait. For example, it is claimed that *Strep. thermophilus* normally produces folate, whereas *Lactobacillus delbrueckii* subsp. *bulgaricus* is a folate consumer.[9]

Dietary vitamin B_6 sources come from wide variety of foods, such as fruits, vegetables, dairy and organ meats. Thus, its consumption should fulfil the requirements, as shown in this study that there was no subject having insufficient blood vitamin B_6 concentrations throughout the pregnancy. However, it revealed in this study that there were significant higher concentrations in the presence of fecal DR10^{TM} at second and third trimesters. This finding shows that the benefit of probiotic *Bifidobacterium animalis* subsp. *lactis* provided throughout the pregnancy to the increased level of vitamin B_6. Thus it confirmed by the strain used in this study that fermentations had been carried out in the milk-based

intervention product.[9] It is also concluded that this is the first study on vitamin B6 related to supplementation of milk-based beverage fermented by *Bifidobacterium animalis* subsp. *lactis* HNO19 (DR10™).

Vitamin B_{12} rich food sources are mostly from animal foods that commonly not consumed frequently by Indonesian pregnant mothers because of the high price. Beside due to inadequate dietary intake, there is also a physiological decline of maternal vitamin B_{12} concentrations, i.e. the increased maternal metabolic rate and active transport by the placenta to the fetus.[10] In return the insufficiency of vitamin B_{12} is evidence especially among pregnant mothers. This study found that there were higher vitamin B_{12} blood concentrations in the presence of fecal DR10™ at third trimesters. So far, it is known that only bacteria and archaea are able to synthesize vitamin B_{12}, i.e. *Lact. reuteri* B_{12}-producing strain with enhanced capacity to produce this essential vitamin.[9] Thus this study also adds the evidence that milk-based beverage fermented by *Bifidobacterium animalis* subsp. *lactis* HNO19 (DR10™) also facilitates the production of vitamin B_{12}. This evidence is proven by the increasing proportions of serum B_{12} insufficiency throughout the pregnancy among subjects having negative fecal DR10™ found in this study.

After showing the benefits of *Bifidobacterium animalis* subsp. *lactis* HNO19 (DR10™) in improving the blood vitamin B_6 and B_{12} concentrations, it raises a question whether there is a need to provide probiotics along with vitamin supplements to pregnant mothers. We should then consider several potential benefits of probiotics. One of it is the widely known that commensal bacteria have the capacity to synthesize vitamins, particularly B vitamins, thus play a major role in meeting our needs for those essential vitamins.[10]. In addition, focusing on absorption of the vitamins, it is also known that most transporters for vitamins are in the duodenum and ileum, not in colon where most of the microbes are found. Thus, it is still unclear if they can be a source of the vitamins, and there is a need to study further to its bioavailability.

Despite the findings in this study, folate, vitamin B_6 and B_{12} especially for pregnant mothers, are potential and closely related as coenzyme in DNA synthesis and numerous methylation reactions that occur in developing embryos. Thus, it is essential for cell multiplication during pregnancy.[11]

Therefore, it can be concluded that there is a need to improve folate, vitamin B6 and B12 concentrations during pregnancy for the benefits of offspring's quality of life. Besides dietary vitamin B's intake, intra-partum maternal gut microbe improvement is also needed, i.e. by the consumption of pre- and probiotic during periconceptional period.

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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Reference

1. Sande HV, Jacquemyn Y, Karepouan N, and Ajaji M. Vitamin B12 in pregnancy: maternal and fetal/neonatal effects – a review. Open Journal of Obstetrics and Gynecology, 2013, 3, 599-602 http://dx.doi.org/10.4236/ojog.2013.37107
2. Sukumar N, Venkataraman H, Wilson S, Goljan I, Selvamoni S, Patel V, et al. Vitamin B12 status among pregnant women in the UK and its association with obesity and gestational diabetes. Nutrients 2016, *8,* 768; doi:10.3390/nu8120768
3. Barua S, Kuizon S, and Junaid MA. Folic acid supplementation in pregnancy and implications in health and disease. J Biomed Sci 2014;21:77-85 http://www.jbiomedsci.com/content/21/1/77
4. Ho C-L, Quay TAW, Devlin AM, and Lamers Y. Prevalence and predictors of low vitamin B6 status in healthy young adult women in Metro Vancouver. Nutrients 2016**,** 8, 538; doi:10.3390/nu8090538
5. Hunt A, Harrington D, and Robinson S. Vitamin B12 deficiency. BMJ 2014;349:g5226 doi: 10.1136/bmj.g5226

6. Wibowo N, Bardosono S, and Irwinda R. Effects of *Bifidobacterium animalis* subsp. *lactis* HNO19 (DR10™), inulin, and micronutrient fortified milk on fecal DR10™, immune markers, and maternal micronutrients among Indonesian pregnant women. Asia Pac J Clin Nutr 2016;25(Suppl 1):S102-S110
7. Eck P and Friel J. Should probiotics be considered as vitamin supplements? Vitam Miner 2013: e124. doi:10.4172/vms.1000e124
8. The United Nations University. Conclusions of a WHO Technical Consultation on folate and vitamin B_{12} deficiencies. Food and Nutrition Bulletin 2008;29(2):S238-44
9. LeBlanc JG, Laino JE, del Valle MJ, Vannini V, van Sinderen D, Taranto MP, et al. B-group vitamin production by lactic acid bacteria – current knowledge and potential applications. J Appl Microb 2011;111:1297–1309
10. Eck P and Friel J. Vitamins & minerals. Vitam Miner 2013: e124. doi:10.4172/vms.1000e124