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World Nutrition Journal (abbreviated: W Nutr J) is an international, English language, peer-reviewed, and open access journal upholding recent evidence related to nutrition sciences. The journal accepts manuscripts in terms of original paper, case report, editorial, and letter to editor.

About

World Nutrition Journal was founded in 2016 as the official journal of Indonesian Nutrition Association. It aims to publish high quality articles in the field of community, clinical, and critical care aspects of nutrition sciences

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All manuscripts submitted will be screened by an editor whether they have the requirements and accordingly to author instructions. Then, the editor will transfer them to Editor-in-chief. Editor-in-chief will choose peer-reviewer for the manuscripts, according to their field of expertise, with help from associate editors and editorial board members. Peer-review process should be based on Committee on Publication Ethics (COPE) standards. This journal uses double-blind review. After the peer review process and the manuscripts are approved, they will be sent back to Editor-in-chief. Afterwards, Editor-in-chief will send the approved manuscripts back to the editor for final editing, layout editing, and proofreading. Finally, the approved and edited manuscripts will be published.

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LETTER FROM EDITOR

We would like to sincerely apologize for the delayed publication of World Nutrition Journal volume 2, issue 1, 2018. This delay is due to World Nutrition Journal website maintenance. We updated the software and website for better security and utility.

World Nutrition Journal supported the 13th Symposium on Nutri Indonesia in conjunction with 5th International Nutrition Symposium: "Nutrition Innovation in Disease Prevention and Treatment" to encouraged participants to publish their scientific presentation to our journal.

We are striving our best to improve WNJ to become one of the leading open-access journal in Nutrition related science.

We thank you for your support and acknowledgement.

Sincerely,

Editor-in-chief of World Nutrition Journal

Dr. dr. Saptawati Bardosono, MSc

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EDITORIAL

Effective Communication Skill: Doctor – Patient Consultation

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Everyone, including physicians/doctors knows how to communicate. Communication skill involves how we apply a systematic cycle of sending message, receiving and interpreting it before we give a feedback. However, people only perceived communication as practicing sending the message. And, when receiving a message the feedback-step is the most often neglected. Actually, the feedback-step is the most critical part in which it closes the communication cycle and confirms the understanding of the message.

Furthermore, there is a deeper development of communication in which we need to stress into three approaches, i.e. being present, active listening and active empathy. By being present then we can clear the clutter of mental distraction and focus on the immediate communication task at hand. Active listening is needed to apply specific listening-for-understanding techniques that confirm awareness, while active empathy is important to process information for a true awareness of other's needs. All this approaches take times, of course, however we can anticipate it by practicing effective communication.

The failure to communicate can occur everywhere in medical practices. We know that in medical world doctors, nurses, medical staff, administrators and office employee communicate with patients, especially doctors. In dealing with patient interaction, research confirms that "no matter how knowledgeable a clinician/doctor might be, if he or she is not able to open effective communication with the patient, then he or she may be of no help."

Doctors are not born with excellent communication skills, as they have different innate talents. Instead they can understand the theory of good doctor-patient communication, learn and practice these skills, and be capable of modifying their communication style if there is sufficient motivation and incentive for self-awareness, self-monitoring, and training.[1,2] Communication skills training has been found to improve doctor-patient communication.[3,4] However, the improved behaviors may lapse over time.[5] Therefore, it is important to practice new skills, with regular feedback on the acquired behavior.[5] Some have said that medical education should go beyond skills training to encourage physicians' responsiveness to the patients' unique experience.[6]

There are several reasons for doctors to sharpen their effective communication skills which include:

1. Ability to successfully interact with a "difficult" patient

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2. Clearly presenting diagnosis and/or treatment options
3. Enhancing patient's compliance with medications or treatments
4. Gaining a clear understanding of patient needs or medical issues
5. Influencing a patient to adopt healthy living or lifestyle changes.

We realize and understand that the many years of professional medical education are considered lacking in the development of good effective communications skills. Fortunately, there are many options for training to polish the effective communication skills in a real-world application for doctors and other medical staffs.

Indonesian Nutrition Association, with their annual event of Nutri Symposium, held a pre symposium workshop of effective communication skill focusing on weight management, targeting participant with medical background (general practitioners and specialist), with a one day workshop to focus on the implementation of consultation practice followed by simulation on how to present the right understanding of patient needs and influencing them in a lifestyle changes and by result, a satisfactory compliance.

This event will regularly be held each year as a solution for doctors who has a difficulties in communication skills to enhance their consultation daily practice.

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ORIGINAL PAPER

Fasting Plasma Glucose Concentration in Relation to Nutritional Status Indicator and Physical Activity Level Among Schizophrenia Patients

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Abstract

Introduction Diabetes mellitus often occurs in schizophrenia patients. This condition probably related to genetic, antipsychotic drugs and the development of schizophrenia which can lead to an unhealthy lifestyle, such as sedentary lifestyle and increased of dietary intake. **Methods** Cross-sectional study was held in Psychiatry Department Cipto Mangunkusumo Hospital in May to June 2014 to determine the correlation between fasting plasma glucose concentration in schizophrenia patient to their nutritional status indicator and physical activity level. **Results** Forty-seven subjects finished the study protocol. The result showed that the fasting plasma glucose concentration in schizophrenia patient has no correlation with nutritional status indicator and physical activity level, in which 91.5% subject had normal fasting plasma glucose. However, further investigation is needed because 31.9% subject were overweight, 48.9% subject were obese and 74.5% subject had central obesity. **Conclusion** No correlation was found between fasting plasma glucose concentration with nutritional status indicators and physical activity in schizophrenia patients. However, most subjects had central obesity.

Keywords Diabetes mellitus, schizophrenia, fasting plasma glucose, nutritional status indicator, physical activity level

Introduction

Eating is human basic daily requirement as energy intake is needed to survive. Physical activity has a contribution in total energy expenditure. The balance between energy intake and energy expenditure will maintain a constant body weight by a complex system of chemical, hormonal and neural mechanisms. Abnormalities of these complex systems will result in weight fluctuations which may cause impairment in the body system.[1]

The body uses energy in form of glucose, which can be detected as blood glucose. The term hyperglycemia is a condition of high blood glucose concentration, which can be due to defects in insulin secretion, defects in insulin actions or both,[2] and any impairment in glucose homeostasis.[3] Chronic hyperglycemia may be caused by several conditions such as obesity and diabetes mellitus (DM). Obesity is also one of the risk factors of DM. In person with DM, abnormalities in the

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metabolism of carbohydrate, protein and fat may present.[1] Furthermore, DM is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart and blood vessels.[2]

In relation to obesity and DM, as the main concern of this study, although schizophrenia is a severe form of the mental illness. Person with schizophrenia have a tendency to have lack of exercise and poor nutritional status (obesity) in which mostly affecting adult population.[4] This conditions may be the result from the illness itself or the medications.[5] In schizophrenia patients, the imbalance between high energy intake and low physical activity will cause obesity.[1] Obesity is known as one of the risk factor of insulin resistance with hyperglycemia as the symptom.[6] Studies by Sweileh,[7] Saddicha,[8] Cohen,[9] and De Hert,[10] supported that hyperglycemia occured in schizophrenia patients. On the other hand, Martynikhin[11] study showed that fasting glucose concentration in schizophrenia patient is generally normal.

There is more concern about these conditions because 60% of premature death in persons with schizophrenia is due to medical conditions, such as cardiovascular, pulmonary and infectious diseases. Cardiovascular diseases risk factors in schizophrenia, which are preventable, are obesity, smoking, DM, hypertension and dyslipidemia.[5] Thus, the need for screening, monitoring and prevention for cardiovascular disease in schizophrenia patients since the initial diagnostic of schizophrenia is becoming important.[12] Thus, this study aims to see the correlation between fasting plasma glucose concentration to nutritional status indicators and physical activity level in schizophrenia patients.

Methods

Subjects

Sixty eight schizophrenia patients, age ranged between 19-59 years old, in Adult Clinic Psychiatry Cipto Mangunkusumo Hospital were recruited. They were diagnosed by the psychiatrist and screened accordingly to the study criteria. The subjects agreed to participate by signing the informed consent and they were assured that all information were confidential. Then they followed the interview, anthropometric measurements and food recall training for filling their 4-day food record. All subjects were informed to come again one week after their recruitment and after 12 hours of overnight fasting for the laboratory fasting glucose concentration measurement. 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 coefficient of correlation value, had finished the study protocols.

Measurements

Data collection was done in May to June 2014. Data collected consisted of subject characteristics, antipsychotic medications during the study, family history of DM, weight, height and waist circumferences, physical activities, food histories and blood samples for fasting glucose concentration. Weight was measured using *Tanita*® digital scale, height was measured using a non-stretchable wall-meter and waist circumference was measured using the tape measurement. From the weight and height measurements, body mass index (BMI) was calculated. Physical activity level was measured by using International Physical Activity short form. Food recall and food record were then analyze with Nutrisurvey 2007 food processor programme with added indonesian food database which were then interpreted as total energy, carbohydrate, protein and fat intake. Fasting plasma glucose were determined enzymatically by using the hexokinase method.

Statistics

Data were analyzed with Kolmogorov-Smirnov test to check the normality distribution of each data. Pearson correlation test was used to analyze the correlations between variables by using SPSS statistical software version 20 for Windows operating system.

Results

The results showed 43 of 47 subjects (91.5%) had normal fasting plasma glucose. The subjects were mostly less than 40 years old (70.2%), male

(57.4%), not married (70%), and not working (70.2%). Most subjects had duration of schizophrenia for more than 2 years (85.1%). Around 85.1% subjects had atypical anti-psychotic mediation for more than 5 years (42.5%). Subject who routinely consumed medication was 95.7%. Subject who were prescribed polypharmacy medications are 57.4%. In terms of nutritional status, 80.8% were overweight-obese and mostly having abdominal or central obesity (74.5%). Almost all the subjects had low-moderate physical activity level. However, there was no significant difference between the subject's characteristics, dietary intake, nutritional status, and physical activities to fasting plasma glucose concentration (Table 1).

Table 2 shows the correlation between fasting plasma glucose concentration with nutritional status indicators and physical activity level in schizophrenia patients. There were no correlation between BMI, waist circumference, total dietary, carbohydrate, protein and fat intake with fasting plasma glucose concentration.

Discussion

To our knowledge, this is the first study in Indonesia to investigate the correlation between fasting plasma glucose concentration with nutritional status indicator and physical activity in schizophrenia patients. In this study, only 8.5% subjects had abnormal fasting plasma glucose. However, regarding to the very high proportions of overweight-obesity (80.8%) and central obesity (74,5%), this study revealed an unexpected finding, i.e. most of the subject's dietary intake were balance with their physical activity and they have a normal fasting plasma glucose.

All subjects with abnormal fasting plasma glucose were below 40 years old. This differs from De Hert study[10] in which the subjects with schizophrenia have the highest tendency of glucose abnormalities at age over 40 years old. In this study, probably only subject with good physical ability could visit the psychiatry clinic at Cipto Mangunkusumo Hospital. Thus, subjects out of the hospital should be included. Fasting plasma glucose abnormality in this study affected only 2.1% versus 6.4% subjects with duration of illness less than 2 years and more than 2 years, respectively. This finding is similar to De Hert[10] study which showed the lowest glucose abnormalities in schizophrenia subject was among those patients with duration of illness less than 1.5 years. The glucose abnormalities were higher in subject with longer duration of illness. Thus the risk of glucose abnormalities may already happen at the beginning of the disease and will increase with longer duration of illness. Furthermore, 8.5% subject with glucose abnormalities in this study received atypical antipsychotic. This result is similar to Haider[16] study in which 8% subject had glucose abnormality. However the mechanism between antipsychotic and hyperglycemia was not investigated in this study.

Dietary intake between subjects in this study was different because it was highly dependent to their family daily food. Most of the subjects have higher fat intake which may be one of the risk factor of obesity for this study's subjects. In addition, 48.9% subjects had low–moderate physical activity, which is different to Yamamoto[17] study, i.e. schizophrenia subject had a low physical activity. It is widely known that low physical activity will need low energy requirement, thus will cause obesity if the total dietary intake was higher. Furthermore, obese subjects with low physical activity may results in metabolic overload in the liver and muscle, then ends with pancreatic beta cell failures.

In this study, no correlation was found between blood fasting plasma glucose concentration with nutritional status indicators and physical activity in schizophrenia patients. This may be due to most of the subjects had normal fasting plasma glucose eventhough they were obese and have low physical activity. However, more than 50% subjects in this study had central obesity, which is known as one of the risk factors for insulin resistance and metabolic syndrome. Patients with metabolic syndrome has double higher risk for death and triple higher risk to have heart attack or stroke compared to those without.

There are some limitations in this study, namely subject's variations, financial problem and family

Table 1. Characteristics of subject schizophrenia, the nutritional status and physical activity compare with fasting plasma glucose concentration (n=47)

Variable	Fasting plasma glucose concentration		p
	<100 mg/dl (n=43)	100–125 mg/dl (n=4)	
Age			0.397
19 – <40 years	29	4	
40 – 59 years	14	0	
Sex			0.425
Male	29	3	
Female	14	1	
Marriage status			0.169
Married or divorce	14	2	
Single	29	2	
Education			0.881
Not graduated from Junior high	5	0	
Junior high graduated and above	38	4	
Work			0.753
Work	13	1	
Not working	30	3	
Duration of schizophrenia			0.822
<2 years	6	1	
>2 years	37	3	
DM history in family			0.417
Yes	13	1	
No	30	3	
Antipsychotic			0.413
Typical	5	0	
Atypical	36	4	
Combination	2	0	
Antipsychotic consumption			0.864
Routine	41	4	
Not routine	2	0	
Duration antipsychotic medication			0.260
<5 years	23	4	
≥5 years	20	0	
Medication			0.526
Monopharmacy*	17	3	
Polypharmacy**	26	1	
BMI (kg/m^2)			0.494
<18,5 kg/m^2	2	0	
18,5 – <23 kg/m^2	7	0	
23 – 27,5 kg/m^2	12	3	
>27,5 kg/m^2	22	1	
Waist circumference			0.130
Male <90 cm	9	0	
Male ≥90 cm	15	3	
Female <80 cm	3	0	
Female ≥80 cm	16	1	
Physical activity			0.524
Low <600 MET minute/week	22	1	
Moderate 600 – 3000 MET minute/week	20	3	
High >3000 MET minute/week	1	0	

Note: *one type of medication (typical or atypical); **combination of typical and atypical medication

Table 2. Correlation between fasting plasma glucose concentration with nutritional status indicators and physical activity in schizophrenia patients

Nutritional status	Fasting Plasma Glucose	
	r	p value
BMI	-0.005	0.972
Waist circumference	0.101	0.498
Total dietary intake	-0.046	0.760
Carbohydrate intake	0.017	0.911
Protein intake	0.026	0.862
Fat intake	-0.196	0.187
Physical activity	0.087	0.562

support to finish the protocol. Their awareness on the importance of family support in the treatment of schizophrenia subject to prevent the cardiovascular events was not good enough.

In conclusion, there was no correlation found between blood fasting plasma glucose concentration with nutritional status indicators and physical activity level in schizophrenia patients in this study. However, there was a high proportion of central obesity found in this study, which indicated schizophrenia may be associated with metabolic syndrome. Thus, the present findings can be regarded as a small step forward practical implication for clinicians. Further investigations are suggested to detect other cardiovascular risk factors in schizophrenia patients.

Conflict of Interest

Authors declared no conflict of interest regarding this study.

Open Access

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ORIGINAL PAPER

Comparing the Efficacy of Ketogenic Diet with Low Fat Diet for Weight Loss in Obesity Patients: Evidence-Based Case Report

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Abstract

Introduction Obesity is a nutritional disease which is still a health burden particularly in Jakarta. The main treatment for obesity is nutritional intervention. Nowadays, several dietary approaches have been developed, including ketogenic diet, which is still controversial. **Methods** Literature search had been done within 4 databases including PubMed®, Cochrane®, Google® Scholar, and Science Direct®, using keywords: obesity, ketogenic diet, low-fat diet, and weight loss. Then, Medical Sub Heading (MeSH) was used. The search resulted in two articles which were appraised according to aspects of validity, importance, and applicability **Results** A randomized-controlled trial study showed similar effect of weight loss with ketogenic diet compared to low-fat diet. On the other hand, a meta-analysis study showed ketogenic diet caused more weight loss than low-fat diet. Both studies showed an increased risk of cardiovascular disease from the ketogenic diet group, which were shown by a decrease of flow-mediated dilatation and an increase of LDL-C. **Conclusion** Ketogenic diet shows a better long-term effect for weight loss in obese patients than low-fat diet. However, ketogenic diet may increase the cardiovascular event risk significantly.

Keywords ketogenic diet, low-fat diet, obesity, weight loss

Introduction

Obesity and overweight, also known as malnutrition, are diseases in nutrition and the metabolic field. These define as conditions in which a patient has an above normal body mass index (BMI).[1] In Indonesia, BMI values are referred from the Asia-Pacific World Health Organization guidelines, with the normal range of 18.5–22.9 kg/m^2. Overweight and obesity are defined as body mass index of 23–24.9 kg/m^2 and >25 kg/m^2, respectively.[2] Obesity is an important issue due to its high prevalence. According to *Riset Kesehatan Dasar* (Riskesdas) Indonesia in year 2013, the prevalence of obesity in Jakarta is 30% in men and 40% in women.[3] In addition, obesity is a major risk factor of chronic degenerative diseases, such as diabetes mellitus, dyslipidemia, and hypertension.[4]

The etiology is mostly due to poor eating behavior, thus patient management focuses mainly in nutritional intervention. The nutritional intervention widely used is calories restriction using low-fat diet.[5,6] However, this nutritional intervention often causes lack of obedience of the patients.[5]

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In order to overcome the problem, several nutritional interventions had been suggested using various macronutrient compositions. Among them is ketogenic diet, which defines as dietary pattern with high-fat and very-low-carbohydrates compositions for daily intake.[7,8] The goal of ketogenic diet is to increase ketogenesis, which happens when the body is lack of adequate energy from carbohydrate, particularly the central nervous system.[7]

Ketogenic diet remains controversial in our population. It can cause weight loss however the long-term effect on body weight and the adverse effects are still unknown.[7] In addition, the effect of weight loss from ketogenic diet compared to other diets is still controversial.[7,8] Therefore, this paper focuses on evidence-based critical review about comparing the efficacy of ketogenic diet with low-fat diet for weight loss in obese patients.

Case Illustration

Male, 46 years old, visited clinic for health consultation. He said during exercise, there was cholesterol check-up and his cholesterol level was 252 mg/dL. The patient was concerned about his condition which could cause health complications in the future. He has family history of cardiovascular disease: his older brother had heart attack 3 months ago and his father had stroke. The patient also complained about his excessive body weight. Antrophometric measurement showed body height of 158 cm and body weight of 82 kg. Thus, the BMI is 32.4 kg/m^2 (grade II obesity). Other physical examinations showed normal results. Therefore, he was suggested to have a lifestyle change (especially in his dietary pattern). He heard from his friends that ketogenic diet could reduce weight faster than other diets. Therefore, patient came to clinic to consult the doctor about ketogenic diet or the appropriate dietary pattern for his health.

"In obese patients, is ketogenic diet intervention better than low-fat diet for weight loss?" Table 1 shows clinical questions formula.

Table 1. Clinical questions formula

Patient/ Problem **(P)**	***Intervention*** **(I)**	***Comparison*** **(C)**	***Outcome*** **(O)**
Obese patients	Ketogenic diet	Low-fat diet	Weight loss
Clinical Question Type	Treatment		
Study Design	Randomized-controlled trials (RCTs) or meta-analysis or systematic review of RCTs		

Methods

Literature search had been done within 4 databases: PubMed®, Cochrane®, Google® Scholar, and Science Direct® by using the keywords obesity, ketogenic diet, low-fat diet, and weight loss. Afterwards, Medical Sub Heading (MeSH) was used. Table 2 shows the strategies for articles search.

The total number of articles found based on keywords was 168 articles. Inclusion criteria for title selection and abstract were researches in patients with overweight or obesity; with randomized controlled trials (RCTs), meta-analysis or systematic review of RCTs as study designs; and available in free English full-text. Ten articles in which titles and abstracts matched with the inclusion criteria were found. Then, duplication equality screening was done, which resulted in remaining 4 articles. Reviews were performed on the 4 full-text articles. Among them, two articles were relevant to the clinical questions. Oneof them was an individual RCT while the other was a meta-analysis of RCTs. Figure 1 shows flow chart of the method used for article searches and selections.

Critical reviews were performed on selected articles using the criterias from Oxford Center for Evidence Based Medicine 2011 including the aspects of validity, importance, and applicability.

Table 2. The strategies for article search

No	Database	Keywords	Findings	Selected
1.	PubMed®	Ketogenic Diet [MeSH] **OR** Diet, Carbohydrate-restricted [MeSH]**AND**Diet, Fat-Restricted [MeSH] **AND**Obesity [MeSH] OR Overweight [MeSH] **AND**Weight Loss [MeSH]	79	6
2.	Cochrane®	Ketogenic Diet [MeSH] **OR** Diet, Carbohydrate-restricted [MeSH]**AND**Diet, Fat-Restricted [MeSH] **AND**Obesity [MeSH] OR Overweight [MeSH] **AND**Weight Loss [MeSH]	52	4
3.	Google® Scholar	Ketogenic Diet [MeSH] **OR** Diet, Carbohydrate-restricted [MeSH]**AND**Diet, Fat-Restricted [MeSH] **AND**Obesity [MeSH] OR Overweight [MeSH] **AND**Weight Loss [MeSH]	17	0
4	Science Direct®	Ketogenic Diet [MeSH] **OR** Diet, Carbohydrate-restricted [MeSH]**AND**Diet, Fat-Restricted [MeSH] **AND**Obesity [MeSH] OR Overweight [MeSH] **AND**Weight Loss [MeSH]	20	0

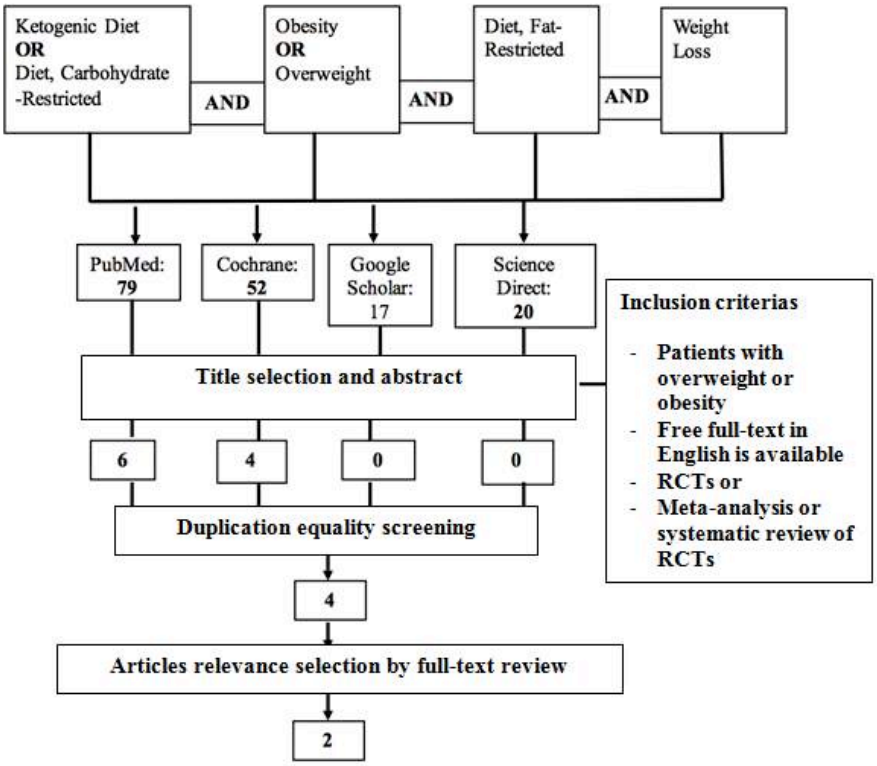

Figure 1. Flow chart of the methods used for article search and selection

Results

Validity

Table 3 shows the critical appraisal on the validity of the study by Wycherley TP et al.[9]

Table 3. Critical appraisal on the validity of study

Parameter of validity	Wycherley TP et al (2010)[9]
Title	Long-term effects of weight loss with a very-low-carbohydrate and low-fat diet on vascular function in overweight and obese patients
Subjects	The total study subjects were 118 patients, consisted of 57 patient with low carbohydrate high fat diet (61%) and 61 patients receiving low fat diet with equally calculated calories. At the end of the study, only 49 patients finished the whole study, i.e subjects in the intervention group and 23 in the control group.
Randomization	Yes, randomization was done on patients who received both ketogenic and low-fat diets.
Randomization blinding *(allocation concealment)*	Yes, blinding technique was used by the investigators in this study, but could not be applied to the study subjects.
Initial characteristics of the subjects/ objects	Yes, both groups of patients have similar demographic characteristics in terms of age, sex, body mass index, blood pressure and cardiovascular risk profile.
Equal treatment	Yes, both groups were equally treated.
Adequate follow up	Yes, both groups underwent a follow-up and nutritional consultation in week-8 and every month afterwards. Data was obtained in the beginning of the study and after 52 weeks.
Intention-to-treat analyses	No, data analysis in this study utilized a per-protocol analysis
Level of Evidence	2 (Individual RCT)

Table 4 shows critical appraisal on the validity of Bueno NB et al[10] study.

Table 4. Critical appraisal on the validity aspect of *meta-analysis*

Parameter **Validity**	Bueno NB, *et al* (2013)[10]
Title	Very-low-carbohydrate ketogenic diet vs low-fat diet for long-term weight loss: a meta-analysis of randomised controlled trials
PICO (Patient, intervention, comparison, outcome)	PICO used during searching strategy was as follows: P: patients with BMI >27.5 kg/m^2; I: ketogenic diet; C: low-fat diet; O: weight loss during the last 12 months
Literature searching	Articles were searched through MEDLINE, CENTRAL, Science Direct, Scopus, LILACS, SciELO and ClinicalTrials.gov using key words: ketogenic diet, weight loss, and cardiovascular risk factors.
Include all relevant studies	Yes, all relevant studies were included; studies which met the PICO criteria and RCTs were included in the analyses.
Validity assessment on each study	Yes, validity assessment was done on each study
Result consistency in each study	Yes, the results were consistent on each study
Level of Evidence	1 (a meta-analysis from RCTs)

Importance

Assessment of the study importance was not done using the 2 x 2 table since the outcomes were numerical variables. Therefore, the results of each study were assessed based on the primary and secondary outcomes, if available. Table 5 shows the critical appraisal of the importance of each study.

Table 5. Critical appraisal of the importance aspect of each study

Study	Results
Wycherley TP, *et al* (2010)[9]	Weight loss was observed during the study period (week-0 to week-52), i.e. a reduction of 14.9 $\pm$ 2.1 kg in the ketogenic diet group and 11.5 $\pm$ 1.5 kg in the low-fat diet. The difference of weight loss was not significant between both groups (p=0.20). Meanwhile, BMI reduction was 5.3 ± 0.7 kg/m^2 in the ketogenic diet group and 3.9 ± 0.5 kg/m^2 in the low-fat diet group (p=0.14). The secondary outcome was the brachial artery flow-mediated dilatation (FMD), which was significantly different between both groups. The FMD reduction was 2.1 ± 0.6% in the ketogenic diet group and 0.3 ± 0.6% in the low-fat diet group (p=0.045). This showed a higher risk of endothelial damage in the ketogenic diet group.
Bueno NB, *et al* (2013)[10]	13 studies were included in the meta-analysis; 9 studies were done in 12 months and the other 4 studies were completed in 24 months. Based on this meta-analysis, weight loss was significantly higher in the ketogenic diet group with weighted mean difference (WMD) of -0.91 (95%CI: -1.65, -0.17) kg, p=0.02; I^2 = 0%, p=0.47. The result was consistent across all subgroup analyses, except for the subgroups with 24 months of follow-up. The secondary outcome was low density lipoprotein cholesterol (LDL-C) levels. Among 12 studies, which included a total of 1255 patients, a significantly greater increase of LDL-C levels was observed in the ketogenic diet compared to low-fat diet group (WMD 0.12; 95% CI: 0.04, 0.2 mmol/L, p=0.002; I^2 = 0%, p=0.7).

Applicability

Table 6 shows critical appraisal on the applicability of both studies.

Table 6. Critical appraisal on the applicability of both studies

Parameter of Applicability	Wycherley TP, *et al* (2010)[9]	Bueno NB ,*et al* (2013)[10]
Resemblance of the study subjects with the case	Subjects were males or females, age 24-64 years old, with BMI of 26-43 kg/m^2 (Asian Pacific criteria of obesity). Each subject also had at least one risk factor of metabolic syndrome, no history of organ dysfunction or malignancy, was not pregnant and had no smoking habit. This study was relevant to the case illustration.	Studies included in the meta-analysis had inclusion criteria that corresponded with PICO. However, the characteristics of the study subjects were not further detailed.
Agreement to the value and preference in the community	Doubtful. Since ketogenic diet might not be appropriate for Indonesian's culture, therefore adjustment for ketogenic diet is needed with Indonesian's local food availability.	
Feasibility of the therapy in the setting of daily clinical practice	Probably. Professional consultation is required before undergoing ketogenic diet, especially with comorbid diseases.	

A summary of the results of critically appraised RCT and meta-analysis is given in Table 7.

Table 7. Summary of results from both studies

Author	End-point	Result	Conclusion
Wycherley TP, *et al* (2010)[9]	Subject's weight loss, calculated from the beginning of study (week 0) to week 52. In addition, the cardiovascular risk was also counted.	Weight loss in subjects receiving ketogenic diet vs low-fat diets were 14.9 ± 2.1 kg vs 11.5 ± 1.5 kg, respectively (p=0.20). Additionally, the FMD reduction was 2.1 ± 0.6% vs. 0.3 ±0.6%, respectively (p=0.045).	Body weight reduction was higher in the ketogenic diet group yet not statistically significant. However, FMD reduction was significantly higher in the ketogenic diet group, which suggested higher cardiovascular risk.
Bueno NB, *et al* (2013)[10]	Body weight changes and indicator of cardiovascular risk among various RCTs involving ketogenic diet intervention.	From all of the 13 studies included, weight loss was ignificantly higher in subjects assigned to ketogenic diet compared to low-fat diet group (WMD -0.91 (95% CI 1.65–0.17) kg, p=0.02, I^2 = 0%). In addition, there was also an increased LDL-C levels in 12 studies (WMD 0.12; 95% CI: 0.04–0.2; p=0.002; I^2 = 0%).	There was a significantly greater weight loss in the ketogenic diet group. The results also showed homogeneity. Secondary outcome assessment showed a homogenous result, i.e. significantly higher increased of LDL-C levels in the ketogenic diet group.

Discussion

After critically assessed the study by Wycherley TP et al,[9] a potential drawback was observed in the validity aspect of the study due to high number of drop out cases, i.e. 69 drop outs of the 118 subjects. Consequently, the analysis could only be done per-protocol. However, since it was difficult to lower the drop out number in this kind of study, we decided to continue critical appraisal for the importance and applicability aspects. In the importance aspect, the results showed that body weight reduction was greater in the ketogenic diet group compared to the low-fat diet group. However, statistical analysis failed to reach significance and thereby making it inapplicable for generalization to wider populations.

Regarding the applicability, the study result is applicable to patients with similar condition. However, it should be noted that there was a secondary outcome showing that subjects treated with ketogenic diet experience significantly greater FMD reduction (2.1% ± 0.6% vs. 0.3 ± 0.6%) implying a greater risk of cardiovascular event. It has been documented that 1% FMD reduction can increase the risk of cardiovascular event to 13%. Therefore, based on the results of this study, ketogenic diet treatment for 12 months can increase the risk of cardiovascular event by approximately 26%.[9]

Critical appraisal done to the meta-analysis by Bueno NB, et al[10] showed a good validity assessment in terms of PICO strategy, study validity and consistency of the results. In the importance aspect, a significant result was shown by the higher reduction of body weight in the ketogenic diet group (WMD –0.91 kg; 95% CI: –1.65, –0.17; p=0.02) with good homogeneity, as shown by the I^2 = 0%. Assessment on the applicability aspect also found that the result from this meta-analysis could be applied to the case. On the other hand, the secondary outcome showed higher LDL-C levels in the ketogenic diet group (WMD 0.12; 95% CI: 0.04, 0.2; p= 0.002; I^2=0%), indicating a statistical significance and homogenous results.[10]

Based on the critical assessment of both studies, ketogenic diet showed a long-term benefit on weight loss, which is better or similar to the low-fat diet. In support of this finding, a review by Paoli *et al*[12] concluded that ketogenic diet had a weight loss effect and was effective in a short period of time to induce weight loss. The mechanisms by which ketogenic diet may reduce body weight include a reduction in appetite by reducing insulin production and by affecting body metabolism that maintain muscle mass and reducing much of the fat mass.[6,11,12]

On the other hand, the secondary outcome suggested that ketogenic diet might increase the risk of cardiovascular event. This finding was supported by the reduction of FMD values in the trial by Wycherley *et al*[9] and increased LDL-C levels in the meta-analysis by Bueno *et al.* Increased LDL-C levels by ketogenic diet is associated with the high consumption of saturated fat. A study by Chiu *et al*[13] stated that high consumption of high saturated fat would increase LDL-C levels and the risk of cardiovascular disease. In term of FMD reduction by ketogenic diet, another study by Schwingshackl and Hoffmann[14] has shown a consistent finding. Moreover, a study by Jonavoskli *et al*[15] also stated that a low-carbohydrate diet of <5% might reduce FMD. However, a short-term trial by Volek *et al*[16] showed an contrasting result; they found that low-carbohydrate diet was better in maintaining the FMD. Therefore, further studies are needed to address this issue.

Based on these two critically appraised articles, it can be concluded that ketogenic diet intervention showed a good efficacy in weight loss, which include the short-term (≤3 months) or long-term (12 to 24 months) effects. However, aside from the desirable body weight loss, ketogenic diet poses a substantially increased risk of cardiovascular event. Therefore, ketogenic diet cannot be recommended as a choice of weight-loss therapy for patients with high risk of cardiovascular disease. Further studies are needed to evaluate the effect and long-term safety of ketogenic diet on cardiovascular risk.

Conflict of Interest

Authors declared no conflict of interest regarding this study.

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ARTICLE REVIEW

Antibiotic Treatment in Infants: Effect on the Gastro-intestinal Microbiome and Long Term Consequences

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Abstract

Introduction: The gastrointestinal microbiome is crucial for the development of a balanced immune system. Antibiotics are frequently administered to infants and cause intestinal dysbiosis. This narrative review highlights the long term health consequences of antibiotic administration to infants and young children. The necessity of administration of antibiotics should be well considered, since an association with short term consequences such as antibiotic associated diarrhoea and long term adverse effects such as overweight, inflammatory bowel syndrome, allergic disease have been reported.

Conclusion: The pros and cons of antibiotic administration to infants and young children should be considered.

Keywords antibiotic, immune system, microbiome

Introduction

The human gut microbiota has been estimated to be equal or probably even 10 to 100 times more important in number than the cells composing the human body.[1] Microbial colonization of the human gut begins in utero since bacteria have been detected in the umbilical cord, placenta, amniotic fluid and also in meconium.[2] After birth, the gastrointestinal tract is colonized by a rapidly diversifying microbiota, and it is during the first years of life that the establishment of a stable gut microbiome occurs that will persist during later childhood and adulthood. Microbial colonization of the infant gastrointestinal tract begins immediately after birth, and is determined by many factors such as the maternal microbiota, delivery mode, feeding and medication such as antibiotics and proton pump inhibitors.[1] Early colonization is crucial for a balanced development of the acquired immune system. In other words: early colonization is a major factor influencing for later health. It has been well established that antibiotics not only kill bacterial pathogens, but they will also profoundly disturb the equilibrium of the gastro-intestinal microbiome and are a well-known cause of dysbiosis. The use of antibiotics increased globally with 36% in a decade.[3] The long-term consequences of gastro-intestinal dysbiosis during early life are the focus of this narrative review. There is a strong association between the microbiota composition and factors such as age, nutrition, stress, and many diseases and conditions such as allergy, diabetes, irritable bowel syndrome, overweight and inflammatory bowel disease. While much of the emerging literature has focused on the potential benefits of probiotic treatment, antibiotics used to treat pathogenic bacterial infections are known to disrupt the diversity and number of microbial organisms in the intestine.

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Antibiotic associated diarrhea

The most frequent and best studied consequence of intestinal dysbiosis as a consequence of antibiotic intake is antibiotic associated diarrhea (AAD). AAD is an immediate or short-term adverse effect of antibiotic treatment, occurs in +/- 20 % of all antibiotic courses and depends on the class of antibiotic, the presence of risk factors in patients (host factors, hospitalization, nosocomial outbreaks). AAD is defined as a change in stool frequency with at least three liquid stools/day occurring during two consecutive days (early onset) or two to six weeks after antibiotic treatment (late onset), and if no other cause can be identified (intercurrent viral or bacterial infection, laxative use, other cause).[4] The class of antibiotics (broad spectrum), the duration of administration and the age of the patient are risk factors to develop AAD. The administration of some probiotic strains such as *Lactobacillus rhamnosus* and *Saccharomyces boulardii* CNCM I-745 reduce the incidence and severity of AAD.[5]

Antibiotics early in life

Antibiotics may have a much broader impact, especially if given perinatal or to young infants. The administration of antibiotics intrapartum both during caesarean and vaginal delivery are associated with infant gut microbiota dysbiosis.[6] Maternal intrapartum antibiotic treatment is a key regulator of the initial neonatal oral microbiome.[7] Maternal intrapartum antibiotic prophylaxis will have a significant impact on the infant faecal microbial population, particularly in that of breastfed infants.[8] Intrapartum antibiotic administration results in a significant reduction in Bifidobacterium spp. strains.[9] The reduced abundance of these beneficial microorganisms, together with the increased amount of potentially pathogenic bacteria, may suggest these infants are more exposed to gastrointestinal or generally health disorders later in age. Dysbiosis acquired perinatal or during early life will induce long term consequences. Maternal antibiotic treatment, administered during pregnancy and lactation results in profound alterations in the composition of the microbiota in mothers and infants.[10] Prenatal antibiotics are associated with a larger body mass index (BMI) at the age of two years.[11] Children experiencing a higher number of respiratory tract infections in the first year of life already demonstrate an aberrant microbial developmental trajectory from the first month of life on.[12] Independent drivers of these aberrant developmental trajectories of respiratory microbiota members were mode of delivery, infant feeding, crowding, and recent antibiotic use .[12] Perinatal administration of antibiotics is often lifesaving and thus a medical need. However, special attention should be given to a balanced development of the gastrointestinal microbiome of infants born in these circumstances.

Antibiotics and weight

Subtherapeutic doses of antibiotics have been used as growth promoters in animal farming since the 1950s .[13] The effect is more pronounced for broad-spectrum antibiotics, and it is attenuated when animals are raised in sanitary conditions. Burgeoning empirical evidence suggests that antibiotics also affect human growth. As early as 1955, a randomized controlled trial in Navy recruits showed that a 7-week course of antibiotics led to significantly greater weight gain in the treated group compared with placebo.[13]

Antibiotic exposure before 6 months of age or repeatedly during infancy, was associated with increased BMI in healthy children.[14] Repeated exposure to antibiotics early in life, especially β-lactam agents, was shown to be associated with increased weight.[15] These adverse effects of antibiotics may play a role in the worldwide childhood obesity epidemic and highlight the importance of judicious use of antibiotics during infancy, favoring narrow-spectrum antibiotics.[14] Administration of three or more courses of antibiotics before children reach an age of two years is associated with an increased risk of early childhood obesity.[16] In a cohort study, 6.4 % children were obese at four years of age and exposure to antibiotics was associated with an increased risk of obesity at four years.[16] The more antibiotic courses, the stronger the risk.[16] Children

receiving antibiotics in the first year of life are more likely to be overweight at 12 years of age compared with those who were unexposed (32.4 *vs* 18.2%, P=0.002).[17] Repeated exposure to broad-spectrum antibiotics at ages 0 to 23 months is associated with early childhood obesity.[15] Sixty-nine percent of children were exposed to a mean of 2.3 antibiotic courses before the age of 24 months.[18] Exposure to antibiotics during the first 12 months of life was associated with a small increase in BMI in boys, but not in girls, aged 5-8 years in a large international cross-sectional survey .[19] The intestinal microbiota of infants is predictive of later BMI and may serve as an early indicator of obesity risk. Bifidobacteria and streptococci, which are indicators of microbiota maturation in infants, are likely candidates for metabolic programming of infants, and their influence on BMI appears to depend on antibiotic use.[20] If causality of obesity can be established in future studies, this will further highlight the need for restrictive antibiotic use.[15]

Because common childhood infections were the most frequent diagnoses co-occurring with broad-spectrum antibiotic prescription, narrowing antibiotic selection is potentially a modifiable risk factor for childhood obesity.[18] Administration early in life, cumulative exposure and broad spectrum antibiotics were additional risk factors associated with later obesity. In comparison to broad-spectrum antibiotics, narrow-spectrum antibiotics were not at any age or frequency associated with a risk for increased weight.[18] However, some studies do report contradictory results. Exposure to antibiotics within the first 6 months of life compared with no exposure was also shown to be not associated with a statistically significant difference in weight gain through age seven years.[21]

In summary, although literature is contradictory and thus the evidence is weak, there are many indicators that administration of broad spectrum antibiotics may be associated with a higher BMI during infancy and childhood.

Antibiotics and immunity and allergy

Synbiotic host and microbe interactions are critical for host metabolic and immune development. Early microbiota colonization may influence the occurrence of metabolic and immune diseases.[1]

Maternal use of antibiotics before and during pregnancy was associated with an increased risk of cow's milk allergy in the offspring, and persisted after adjusting for putative confounders.[22] A clear association was found between three or more courses of antibiotics during early life and cow's milk allergy, non-milk food allergy and other allergies in a longitudinal data analysis of 30,060 children.[22] The associations became stronger for younger age and differed by antibiotic class.[22] The risk of cow's milk allergy increased with increasing number of child's antibiotics used from birth to diagnosis of the allergy (test for trend $P < 0.001$).[23]

Antibiotics and the respiratory tract

Early introduction of solid foods such as fish and environmental factors such as living on a farm are protective factors for the development of later allergic disease. But administration of antibiotics during early life are a risk factor for allergic rhinitis and wheezing. Antibiotics during the first year of life are associated with an increased risk for wheezing and asthma up to the age of three and six years, independent of lower respiratory tract infections during the first year of life.[24-28] The strength of the association differs with the class of antibiotics, correlating with their effect on the gastrointestinal microbiome.[24] A dose-response effect was observed: when five or more antibiotic courses were administered, the risk to develop asthma increased significantly ($p<001$). There is no association between antibiotic use and late-onset asthma.[26] The adverse effect of antibiotics was particularly strong in children without a family history of asthma ($P(\text{interaction})=0.03$).[25] Retrospective studies had the highest pooled risk estimate for asthma compared with database and prospective studies. Respiratory infections, later asthma onset (asthma at or after two years) and exposure to antibiotics during pregnancy are all independent risk factor.

Antibiotics and Irritable Bowel Syndrome (IBS)

A statistically significant link between early life infections and IBS in adults aside from bronchitis could not be demonstrated.[29] These data confirm an early report concluding that antibiotic treatment

does not seem to be a major risk factor for recurrent abdominal pain at 12 years of age.[30] However, antibiotic use during the neonatale period was reported to be associated with infantile colic.[31]

Antibiotics and Inflammatory Bowel Disease (IBD)

Exposure to antibiotics throughout childhood is associated with IBD, and this relationship decreased with increasing age of exposure to antibiotics. Exposure before one year of age had the highest risk, decreasing at five and 15 years, although even antibiotics at the age of 15 still indicated a significant risk factor to develop IBD.[32] Each antibiotic course increased the risk to develop IBD with 6% (4%–8%).[32] Antibiotic use is common in childhood and its potential as an environmental risk factor for IBD warrants scrutiny.[33] Antibiotic exposure was significantly associated with Crohn's disease, being stronger in children, but was not significant for ulcerative colitis.[34] However, the antibiotic courses may also be the consequence of unrecognized and undiagnosed symptoms of IBD. Therefore, causality cannot be confirmed since antibiotics may be prescribed to children with intestinal symptoms of as yet undiagnosed IBD.[33]

Antibiotics and diabetes

Exposure to a single antibiotic prescription was not associated with higher adjusted diabetes risk, whereas treatment with two to five antibiotic courses was associated with an increase in diabetic risk for penicillin, cephalosporins, macrolides and quinolones.[35,36] The risk increased with the number of antibiotic courses. There was no association between exposure to anti-virals and anti-fungals and diabetes risk.[35] Exposure to antibiotics is likely to increase type 2 diabetes risk, but not for type 1 diabetes.[36,37] However, the findings may also represent an increased demand for antibiotics from an increased rate of infections in patients with yet undiagnosed diabetes.[36]

Conclusion

The most prevalent childhood bacterial infections in primary healthcare are respiratory, gastrointestinal and urogenital infections. Antibiotics are often unavoidable and sometimes life-saving. In many developing countries, antibiotic dispensing and its use in medicine, cattle breeding and agriculture are inadequately regulated, or existing laws are not being appropriately implemented. In addition, human travel contributes to antimicrobial drug resistance around the world. All of these factors have led to a very high level of bacterial resistance. However, antibiotics also cause intestinal dysbiosis, which on its turn is associated with an increased risk for adverse outcomes such as AAD, IBS, IBD, allergy, overweight, etc. Prudent use of antibiotics is paramount not only to reduce the propagation of antibiotic-resistant organisms but also to minimize the potentially detrimental long-term metabolic consequences of early antibiotic exposure. The long term adverse effects of broad spectrum antibiotics should be considered before these drugs are administered to young infants. The administration of some specific probiotics strains such as *Saccharomyces boulardii* have been shown to reduce the risk of short term adverse effects of antibiotics such as the risk to develop AAD. Whether probiotics may also reduce the risk to develop long term adverse effects of intestinal dysbiosis associated with repetitive antibiotic administration has not been validated and should be a focus of future research.

Future studies should investigate the effects of multiple exposures to broad-spectrum antibiotics during the second year of life. However, future studies should focus on the possible benefit of a rapid restoration of the dysbiosis caused by broad spectrum antibiotics.

Table 1. Antibiotics during early life and health effect.

Reference	Topic	OR	95 % CI
Metsälä [41]	CMPA (AB mother before pregnany)	1.26	1.20-1.33
	CMPA (AB mother during pregnancy)	1.21	1.14-1.28
Scott [16]	Obesity at 4 years	1.21	1.07-1.38
	Obesity at 4 years (< 3 AB courses)	1.07	0.91-1.23
	Obesity at 4 years (3-5 AB courses)	1.41	1.20-1.65
	Obesity at 4 years (> 6 AB courses)	1.47	1.19-1.82
Azad [17]	Obesity risk in boys	5.35	1.94-14.72
	Obesity risk in girls	1.13	0.46-2.81
	Obesity risk in boys (9 years)	2.19	1.06-4.54
	Obesity risk in girls (9 years)	1.20	0.53-2.70
	Obesity risk in boys (12 years)	2.85	1.24-6.51
	Obesity risk in girls (12 years)	1.59	0.68-3.68
Bailey [18]	Obesity (≥ 4 AB courses)	1.11	1.02-1.21
	Obesity (broad spectrum AB)	1.16	1.06-1.29
	Obesity (AB between 0-5 months)	1.11	1.03-1.19
	Obesity (AB between 6-11 months)	1.09	1.04-1.14
Hirsch [22]	Milk allergy	1.78	1.28-2.48
	Non-milk food allergy	1.65	1.27-2.14
	Other allergies	3.07	2.72-3.46
Risnes [25]	Asthma (>6 years)	1.52	1.07, 2.16
	Asthma (>3 years)	1.66	0.99, 2.79
	Asthma (no LRTI < 1 year)	1.66	1.12, 3.46
	Asthma (neg fam history)	1.89	1.00, 3.58
	Pos allergy test	1.59	1.10, 2.28
Ong [26]	Transient wheezing	2.0	1.9-2.2
	Asthma	1.6	1.5-1.7
	Asthma (>5 AB courses)	1.9.	1.5-2.6.
Alm [39]	Allergic rhnitis	1.75	1.03, 2.97
Metsälä [40]	Asthma (AB mother)	1.31	1.21-1.42
	Asthma (AB infant)	1.60	1.48-1.73
Murk [42]	Asthma (review, all studies)	1.52	1.30-1.77
	Asthma (retrospective studies)	2.04	1.83-2.27
	Asthma (database, prospective studies)	1.25	1.08-1.45
	Asthma (adjusted for resp inf)	1.16	1.08-1.25
	Asthma (onset> 2 years)	1.16	1.06-1.25
	Asthma (AB during pregnancy)	1.24	1.02-1.50
Pedersen [43]	Otitis media (AB during pregnancy)	1.30	1.04-1.63
	Otitis media (n° of AB courses)	1.20	1.04-1.40
	Ventilation tubes (AB third trimester)	1.60	1.08-2.36
Kronman [32]	IBD (AB < 1 year)	5.51	1.66-18.28
	IBD (AB < 5 years)	2.62	1.61-4.25
	IBD (AB < 15 years)	1.57	1.35-1.84
	IBD (1 or 2 AB courses)	3.33	1.69-6.58
	IBD (> 2 AB courses)	4.77	2.13-10.68
Hviid [33]	IBD	1.84	1.08 to 3.15
	Crohn's disease	3.41	1.45-8.02
	IBD (> 7 AB courses)	7.32	2.14-24.99
Ungaro [34]	Crohn's disease	1.74	1.35-2.23
	Ulcerative colitis	1.08	0.91-1.27
	Chrohn's disease (in children)	2.75	1.72-4.38
	Crohn's disease (metronidazole)	5.01	1.65-15.25
	Crohn's disease (fluoroquinolones	1.79	1.03-3.12
Boursi [35]	Diabetes (> 1 AB course, penicillin)	1.08	1.05-1.11
	Diabetes (> 1 AB course, quinolones)	1.15	1.08-1.23
	Diabetes (> 5 AB course, quinolones)	1.37	1.19-1.58

AB: antibiotic; IBD: inflammatory bowel disease; n°: number; pos: positive; resp inf: respiratory infection

Conflict of Interest

Authors declared no conflict of interest regarding this study

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ORIGINAL PAPER

Early Detection of Childhood Obesity Through Extended Routine Growth Monitoring of Children Below Two Years of Age in Asia Pacific Region

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Abstract

Introduction Increased body fat deposition during early life predisposes to higher obesity and metabolic disorder risks in later life. This is particularly relevant in the Asia Pacific region where historically prevalent under-nutrition is now been paralleled or even overruled by over-nutrition over the last few decades. This overview aims to evaluate the potential of early detection of obesity (risk) among experts through addition of specific growth monitoring assessments in children during the first two years of life. **Methods** A discussion among experts from Malaysia, Singapore, Sri Lanka and Australia on infant growth and a qualitative evaluation of current practice highlighted the need to measure body composition to assess the quality of growth. Current tools are mainly directed towards simple anthropometric measures such as body weight, length and head circumference which do not adequately reflect concurrent changes in body composition to detect early life adiposity development. Recent findings have shown benefits of measurement such as the sum of four skinfold thickness (S4SFT) during the first two years of life for risk assessment of later overweight/obesity. We recommend this assessment for routine practice as a proxy for fat deposition in young children. Further studies to understand implementation hurdles and cost-effectiveness of S4SFT and health outcomes in young children in the Asia Pacific region are necessary. **Conclusion** Inclusion of four skinfold thickness measurements as part of routine growth monitoring assessment, in addition to weight and height, could be recommended to assess adiposity development in early life allowing identification of infants at risk for obesity.

Keywords early life, children, obesity, four skinfold thickness

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Introduction

Several cohorts in Europe and Asia have traced the origins of childhood obesity to the first year of life attributing it to differences in BMI development.[1-3] In 2014, the World Health Organization (WHO)

estimated that about 41 million children under five year of age were overweight or obese, of which 48% live in Asia.[4] Current growth monitoring practices among young children are traditionally targeted to detect under-nutrition and any upward deviations are considered favourable.

Asians are reported to have significantly more body-fat per kilogram body weight than Caucasians which is typically referred to as the "thin-fat phenotype".[5] Although it is clear that origins of childhood obesity are from early childhood, current growth monitoring practices were not used for early detection of excess adiposity. However, because of the epidemic of childhood obesity and its contribution to an ever increasing prevalence of non-communicable diseases, it is of paramount importance that excess gains of adiposity are identified early in life.

This overview aims to evaluate the potential of early detection of obesity (risk) among experts through addition of specific growth monitoring assessments in children during the first two years of life.

Methods

Experts from the field of infant growth (paediatricians, researchers, nutritionists) from Asia Pacific and Europe met in 2013 to discuss practices and potential research gaps in growth and body composition assessment of children in the Asia Pacific region. Although qualitative approach using Delphi method was not administered, one highlighted area was how to include effective anthropometric measurements in early growth monitoring to detect excess adiposity gain. Some of the practices and the gaps in this sphere were highlighted in this review.

Discussion

Current routine growth monitoring in selected Asia Pacific countries

The four countries included for assessment (Sri Lanka, Malaysia, Singapore, Australia) may not be representative of the whole of the Asia Pacific region, however they are at different stages of economic development with varied burdens of overweight and obesity. Current growth monitoring practices in these countries are primarily conducted to monitor physical growth (weight, height and head circumference) as a whole and not to evaluate changes in body composition (Table 1) with differences in practice influenced by the availability of resources' and national requirements.

Challenges in measuring body composition in early life

Several methods are well-established to assess body composition among adults *(*Air Displacement Plethysmography (ADP), Dual-Energy X-ray Absorptiometry (DEXA) and Body Impedance Analysis (BIA)). However, sensitivity and practicality of these tests to assess fat deposition in children during the first two years of life requires further validation and research.

An alternative yet sensitive assessment which could be implemented in daily practice using a simple tool is skinfold thickness (SFT).[6] This consists of individual values from the independent assessment of subscapular, supra-iliac, biceps and triceps skinfolds or combined central or peripheral SFT or the sum of four sites (S4SFT) or specific SFT ratios. The S4SFT is identified as a good predictor of the changes in the fat mass during the first year of life and measures are required for younger children.[7,8] S4SFT within the first few months of life has been associated with cardiovascular health risk with an increase of aortic intima media thickness at 6 weeks[9] and obesity risk at 6 years of age (OR 1.61, 95% CI 1.09, 2.38).[10]

Measurement of SFT has several requirements for successful implementation that include a standard protocol, adequate training of the measurement techniques to avoid observer variability[11] (because it takes longer than standard anthropometry to complete) and translation of S4FT into an estimated total body fat mass for Asian children. The existing limited translation is due to a lack of population specific equations as existing equations have not yet been validated for Asian populations in younger age.[12]

Table 1. Overview of current practices for growth monitoring among children 0-5 years of age across the four countries

Countries/ Practices	Sri Lanka	Malaysia	Singapore	Australia
Demographics	Birth rate: 20/ 1000 birth, GDP: $3,368. Prevalence of childhood overweight: 6.1%	Birth rate: 17/1000 birth, GDP: $10,878. Prevalence of childhood overweight: 12–16%	Birth rate: 9.7/ 1000 birth, GDP: $ 51,855. Prevalence of childhood overweight: 12–16%	Birth rate: 12.8/1000 birth, GDP: $54,708. Prevalence of childhood overweight: 25%
Venue and personnel to monitor growth	Medical Officer of Health at every village	Hospitals, general clinics, maternal & child clinic (nurses)	well-child clinics in government-run polyclinics and private paediatrician offices.	child health nurses in well-child clinics in community hospitals and private paediatrician offices.
Recording system	Child Health Development record (50 page)	Health book (118 page)	Health book	"Purple" growth and development book.
Anthropometric measures	weight, length/ height, head circumference	weight, length/ height, head circumference	weight, length and head circumference	weight, length and head circumference
Frequency of assessment	monthly up to 24 months of age, then 2–3 monthly from 3–5 years of age.	monthly for the first 6 months, every 2 months for the second 6 months, every 3 months between 1–3 years of age, every 6 months between 2–4 years of age and annually between 4–6 years of age	1 month, 3 months, 4 months, 5 months, 6 months, 9 months, 15 months and 18 months.	1 month, 3 months, 4 months, 5 months, 6 months, 9 months, 15 months and 18 months.

A call for action for daily practice and further research

As currently used anthropometric measures do not provide an opportunity for the detection of increased adiposity during early life, a measure of SFT could be used as an alternative. S4SFT has shown to be an accurate, practical, relatively low cost and easy to implement measure of fat mass in various cross-sectional and longitudinal studies amongst younger children.[7,10]

To enable the use of S4SFT as part of routine growth assessment, several initiatives need to be taken that include a feasibility study on the use of S4SFT in day to day practice; a concise but comprehensive easy-to-use measurement protocol, validation with other gold standard methods, standard reference to identify intervention levels, and comprehensive training for staff. Cost-effectiveness studies and a referral system when adverse levels of adiposity are detected are also important.[13]

There could be increased pressure in the implementing these initiatives to measure all children in a busy clinic. Therefore, measurement of S4SFT could be a required assessment after initial screening using traditional anthropometry for children at risk for overweight/ obesity. Adopting

S4SFT measures into routine child health monitoring would assist in early detection of children at risk of excess adiposity and introducing this initiative into each country's national program of healthcare is of paramount importance.

Conflict of Interest

Leilani Muhardi, Eline M van der Beek and Marieke Abrahamse-Berkeveld are employees of Danone Nutricia Research-Early Life Nutrition. None of the other authors have conflict of interest. No educational grant is provided to the rest of authors. Ethical Approval is not obtained as the manuscript is based on observation of current practice.

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ORIGINAL PAPER

Association between Breakfast and Dysmenorrhea Degrees of SMAN 2 Students in Banda Aceh, Indonesia

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Abstract

Introduction: Dysmenorrhea is a common problem in women which can affect personal health and quality of life. Several risks of dysmenorrhea including age, age of menarche, nutritional status, marital status, family history, physical activity and food intake. Breakfast is a energy supply needed in the first hours of daily activities. The purpose of this study was to determine the relationship of breakfast with dysmenorrhea degree in high school students of SMAN 2 Banda Aceh, Indonesia. **Methods:** The design of the study was analytic observational with cross sectional approach in first, second and third year students of SMAN 2, Banda Aceh, Indonesia. **Results:** There were 24 students (18.2%) who routinely consumed breakfast, 36 students (27.2%) sometimes and 41 students (31.1%) rarely consumed breakfast, respectively. The total of 60 students (45.5%) experienced mild dysmenorrhea pain, 5 students (3.8%) with unbearable and 35 students (26.5%) with moderate pain. Statistical analysis showed there was a significant relationship between breakfast with degrees of dysmenorrhea (p = 0.022) with strong correlation coefficient (r = 0.2). **Conclusion:** We concluded that regular breakfast habit can reduce the degree of dysmenorrhea.

Keywords breakfast, dysmenorrhea degrees, visual analog scale

Introduction

Optimal health is important for every person including women, which can be achieved by healthy lifestyle. This includes breakfast and physical activity.[1] Food consumed will affect the body's metabolism and provide energy.[2] Many teenagers are often on a diet to maintain physical appearances. One of the diet methods teens or students do is having an irregular breakfast or even none at all.[3]

Dysmenorrhea can lead to decreased productivity as well as can majorly cause decrease of the quality of life (QoL) status.[3,4] Prevalence of dysmenorrhea in the world is 28%–71.7%.[2] In the United States, reports showed almost 90% of women suffered from dysmenorrhea, 10–15% had heavy menstrual pain, and lost 1.7 million workdays every month due to menstrual pain.[3] The prevalence of menstrual pain in Indonesia is 54.89% which, among them, 14% of adolescents and students were absent from school due to menstrual pain.[3] Primary dysmenorrhea often occurs at the age 17–22 years old whereas secondary dysmenorrhea occurs at age above 23 years old due to pelvic organ abnormalities. Women who are less than 25 years old have twice

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the risk of developing dysmenorrhea with moderate to severe pain compared to those who are 25–35 years old. Primary dysmenorrhea, which often affects growing and developing adolescents, can affect psychologically.[4]

Research by Fujiwara[4] in Japan found that young women who did not have breakfast had higher degrees of menstrual pain in comparison with those who had breakfast regularly. Nearly 50% of women who experienced dysmenorrhea and 10% of women suffer from severe menstrual pain for 1-3 days on each menstrual cycle.

Poor nutrition can affect growth and reproductive function, which then can cause menstrual disorders. During menstruation, especially in the luteal phase, there is an increase of nutritional needs, thus balanced nutrition can reduce dysmenorrhea.[5,7] Dysmenorrhea affects individual health, quality of life and family economy.[2]

Dysmenorrhea is characterized by cramping pain which begins before or immediately after menstruation and may last for 28–72 hours.[6] Premenstrual Syndrome (PMS) is an abdominal symptoms (abdominal pain or bloating), headache, back and calf pain. Women with PMS are 56.1 times more likely to have dysmenorrhea.[8] Women who experienced discomfort are 1.75 times more tendency to have dysmenorrhea and anxious women tends to be 2.17 times more likely to experience dysmenorrhea.[1,9]

Several studies in Indonesia regarding the relationships of breakfast with students' achievement and concentration, the effect of and the habit in having breakfast were done. The research regarding relationship between breakfast and the degree of dysmenorrhea in high school students has not been done in Aceh, even though dysmenorrhea can disrupt the body's immune system thus increase their absent in school which then affect their achievement. Aceh people are not used to eat breakfast at 7 or 8 am thus they generally have breakfast during break time around 10 am. This research was done in SMAN 2 school because it is located in the coastal area where most students were from families of fishermen and traders, who often do daily activities starting early in the morning. Therefore breakfast was eaten after completing their activities.

Methods

Subject and Study Design

This study used observational analytic design with cross sectional approach. The study was conducted from 6th to 13th of January 2018 in the first, second and third year of high school students of SMAN 2, Banda Aceh, Indonesia. A total subject of 132 students were taken by nonprobability sampling with stratified random sampling method. Inclusion criteria are all students of SMAN 2 (first, second and third year), had history of dysmenorrhea since menarche, not suffering from chronic disease (diabetes, hypertension, hyperthyroidism, ovarian cyst, or uterine fibroids), not suffering from secondary dysmenorrhea, not taking NSAID (nonsteroidal anti-inflammatory drugs), unmarried, and not doing routine physical activity. Measurement of dysmenorrhea was done by visual analogue questionnaire scale (VAS) with pain ruler 0–10 cm. Breakfast data was obtained using Food Frequency Questionnaire (FFQ) interview technique. Then, data were analyzed. Bivariate analysis was done with Spearman correlation test with 95% confidence interval (CI) $\alpha < 0.05$.

Results

There were a total of 132 subjects. The subjects' characteristics are shown in Table 1. The results showed that most subjects are 17 years old (69.7%) and age of menarche at age 10 years old (32.6%). Most subjects had normal nutritional status (53.8%), did not use any NSAID medicine (79.3%) and did not do routine physical activity (39.4%).

Table 1. Characteristics of the subjects (n=132)

Characteristics	Frequency (n)	Percentage (%)
Age, y		
16	10	7.6
17	92	69.7
18	27	20.4
19	3	2.3
Age of Menarche, y		
8	1	0.8
9	17	12.9
10	43	32.6
11	35	26.5
12	25	18.9
13	9	6.8
14	2	1.6
Nutritional status		
Thin	28	21.2
Normal	71	53.8
Fat	22	16.7
Obesity type I	10	7.6
Obesity type II	1	0.8
Medicine Use		
Yes	27	20.3
No	105	79.3
Marital Status		
Single	132	100
Married	-	-
Smoking		
No	132	100
Yes	-	-
Physical Activity		
5x/Week	-	-
4x/Week	9	6.9
3x/Week	10	7.6
2x/Week	14	10.6
1x/Week	47	35.6
Never	52	39.4

The frequency distribution of breakfast pattern of the subjects can be seen in Table 2.

Table 2. Frequency of subjects' breakfast pattern (n=132)

Breakfast	Frequency (n)	Percentage (%)
Never	3	3.2
Rarely	41	31.1
Sometimes	36	27.2
Often	28	21.2
Always	24	18.2

As shown in Table 2, most students rarely eat breakfast (31.1%). There were only 24 students (18.2%) who consumed breakfast routinely.

The frequency distribution of dysmenorrhea pain degree of the subjects can be seen in Table 3.

Table 3. Dysmenorrhea pain degree frequencies (n=132)

Dysmenorrhea Degrees	Frequency (n)	Percentage (%)
Unbearable Pain	5	3,8
Severe Pain	17	12,9
Moderate Pain	35	26,5
Mild Pain	60	45,5
No Pain	15	11,3

As shown in Table 3, most subjects had mild degree of pain (45.5%). Unbearable pain was noted in as many as 5 students (3.8%).

Table 4 shows the analysis of association between breakfast patterns to dysmenorrhea degrees. According to data analysis results in Table 4, subjects who had "rarely" and "sometimes" breakfast patterns experienced mild (41.5%) and moderate dysmenorrhea pain (33.3%), respectively. However, those who never had breakfast tend to have moderate pain dysmenorrhea degree (66.7%). Subjects who always had breakfast were mostly experienced mild (50%) and no pain (20%). There was a significant relationship between breakfast with the degree of dysmenorrhea ($p=0.022$), in which the correlation coefficient were strong ($r=0.2$).

Table 4. Association between Breakfast to Degrees of Dysmenorrhea (n=132)

Breakfast	Dysmenorrhea Degrees (n, %)										p value	r
	Unbearable pain		Severe pain		Moderate pain		Mild pain		No pain			
Never	-	-	-	-	2	(66.7)	-	-	1	(33.7)	0.022	0.2
Rarely	1	(2.4)	7	(17.1)	13	(31.7)	17	(41.5)	3	(7.3)		
Sometimes	1	(2.8)	7	(19.4)	12	(33.3)	12	(33.3)	4	(11.1)		
Often	2	(7.1)	2	(7.1)	6	(21.4)	14	(50)	4	(14.3)		
Always	1	(20)	1	(5.9)	2	(5.7)	17	(28.3)	3	(20)		

Discussion

The results of this study showed most students rarely consumed breakfast (31.1%) compared to those who always had breakfast (18.2%). These results are different from the Fujiwora[11] research in Japan, which shown as much as 65.8% schoolgirl routinely consumed breakfast. Research by Adesola[2] in Nigeria showed 73% routinely ate breakfast. Study by Eittah[12] in Egypt, which were conducted in medical students, showed 73% students routinely consumed breakfast every day, 28% occasionally had breakfast (around 3-4 days per week), 21% often, and 2.5% never. The research concluded the intensity of dysmenorrhea decreased in subjects who were accustomed to eat breakfast. Majority of the students who routinely ate breakfast had more regular menstrual cycles, better nutritional statuses and general health conditions. Routine morning breakfast is recommended because it is ideal for better metabolism and also overcoming dysmenorrhea.

A study by Abbaspour[1] in Iran reported 3% of women experienced severe, 2% unbearable, 44% moderate and 40% mild dysmenorrhea pain, respectively, while around 10% did not experience dysmenorrhea. In this study, among 132 female students, mostly experienced mild degree of dysmenorrhea (45.5%). This differs from research by Caro[9] in India which showed 68% subjects had severe dysmenorrhea. A study by Rigon[13] in Italy showed 56% subjects experienced severe dysmenorrhea. Different degrees of dysmenorrhea pain in each country may be due to differences in breakfast habits, physical activity, nutritional status and other factors such as age, age of menarche, smoking, and genetics which affect dysmenorrhea.[12,13] Socioeconomics may also become the cause of the different coping of menstrual pain.[14] Dysmenorrhea is related to prostaglandin hormone in the uterus which causes stronger and more frequent contractions of the uterus muscles. This reduces the blood flow and thus causes the nerves to be more sensitive to pain. This mechanism happens due to interaction of ovary hormones with the immune system which occurs as a response to progesterone withdrawal.[16]

This study showed significant relationship between breakfast patterns and the degree of dysmenorrhea (p=0.022). This result is similar with study by Eittah[12] which showed breakfast pattern was related to menstrual and premenstrual pain.[12] Study by Fujiwara[4] in Japan showed subjects who had breakfast had lower degree of menstrual pain in comparison with those who had none. Around 71% respondents who did not consume breakfast early would have dysmenorrhea. Excessive or poor nutritional statuses may induce dysmenorrhea, whereas well-balanced nutritional intake with normal nutritional status can reduce the risk of dysmenorrhea.[11]

Diet may help in reducing dysmenorrhea. Intake of nutrients such as soybean fiber, fruits, vegetables and calcium may help to reduce menstrual pain.[2] High salt content food may worsen dysmenorrhea. Fruits, vegetables and seeds contain nutrients which are beneficial to optimizing uterus muscles function, such as magnesium, calcium, and potassium. Food with high arachidonic acid level, such as red meat and poultry products, should be avoided due to its action as PGF_2-alpha precursor and PGE_2.[7,17]

Physical activities or exercises are helpful to reduce dysmenorrhea. Regular exercise can increase the release of beta endorphin into the blood flow, which serves to reduce menstrual

pain.[2,7] Breakfast is a powerful intake of nutrients needs. Young women often skip two meals and prefer snacks which can interfere with appetite. Adolescents have rapid growth, high activity level and, thus, increased nutritional needs. They also require higher source of iron for monthly menstrual cycle.

However, they are more interested in consuming snacks rather than having a proper breakfast at home. Additionally, consuming strict and unhealthy dietary patterns are often practiced to lose weight for unrealistic body image.[5,10] Nevertheless, routine breakfast habit benefits for regular menstrual cycle, normal BMI, reduced menstrual pain and better general health condition.[12] While over and poor nutritional statuses may worsen menstrual pain. Well balanced nutritional intake and accordingly to daily needs may reduce the risk of dysmenorrhea.[11]

Conclusion

This study found significant relationship between breakfast and the degree of dysmenorrhea in high school students of SMAN 2, Banda Aceh. There was a positive correlation between irregular breakfast habits and the increase of dysmenorrhea degree. It is advisable to always have breakfast regularly in order to reduce dysmenorrhea pain and improve general health for women. Students are also encouraged to do regular physical activity and consume well-balanced nutrition to reduce dysmenorrhea.

Conflict of Interest

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

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ORIGINAL PAPER

Effectiveness of Starting Weaning at 4 Months Compared to 6 Months Old to Reduce Anemia Among Infants: An Evidence-Based Case Report

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Abstract

Introduction This article aims to compare the effectiveness of introducing complementary foods at four months compared to six months of age to reduce the incidence of iron-deficiency anemia among healthy full-term infants. **Methods** A systematic search was conducted on PubMed, EBSCO, and Cochrane on 28th September 2017. The selection of title and abstract was done using the predefined inclusion and exclusion criteria. Twelve original articles were found, however, after full-text assessment, only two studies were considered relevant. These two studies were further critically appraised for their validity, importance, and applicability to measure their usability degree in this study. **Results** These two included studies showed no significant difference of iron-deficiency anemia incidence between the two complementary feeding groups. This can be shown by the absolute risk reduction which varied from -3.1% to 13.4%, relative risk reduction which varied from -22.8% to 18.4%, and number needed to treat which varied from -33 to 8. Both studies found that the ferritin was significantly different between both groups. However, the hemoglobin concentration was significantly higher in the complementary fed group in only one study. **Conclusion** The introduction of complementary feeding at 4 months of age is not effective to reduce the incidence of iron-deficiency anemia.

Keywords infant, complementary feeding, iron-deficiency anemia, hemoglobin, ferritin

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Introduction

Worldwide, anemia affects up to one of every two children younger than five years old.[1] According to World Health Organization (WHO), anemia is defined as a hemoglobin level at two standard deviations below the mean for a normal population of the same gender and age range.[2] In 2002, iron-deficiency anemia (IDA) was deemed to be among the most important contributing factors to the global burden of disease.[3] Anemia causes potentially irreversible negative consequences on cognitive and physical development of children, also physical performance – particularly work productivity in adults – are of major concern.[4]

WHO stated that the best source of nutrition for infants is breast milk. Therefore, WHO recommends infants to be exclusively breastfed (EBF) up to six months of age and be introduced to complementary feeding (CF) thereafter.[5] However, the iron content in breast milk is very low and even full-term infants usually only have sufficient iron stores until four to six months of age. A cohort study in Brazil revealed that 5.7% and 3.4% of healthy full-term infants age four months old presented with iron deficiency and iron deficiency anemia, respectively.[6] For current practice, in settings where IDA is frequent, WHO recommends the provision of iron supplements to infants and young children. Food-based approaches through food fortification and dietary diversification are also encouraged.[1] Therefore, the introduction of CF should start at age four months to accompany the critical window of vulnerability.

Many studies show the effectiveness of complementary feeding in improving iron status among healthy full-term infants.[8] Normal iron status will reduce the occurrence of IDA and prevent its negative effects on infant eventually. This article is made to identify whether the introduction of CF at four months compared to six months is effective as a primary prevention of IDA among healthy full-term infants.

Case Illustration

A 22 years old woman brought her son (four months old) to the primary health center for a routine vaccination. The doctor said that at the age of four months old, the iron stores of infants start to deplete. Therefore, he suggested that her son should consume an oral iron supplement daily to prevent him from getting anemia. However, the mother asked whether it can be prevented by starting the complementary food at the age of four months old. Her son was born full term with a good APGAR (appearance, pulse, grimace, activity and respiration) score.

Clinical Question

Among healthy full-term infants, does the introduction of complementary feeding at four months old reduce the incidence of iron-deficiency anemia compared to its introduction at six months old?

Methods

Search Strategy

The search was conducted on *PubMed®*, *Cochrane®*, and *EBSCO®* on 28th September 2017 with the Medical Subject Headings (MeSH) and text words listed in Table 1. Search strategy, results, inclusion, and exclusion criteria are shown in a flowchart (Figure 1). Additional searching by checking the reference lists of some relevant articles (snowballing) was also done.

Critical Appraisal

After the selection, the included articles were appraised using appraisal tools for randomized controlled trial from Centre of Evidence-based Medicine, University of Oxford (www.cebm.net), every text was appraised individually by a reviewer. However, any confusion was discussed and decided based on the agreement of all authors. The critical appraisal results are showed in Table 2.

Results

This evidence-based case report reviews the effectiveness of the introduction of complementary feeding at four months (CF) compared to six months – or exclusively breastfed for the first six months (EBF) – in reducing the risk of anemia among healthy full-term infants. The primary

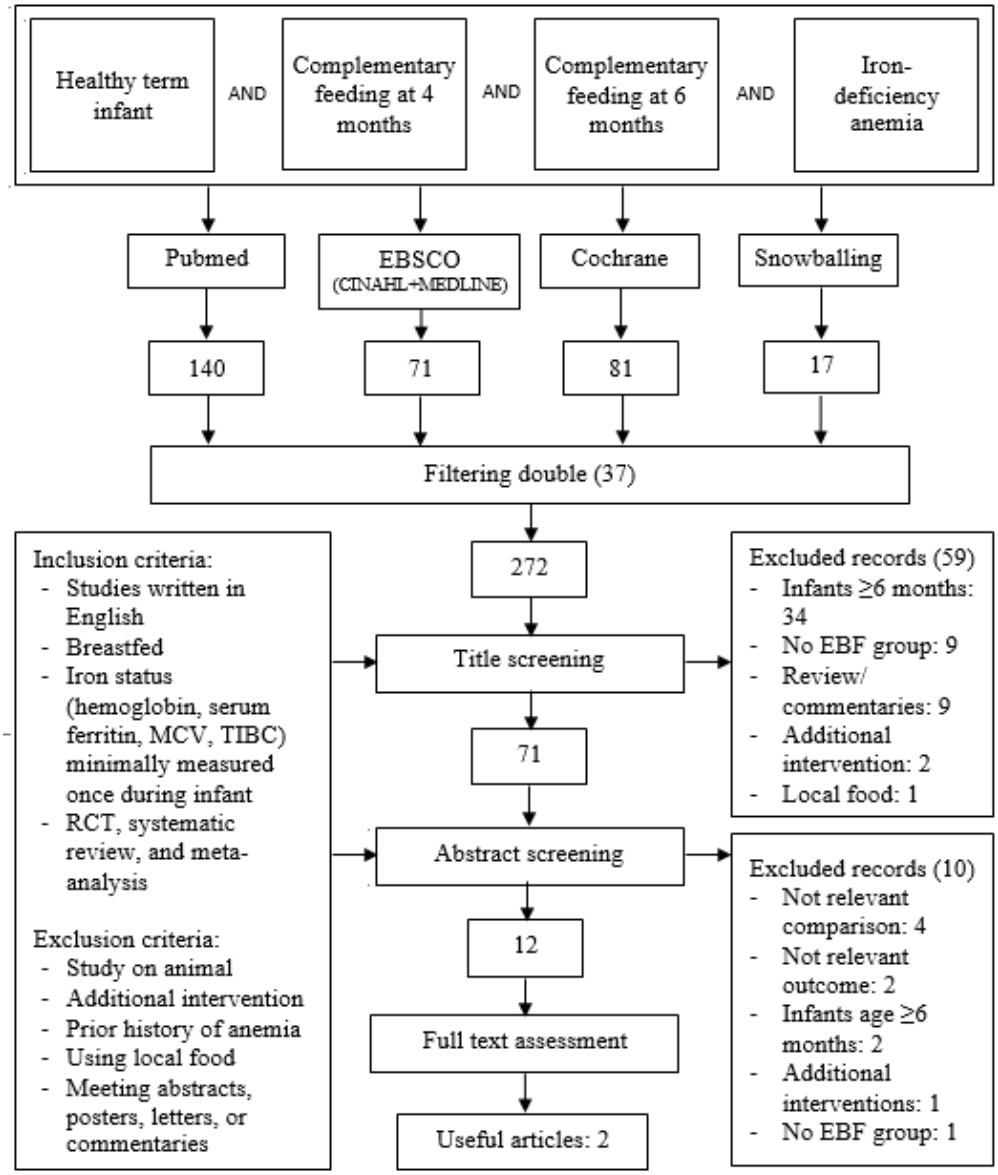

Figure 1. Flowchart of search strategy
Note: MCV: mean corpuscular volume; TIBC: total iron binding capacity; EBF: exclusive breastfeeding, RCT: randomized controlled trial

outcome was the reduction of incidence of IDA among infants.

From the selection and filtration mentioned above, seventy one articles were obtained, out of which only two full-text articles were deemed eligible and relevant to this searching. The validity, importance, and applicability of each paper is appraised by Oxford Randomized Controlled Trials Appraisal Sheet as depicted at in Table 1. The summary of those two RCTs is depicted in Table 2.

The occurrence of IDA and iron deficiency were not significantly different between CF and EBF group, according to both studies.[9] However, in Dewey et al,[10] the hemoglobin (Hb), hematocrit (Ht), and serum ferritin (SF) values were significantly higher in CF group than in EBF group at six months of age.[10] In Jonsdottir et al,[9] even though SF level was significantly higher in the CF group, but there was no significant difference in hemoglobin concentration.

The anemia status was determined by hemoglobin level measured at six months of age in both studies. The cut off for anemia determination in Dewey et al[10] and Jonsdottir et al[9] was 11.0 g/dL

and 10.5 g/dL, respectively. In Jonsdottir et al,[9] hemoglobin, mean corpuscular volume, serum ferritin values were measured using an automated hematology analyzer. Meanwhile, in Dewey et al,[10] hemoglobin and hematocrit values were also measured using an automated analyzer, while the serum ferritin was analyzed by radioimmunoassay.

Discussion

There were only two eligible RCT articles obtained, which were Jonsdottir et al.[9] and Dewey et al.[10] Both Jonsdottir et al[9] and Dewey et al[10] showed similar results that introduction of complementary feeding four months is not effective to reduce the risk of IDA compared to its

Table 1. Search strategy in PubMed, EBSCO, and Cochrane (conducted on 28th September 2017)

Database	Search Strategy	Hits	Selected articles
PubMed®	(((healthy[All Fields] AND ("infant"[MeSH Terms] OR "infant"[All Fields])) OR ("infant"[MeSH Terms] OR "infant"[All Fields]) OR (("term birth"[MeSH Terms] OR ("term"[All Fields] AND "birth"[All Fields]) OR "term birth"[All Fields] OR "term"[All Fields]) AND ("infant"[MeSH Terms] OR "infant"[All Fields]))) AND (("infant nutritional physiological phenomena"[MeSH Terms] OR ("infant"[All Fields] AND "nutritional"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "infant nutritional physiological phenomena"[All Fields] OR ("complementary"[All Fields] AND "feeding"[All Fields]) OR "complementary feeding"[All Fields]) OR ("infant nutritional physiological phenomena"[MeSH Terms] OR ("infant"[All Fields] AND "nutritional"[All Fields] AND "physiological"[All Fields] AND "phenomena"[All Fields]) OR "infant nutritional physiological phenomena"[All Fields] OR ("supplementary"[All Fields] AND "feeding"[All Fields]) OR "supplementary feeding"[All Fields]) OR ("weaning"[MeSH Terms] OR "weaning"[All Fields])) AND (("Age"[Journal] OR "age"[All Fields] OR "Age (Omaha)"[Journal] OR "age"[All Fields] OR "Age (Dordr)"[Journal] OR "age"[All Fields] OR "Adv Genet Eng"[Journal] OR "age"[All Fields]) OR (4[All Fields] AND months[All Fields])) AND (("Age"[Journal] OR "age"[All Fields] OR "Age (Omaha)"[Journal] OR "age"[All Fields] OR "Age (Dordr)"[Journal] OR "age"[All Fields] OR "Adv Genet Eng"[Journal] OR "age"[All Fields]) OR (6[All Fields] AND months[All Fields])) AND (("anaemia"[All Fields] OR "anemia"[MeSH Terms] OR "anemia"[All Fields]) OR "haemoglobin"[All Fields] OR "hemoglobins"[MeSH Terms] OR "hemoglobins"[All Fields] OR "hemoglobin"[All Fields]) OR ("ferritins"[MeSH Terms] OR "ferritins"[All Fields] OR "ferritin"[All Fields]))) AND ((Meta-Analysis[ptyp] OR Randomized Controlled Trial[ptyp] OR systematic[sb]) AND "humans"[MeSH Terms])	140	12
Cochrane®	((full-term infant) OR (healthy infant) OR infant) AND ((complementary feeding) OR (supplementary feeding) OR weaning) AND (Age OR 4 months) AND (age OR 6 months) AND (((((((anemia) OR iron status) OR hemoglobin) OR ferritin) OR mean corpuscular volume) OR Total iron-binding capacity) OR transferrin iron-binding capacity)	81	25
EBSCO®	infant AND ((complementary feeding) OR (supplementary feeding)) AND (age OR (4 months)) AND (Age OR (6 months)) AND (anemia OR hemoglobin OR ferritin)) NOT (prenatal)	71	19

introduction at six months, in accordance with current global recommendations, because the incidence of IDA between groups was not significantly different.

Dewey et al[10] showed that introducing CF at 4 months reduced the occurrence of anemia by 13.4% using Intention to Treat analysis (ITT). Meanwhile, with the same intervention, in Jonsdottir et al's[9] study, the occurrence of anemia was increased by 3.1% (ITT). No specific type of food given to the infants in Jonsdottir et al[9] study might contribute to this discrepancy because the average energy and iron intake that the infants received was small, only 59% of the mean energy intake (451 kJ/ day) and 15% of the mean iron intake (4.1 mg/ day) taken by infants in Dewey et al's[10] study. Moreover, vitamin C supplementation in Jonsdottir et al's[9] study may also affect the iron absorption, even though there is no association between vitamin C intake and measures of iron status in both group. A randomized cross-over study proved that ascorbic acid or vitamin C enhanced iron absorption by 1.5%.[10] Poor intake of complementary food might cause low intake of both iron and vitamin C among CF infants which lead to poor iron status in spite of complementary food consumption.

In addition to the low intake of CF, early introduction of complementary food was shown to increase infant morbidity and mortality, as a result of reduced ingestion of protective factors present in breast milk, in addition to the early introduction of contaminant from complementary food.[12] Introduction of weaning process may also cause several difficulties such as often refusal to eat followed by vomiting, colic, allergic reactions, and diarrhea.[14]

For current practices, WHO recommends infants to start weaning at six months of age in addition to breastfeeding, starting from 2–3 times a day between age 6–8 months, increasing to 3–4 times daily between 9–11 months, and 1–2 times additional nutritious snacks per day on 12–24 months, as desired. Food should be given in appropriate way, meaning that foods are of appropriate texture for the age of the child and apply the responsive feeding technique following the principles of psycho-social care.[13] WHO also suggests daily supplementation of 10–12.5 mg elemental iron for 6–23 months old infants who live in high anemia prevalent population. It is given daily for 3 consecutive months in a year.[15]

In general, the nutritional needs of infants less than six months can still be met by breastfeeding. After six months of age, infants start to be more active and tend to eat more to fulfill their daily energy requirement. Moreover, by this time, baby's gastrointestinal system should be already developed and ready to process the solid foods.[12]

In conclusion, the two studies gave same results that the introduction of CF at age four months compared to six months is not an effective way to reduce IDA. Infants should be exclusively breastfed for six months and start weaning thereafter to prevent IDA and fulfill the increasing daily energy requirement. Current WHO recommendation regarding the introduction of complementary food at six months of age is still valid and should be encouraged more.

Conflict of Interest

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

Open Access

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Table 2. Critical appraisal of the 2 studies based on criteria by center of evidence medicine University of Oxford

Article	Year	Number of samples	Validity					Importance					Relevance			
			Randomization	Similarity treatment and control	Blinding	Equal treatment	ITT	Control event rate	Experimental event rate	Relative risk reduction	Absolute risk reduction	Number needed to treat	Domain	Determinant	Measurement of outcome	Level of evidence *
Jonsdottir et al. [9]	2012	100	+	+	NA	+	+	0.136 [a]	0.167 [a]	0.228 [a]	-0.031 (-0.088 – 0.150) [a]	-33 [a]	+	+	+	1B
								0.017 [b]	0.016 [b]	0.063 [b]	0.001 (-0.045 – 0.047) [b]	1000 [b]				
Dewey et al. [10]	1998	164	+	+	NA	+	-	0.730 [a]	0.596 [a]	0.184 [a]	0.134 (-0.012 – 0.28) [a]	8 [a]	+	+	+	1B
								0.660 [b]	0.551 [b]	0.165 [b]	0.109 (-0.058 – 0.276) [b]	10 [b]				

Legend: + stated clearly in the article; - not being done. ITT: Intention to Treat analysis

* Levels of evidence based on the Oxford Centre of Evidence-based Medicine

a Analyzed using Intention to Treat method

b Analyzed using Per Protocol method

Table 3. Results of the two included studies

Author	Study design	Result
Jonsdottir et al.[9]	Masked RCT in seven health care centers in Iceland with 119 samples. Both groups receive vitamin D supplements and the mothers received counseling. EBF means no additional liquid or solid foods other than vitamins and medications. The food types for CF group were not regulated. Hb, mean corpuscular (MCV), red cell distribution width (RDW), SF, and total iron binding capacity (TIBC) value were obtained at age six months (± seven days). The criteria for IDA was: Hb < 105 g/L, MCV < 74 fl, and SF < 12 mg/L.	At six months of age, one infant in EBF group and one infant in CF group had IDA (p = 1.00). Infant in CF group had significantly higher SF levels than those in EBF group (p = 0.02). Excluding 16 infants who might have any problem affecting the ferritin level, SF level remained significantly higher in CF group (67.0 ± 61.0 mg/L vs 34.0 ± 44.5 mg/L in the EBF group; P = .003). For Hb, MCV, TIBC, and RDW, no significant differences were found between groups.
Dewey et al. [10]	RCT in two public maternity hospitals in Honduras, Brazil with 164 samples. Lactation guidance was provided to all mothers throughout the study. EBF means no additional liquid (water, milk, or formula) or solids. CF included iron-fortified rice cereal (16-18 weeks), iron-fortified rice cereal with egg yolk (18-26 weeks), non-iron-fortified fruit (banana, papaya, and pineapple, 17-26 week), and vegetables (17-26 weeks). Hb, Hct, and ferritin data were obtained at the age of 26 weeks. The criteria for anemia is Hb < 11.0 g/dL.	At six months of age, there were 49 and 33 anemic infants in CF and EBF group, respectively. CF group had significantly higher iron intake than EBF group (4.32-4.76 mg/day vs 0.16-0.17 mg/day). Mean Hb and Ht value were also higher in CF group (for Hb cutoff of 10.3 g/dL and 11.0 g/dL). Anemia incidence did not differ significantly between groups, but CF group had fewer infants with low Ht (< 0.33) than EBF group (21.4% vs 32%, p = .17). Moreover, CF group had significantly more infants with SF <12mg/L than EBF group (17% vs 7%; 67.3 ± 64.5 vs 48.4 ± 44.2)

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