

Original Article

Prevalence of and factors associated with thiamin deficiency in obese Thai children

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Background and Objectives: Obesity is a state that results from excessive energy consumption, and obese people often have micronutrient deficiencies. The objective of this study was to investigate the prevalence of and factors associated with thiamin deficiency in obese Thai children. **Methods and Study Design:** This cross-sectional study was conducted at Faculty of Medicine Siriraj Hospital, Mahidol University during 2014 to 2017. Children aged 7-15 years old with exogenous obesity were recruited. Symptoms and signs of thiamin deficiency were evaluated. Erythrocyte transketolase activity was measured by thiamin pyrophosphate effect (TPPE), with $\geq 15\%$ indicating thiamin deficiency. Dietary consumption from a 5-day food diary and food frequency questionnaire was calculated by INMUCAL software. Other medical complications of obesity were also evaluated. **Results:** One hundred and twenty-four subjects (81 males and 43 females) were enrolled, with a mean age of 10.9 years. Fifty-two subjects had abnormal TPPE for an overall prevalence of thiamin deficiency of 42%. Manifestations of thiamin deficiency included numbness, weakness, and calf muscle cramping. TPPE test results were correlated with at least one symptom or a sign of thiamin deficiency ($p < 0.01$). The thiamin-deficient group tended to have higher proportion of morbid obesity and larger waist circumferences than thiamin-sufficient group. The thiamin-deficient group tended to consume less thiamin in relation to energy intake than the thiamin-sufficient group ($p = 0.057$). Items of foods consumed were statistically indistinguishable between groups. **Conclusions:** The results of this study revealed a 42% prevalence of thiamin deficiency among obese Thai children, and most of those cases were subclinical.

Key Words: obese children, erythrocyte transketolase activity, prevalence, thiamin deficiency, thiamin pyrophosphate effect

INTRODUCTION

Obesity is a state that results from excessive energy consumption mainly from high-fat and high-carbohydrate diets; however, obese people often have deficiencies of important micronutrients. These deficiencies may result from selective intake of foods with low nutritional value and/or inappropriate proportions of nutrients. Adults with morbid obesity have a high prevalence of vitamin deficiencies that results in high-calorie malnutrition.¹ Pre-operative thiamin deficiency was detected in 29% of 379 adults with morbid obesity undergoing Roux-en-Y gastric bypass (RYBG),² and in 15.5% of 303 adults with obesity undergoing laparoscopic RYGB or laparoscopic adjustable gastric banding.³ The prevalence of thiamin deficiency among obese Thai adults is somehow not different from that of their normal weight counterparts (10.4% vs. 10.3%, respectively).⁴ Childhood obesity has been increasing worldwide; and has now reached an epidemic level.⁵ The 5th Thai National Health Examination Survey (NHES), which was

conducted in 2014, reported an increasing prevalence of overweight and obese status among Thai children when compared to the 4th Thai NHES that was conducted during 2008-2009, as follows: 14.6% vs. 13.2% in boys, and 16.4% vs. 13.2% in girls for children aged 2-5 years; and 26.1% vs. 16.7% in boys, and 19% vs. 15.2% in girls for those aged 6-14 years – all respectively.⁶ Similar to adults, thiamin deficiency can also be found in obese children. A case of an obese female adolescent with numbness in both legs and weakness followed by symptoms of Wernicke's encephalopathy has been reported.⁷

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We previously reported three obese Thai children that were adversely affected by thiamin, ascorbic acid, and iron deficiencies.⁸ To our knowledge and based on our review of the literature, no conclusive data have been reported specific to the prevalence of thiamin deficiency among obese children.

Accordingly, the aim of this study was to investigate the prevalence of and factors associated with thiamin deficiency in obese Thai children.

METHODS

Subjects

This cross-sectional was conducted at the Division of Nutrition, Department of Pediatrics, Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand during the November 2014 to November 2017. The study protocol was approved by the Siriraj Institutional Review Board (SIRB) (COA number: Si 656/2014) and was registered at ClinicalTrials.gov (reg. no. NCT02464865). This study complied with the principles set forth in the Declaration of Helsinki and all of its subsequent amendments. Informed assent was obtained from all study participants, and written informed consent was obtained from each respective parent or legally authorized guardian.

The inclusion criteria were children aged 7-15 years diagnosed with exogenous obesity, defined as weight-for-height $>$ median+3 standard deviation (SD). Severity of obesity was categorized by percentage of weight-for-height (%WH) as obesity (%WH $>$ 140-200) or severe obesity (%WH $>$ 200). Subjects who consumed certain medications (vitamin B1, thiamin-containing vitamins, diuretic or steroid drugs), received hemodialysis or peritoneal dialysis, underwent bariatric surgery, or had short bowel syndrome or red cell abnormalities were excluded. Subjects' demographic data, dietary history, medical history, obesity-related comorbidities, and anthropometric measurements were reviewed and recorded. Manifestations of thiamin deficiency (including numbness, paresthesia of the extremities, weakness, aching of the calf muscles, decreased tendon reflexes, and heart failure) were evaluated by means of interview and physical examination.

Dietary data

Subjects and caregivers were trained by a dietitian to measure and record food items that the study subjects consumed. Energy and nutrient data from a 5-day food diary and a food frequency questionnaire were analyzed using the INMUCAL-Nutrients V.3 computer software that was developed based on Thai food database by the Institute of Nutrition, Mahidol University (Nakhon Pathom, Thailand).^{9,10}

Reagents

A 96-well, clear polystyrene, flat-bottom microtiter plate (MicroWell™ Plate with a MaxiSorp surface™) was purchased from Thermo Fisher Scientific Nunc A/S (Roskilde, Denmark). The multi-detection microplate reader (Biotek Synergy H1) was purchased from BioTek Instruments, Inc. (Winooski, VT, USA). Sterox SE, 1% (w/v) aqueous solution was purchased from Ricca Chemical

Company (Arlington, TX, USA). Tris (hydroxymethyl) aminomethane in the form of neutralized crystalline hydrochloride salt (Tris-HCl), thiamin pyrophosphate chloride (TPP), D-ribose-5-phosphate disodium salt hydrate, α -glycerophosphate dehydrogenase-triosephosphate isomerase from rabbit muscle (GDH/TIM buffer), and β -nicotinamide adenine dinucleotide (NADH) were purchased from Sigma-Aldrich, Inc. (St. Louis, MO, USA).

Erythrocyte transketolase assay

Erythrocyte transketolase (ETK) activity was measured using the nicotinamide-adenine dinucleotide (NADH)-dependent method.¹¹ The method was modified slightly by reducing the reaction volume to 200 μ L in order to perform the assay in a microplate format. The ETK activity before (basal activity) and after (activated activity) adding thiamin pyrophosphate (TPP) was determined and expressed in international units (U) per gram of hemoglobin (Hb). The thiamin pyrophosphate effect (%TPPE) was calculated using the following formula: [(ETK activated - ETK basal)/ETK basal] \times 100. Basal ETK activity levels are typically low in thiamin-deficient subjects, and they increase after the addition of TPP. Thiamin deficiency was defined as a TPPE value of 15% or higher, with marginal deficiency diagnosed when the TPPE was within the range of 15-24%, and definite deficiency being diagnosed when the TPPE was 25% or higher.^{12,13}

Statistical analysis

Categorical data were expressed as number and percentage, and were compared between groups using Pearson's chi-square test or Fisher's exact test. Normally distributed continuous data were presented as mean \pm SD, and were compared between groups using unpaired Student's t-test. Non-normally distributed continuous data were shown as median (P25, P75), and were compared between groups using the Mann-Whitney U test. The data were analyzed with SPSS Statistics version 20 (SPSS, Inc., Chicago, IL, USA). All tests of statistical significance were 2-sided, and a *p*-value of less than 0.05 signified statistical significance.

RESULTS

One hundred and twenty-four subjects (81 males and 43 females) were enrolled, with a mean age (\pm SD) of 10.9 (\pm 2.2) years. Fifty-two subjects had abnormal TPPE for an overall prevalence of thiamin deficiency of 42%. Of those, 32 subjects had marginal deficiency (26%), 20 subjects had definite deficiency (16%), and 40 of them were asymptomatic (77%). Manifestations of thiamin deficiency included numbness (*n*=17), weakness (*n*=1), and aching of the calf muscle (*n*=1), and some subjects presented with more than one. TPPE test results were correlated with at least one symptom or sign of thiamin deficiency (*p*<0.01).

There were no differences in age, gender, percentage of weight-for-height, or percentage of height-for-age between the thiamin-sufficient group and thiamin-deficient groups (Table 1). The thiamin-deficient group tended to have more cases with morbid obesity and larger waist

Table 1. Characteristics and obesity-related comorbidities of subjects compared between TPPE results

Characteristics and comorbidities	TPPE		p-value
	0-14% (n=72)	≥15% (n=52)	
Male gender, n (%)	45 (62.5)	36 (69.2)	0.437
Age (years)	10.7±2.3 [†]	11.2±2.2	0.173
Percentage of weight-for-height	176.8 (156.1, 189.6) [‡]	174.8 (162.4, 205.3)	0.444
Percentage of height-for-age	107.3±4.8 [†]	107.3±8.4	0.946
Waist circumference (cm)	95.8±21.1 [†]	101.9±13.2	0.069
Morbid obesity, n (%)	11 (15.3)	15 (28.8)	0.067
Symptoms of thiamin deficiency, n (%)	5 (6.9)	12 (23.1)	0.01
TPPE values (%)	6.8±4.9 [†]	22.8±5.6 [†]	0.000
Hypertension, n (%)	10 (13.9)	8 (15.4)	0.816
Diabetes mellitus, n (%) [n=119]	3 (4.3)	0 (0.0)	0.263
Dyslipidemia, n (%) [n=120]	43 (62.3)	28 (54.9)	0.414
Idiopathic intracranial hypertension, n (%)	0 (0.0)	0 (0.0)	-
Non-alcoholic fatty liver disease, n (%)	23 (31.9)	11 (21.2)	0.184
Polycystic ovarian syndrome, n (%)	1 (1.4)	0 (0.0)	-
Obstructive sleep apnea, n (%) [n=111]	14 (22.2)	17 (35.4)	0.125
Blount's disease, n (%)	1 (1.4)	1 (1.9)	1.000

TPPE: thiamin pyrophosphate effect.

A p-value<0.05 indicates statistical significance.

[†]Values presented as mean±SD.

[‡]Values presented as median (P25, P75).

Table 2. Daily energy, macronutrient, and thiamin intake of subjects compared between TPPE results

Subject intake	TPPE		p-value
	0-14% (n=72)	≥15% (n=52)	
Energy intake (kcal)	1311 (1094, 1647) [‡]	1310 (1065, 1742)	0.996
Carbohydrate (g)	164 (133, 201) [‡]	159 (130, 209)	0.905
Protein (g)	54 (44, 72) [‡]	52 (43, 64)	0.438
Fat (g)	44 (36, 65) [‡]	49 (36, 66)	0.415
Thiamin (mg)	0.87 (0.63, 1.19) [‡]	0.76 (0.55, 1.27)	0.406
Thiamin to energy ratio (mg/1,000 kcal)	0.73±0.30 [†]	0.69±0.37	0.511
Thiamin to energy <0.5 mg/1,000 kcal, n (%)	14 (19.4)	18 (34.6)	0.057

TPPE: thiamin pyrophosphate effect.

A p-value<0.05 indicates statistical significance.

[†]Values presented as mean±SD.

[‡]Values presented as median (P25, P75).

circumference. Obesity-related comorbidities were not significantly different between groups, except for symptoms of thiamin deficiency ($p<0.01$) (Table 1).

Daily energy and macronutrient intakes were not different between groups; however, the thiamin-deficient group tended to consume less thiamin in relation to energy intake (Table 2). Items of food consumed, including rice, raw fermented fish, sundried meat or fish, vegetables, sweetened milk tea drinks, sweetened green tea beverages, and coffee, were statistically indistinguishable between groups (Table 3).

Among the 52 subjects with abnormal TPPE, 50-100 mg thiamin and nutritional counseling alleviated symptoms and signs of thiamin deficiency, and normalized TPPE values in 41 subjects (79%). The remaining 11 subjects were lost to follow-up.

DISCUSSION

This study described the prevalence of thiamin deficiency in obese Thai children, which was 42%. Three-fourths of

those had subclinical thiamin deficiency. Numbness was the most common symptom of thiamin deficiency in this cohort. The thiamin-deficient group tended to have more subjects with morbid obesity and larger waist circumference. They also tended to consume less thiamin in relation to energy intake.

Multiple vitamin and mineral deficiencies are being increasingly reported in obese individuals even though obesity is commonly thought of as an over-nutrition state. A large number of obese adults have iron, thiamin, and vitamin D deficiencies prior to bariatric surgery.^{2,3} Children and adolescents with overweight or obese status also have a high prevalence of iron deficiency with increased hepcidin level,^{14,15} and vitamin D deficiency.^{16,17} We previously reported three obese Thai children that presented with isolated iron deficiency caused by increased hepcidin, thiamin deficiency, and ascorbic acid deficiency.⁸ Other reports on the prevalence of thiamin deficiency in obese children are relatively scarce. This study, to our knowledge, is the first to report the prevalence of thiamin

Table 3. Food items consumed by subjects compared between TPPE results

Foods consumed	TPPE		p-value
	0-14% (n=72)	≥15% (n=52)	
Polished rice ≥4 times/week, n (%)	71 (98.6)	48 (92.3)	0.078
Brown rice ≥4 times/week, n (%)	17 (23.6)	11 (21.2)	0.747
Raw fermented fish or raw fish ≥1 time(s)/week, n (%)	21 (29.2)	10 (19.2)	0.207
Sundried meat or fish ≥1 time(s)/week, n (%)	44 (61.1)	35 (67.3)	0.479
Vegetables >1 type/week, n (%)	53 (73.6)	44 (84.6)	0.143
Sweetened milk tea drinks ≥1 time(s)/week, n (%)	42 (58.3)	32 (61.5)	0.720
Sweetened green tea beverages (bottles/week)	3 (1, 6) [†]	2.5 (1, 5) [†]	0.311
Coffee ≥1 time(s)/week, n (%)	2 (2.8)	4 (7.7)	0.236

TPPE: thiamin pyrophosphate effect.

A p-value<0.05 indicates statistical significance.

[†]Values presented as median (P25, P75).

deficiency in obese children. Our results revealed that 23% of subjects with abnormal TPPE values had overt clinical thiamin deficiency. All subjects with either numbness or abnormal sensory test failed to self-recognize the abnormalities, which is not unusual since mild manifestations often go unnoticed.

Thiamin deficiency has been increasingly found in people with obesity.¹⁸ Possible explanations include: (a) high consumption of carbohydrates and energy-dense foods; (b) low intake of thiamin-enriched foods, such as whole grains, legumes, lean meat, and fortified bread; (c) high intake of thiaminase or thiamin antagonists; (d) increased urinary thiamin loss in obese subjects with type 2 diabetes or diuretic use; and, (e) malabsorption after bariatric surgery.

Thiamin plays a vital role in carbohydrate metabolism. The recommended daily dietary intake of thiamin is 0.5 mg per 1,000 kcal of energy for children, adolescents, and adults.¹⁹ The present study found the thiamin-deficient group to be more morbidly and centrally obese than the thiamin-sufficient group, but the difference between groups was not statistically significant. This might indicate higher energy consumption relative to energy expenditure in the thiamin-deficient group; however, we observed no difference in the intake of energy or macronutrients between groups. We did not evaluate energy expenditure in either group. The thiamin-deficient group tended to consume less thiamin in relation to energy intake, which may have contributed to thiamin deficiency.

Thiamin is a water-soluble vitamin that is easily destroyed by high temperature, and additional steps of food processing, such as repeated exposure to heat in meat cooking or discarding of cooking water, may lead to a reduction in thiamin content in foods.²⁰ Moreover, milling causes removal of the thiamin-rich parts in germs of grains and legumes. This study could not identify any differences in consumption of either thiamin-enriched foods (e.g., brown rice) or thiamin-depleted foods (e.g., polished rice and sundried meat or fish) between groups. One explanation may be that our subjects had noodles, breads, or potatoes as the major sources of carbohydrates in their diets, instead of those two types of rice. We did not investigate these dietary details or the cooking methods used to prepare the food consumed by the participants in our study cohort.

Thiaminase type I (EC 2.5.1.2), a heat-labile thiamin-cleaving enzyme, has been identified in raw or fermented freshwater fish viscera and raw shellfish.²¹ It breaks down thiamin at a methylene linkage of thiamin during food storage before ingestion. Therefore, frequent intake of these particular foods places an individual at risk of developing thiamin deficiency.²² Consumption of these foods after cooking by heat should be encouraged, because thiaminase type I is destroyed at high temperature. On the other hand, thiamin antagonists, which are heat-stable non-enzymatic substances, are found in tea, coffee, betel nut, red cabbage, blueberries, red currants, red beets, and fern.^{21,23} The antagonistic property of these polyphenols is derived from their ability to change thiamin structure to a non-absorbable thiamin disulfide.^{22,24} The antithiamin activity of several local vegetables in Thailand has been studied in detail.²⁵ Our study did not reveal any significant differences in the consumption of raw fish (with or without fermentation), tea, coffee, or vegetables between the thiamin-deficient and thiamin-sufficient groups. This may be due to the fact that these types of raw fish and vegetables are not commonly consumed by obese children living in Bangkok and the central region of Thailand, where most of our study subjects reside. Sweetened green tea beverages and sweetened milk tea drinks are currently popular and widely consumed among obese adolescents. Intake of these drinks may increase thiamin requirement due to increased metabolism of simple sugar. In contrast, our results revealed coffee consumption to be far less common than tea-related consumption in both the thiamin-deficient and thiamin-sufficient groups.

Urinary thiamin clearance can increase up to 16-fold in obese adults affected by type 2 diabetes, which results in low plasma thiamin status.²⁶ Our study had a too small number of patients with diabetes to analyze this aspect.

General advice for the prevention of thiamin deficiency in all populations, including individuals with obesity include: (a) appropriate weight reduction if obesity is present; (b) limiting intake of energy-dense foods, especially carbohydrates obtained predominantly from polished rice, white flour in bread or snack, and sugar in sweetened beverages or desserts; (c) thorough cooking fish and shellfish prior to intake; (d) consuming a variety of foods as opposed to repeated consumption of only a few food items to avoid thiamin antagonist activity in such foods; and, (e) avoiding excessively heat-processed foods. A

clinical implication from this study is that screening for thiamin deficiency, including early recognition of symptoms - such as minor sensory loss, profound weakness, ataxia, ophthalmoplegia, and confusion - or TPPE test should be recommended in the evaluation of obese patients at baseline. As thiamin deficiency could be asymptomatic, we recommend that thiamin deficiency be assessed in taking care of obese children with obesity regardless of symptoms and signs of thiamin deficiency. Also, thiamin supplementation should be considered as an adjunct to therapeutic lifestyle modification in the treatment of obesity.

Limitations

There are few limitations of this study. First, the questionnaire that we used may have underestimated dietary factors that contributing to thiamin status, because it relied upon the subject recall. Although a research dietitian trained all study subjects and their caregivers to record food intake in a 5-day food diary, the dietary data could not accurately reflect subject food intake. Second, cooking methods of subject's family were not evaluated either.

In conclusion, thiamin deficiency was found to be prevalent (42%) in Thai children with obesity, and most cases were subclinical. Future study should investigate thiamin status and contributing factors in obese children from other areas in Thailand, and to supplement thiamin in addition to lifestyle modification in children with obesity-related co-morbidities.

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