Effect of Folic Acid Supplementation on Plasma Homocysteine in Obese Children: A Randomized, Double-Blind, Placebo-Controlled Trial

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Background: *Obese children tend to consume less dietary folate, which is an important cofactor in remethylation of homocysteine to methionine. The deficiency of folate can lead to hyperhomocysteinemia.*
Objective: *To determine whether folic acid supplementation could reduce plasma homocysteine in obese children.*
Material and Method: *Obese children, aged 9-15 years with body mass index >median plus 2 SD according to WHO reference, were randomly assigned to 2 groups: receiving either 5 mg folic acid or placebo for 2 months. Fasting homocysteine, creatinine, folate, vitamin B12, insulin, glucose and lipid profiles were taken at baseline and the end of the study. Dietary vitamin B12, folate intake and physical activity were assessed using validated questionnaires.*
Results: *Fifty obese children (31 boys and 19 girls) took part in the study. Their mean age was 10.9±1.6 years and mean BMI Z-score was 3.41±0.69. After the intervention, plasma homocysteine decreased by 15.75% and 6.99% in the folic acid and placebo group, respectively (mean difference 8.76%; 95% CI: 0.26%, 17.25%, p = 0.044). This divergence was more pronounced in boys and it remained significant after adjusting for baseline homocysteine and other confounders. Subgroup analysis showed a larger magnitude of plasma homocysteine reduction in the low folate group (mean difference 12.24%; 95% CI: 1.39%, 23.09%).*
Conclusion: *The homocysteine lowering effect of folic acid supplementation was found in obese children, especially in boys and those with low serum folate. Further long-term interventional studies are needed to determine the effects of the lowered plasma homocysteine on the cardiovascular outcomes of obese children. This trial was registered on clinicaltrials.gov (NCT01766310).*

Keywords: *Folic acid, Homocysteine, Obese, Children, Randomized trial*

J Med Assoc Thai 2014; 97 (Suppl. 6): S195-S204
Full text. e-Journal: *http://www.jmatonline.com*

Homocysteine is a sulfur-containing intermediate product of the normal metabolism of the essential amino acid methionine. Hyperhomocysteinemia has been found to be an independent risk factor for atherosclerosis and cardiovascular disease (CVD); it is responsible for about 10% of total CVD risks[1,2]. Mechanisms of hyperhomocysteine associated with atherosclerosis are alteration of vascular morphology, inflammatory stimulation, blood clotting cascade, and inhibition of fibrinolysis[2,3]. Contributing factors for hyperhomocysteinemia are increasing age, male gender, gene mutation, drugs, smoking, excessive caffeine intake, physical inactivity, renal dysfunction, and vitamin deficiency. Several studies in adults showed that reduction of elevated plasma homocysteine may prevent up to 25% of cardiovascular events[2,4].

Many studies have suggested that obesity induced atherosclerosis may begin during childhood because an increase in intima-media thickness, impaired flow-mediated dilatation, endothelial dysfunction and vascular damage have been demonstrated in obese children[5,6]. Early intervention to improve endothelial function in obese children, in addition to metabolic and weight control, could potentially prevent atherosclerosis in their adult life. More recent studies revealed that plasma homocysteine levels in obese children were higher than their non-obese peers[7,8].

One of the modifiable causes of hyperhomo-

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cysteinemia is vitamin deficiency, especially folate, because it is an important cofactor in the remethylation of homocysteine to methionine. Previous studies have shown that obese children consumed less dietary folate according to the Dietary Reference Intake (DRI) than non-obese children[9,10]. Folic acid supplementation is safe, inexpensive and has been found to improve homocysteine levels in children with different types of diseases[11-16].

The authors postulated that obese Thai children might be at risk of folate deficiency due to an unbalanced diet (low vegetables and high fat intake) as well as a high prevalence of thalassemia in Thailand. Currently, there is scant data on the effects of folic acid supplementation on homocysteine levels in obese children. Therefore, the aim of the present study is to investigate whether oral folic acid supplementation could reduce plasma homocysteine in this group. The secondary aim is to determine the association between baseline of homocysteine levels with various metabolic and dietary factors.

Material and Method

Study design

The present study was a randomized, double-blind, placebo-controlled trial, comparing two groups of obese children receiving folic acid supplement and placebo. The study protocol was approved by the Research Ethic Review Committee of Queen Sirikit National Institute of Child Health. Written informed consents from parents were obtained.

Study populations

Obese children were recruited from the Nutrition Clinic, Queen Sirikit National Institute of Child Health, Ministry of Public Health, Thailand, from May 2012 to February 2013. Participants were eligible if they were between 9-15 years of age and had a body mass index (BMI, weight in kilograms divided by the square of height in meters) more than the median plus two standard deviations for their age and gender according to the WHO reference 2007[17]. Exclusion criteria were vitamin supplementation one month prior to this study, secondary obesity, thalassemia disease, renal or hepatic dysfunction, the use of medications that altered blood pressure, homocysteine, and glucose or lipid profiles.

The sample size was calculated by using the results from a previous study[18]. The pooled variance at 6.08 and mean change in plasma homocysteine at 2.5 μmol/L represented the minimal clinically significant difference. To provide 90% power and significance of 0.05, a minimum of 20 participants was needed in each group. The authors estimated 20% drop out; therefore, fifty participants were required.

Method

The participants were stratified by gender before being randomly allocated into two groups, receiving either 5 mg folic acid or placebo orally, for two months. Both folic acid and placebo tablets were produced by the Government Pharmaceutical Organization, Ministry of Public Health, Thailand; they were similar in characteristic and taste. Randomization was performed using computer generated mixed size block random assignment. Each treatment code was concealed in an opaque envelop. The investigators, participants and personnel involved in the present study were blinded to the treatment assignment. Only one pharmacist, who was unrelated to the study, knew the codes of treatment and placebo, which were revealed after data analysis. All participants were advised to follow a standard weight management program that was based on current dietary recommendations for obese children[19]. They were followed-up every month. In order to control co-intervention, other vitamins supplementations were not allowed during the study.

Height and weight were measured without shoes and with light clothing using a stadiometer to the nearest 0.1 cm and an electronic digital scale to the nearest 0.1 kg, respectively. BMI and BMI Z scores were calculated based on WHO 2007 growth reference using WHO AnthroPlus program[17]. Waist circumferences of the participants were measured with participants in standing position at the midpoint between the lower edge of the ribs and the top of the iliac crest after normal exhalation. Blood pressure was measured 10 minutes after rest, in sitting position using a sphygmomanometer and appropriate cuff, according to the size of the upper arm.

Trained nurses collected venous blood samples from participants after they had fasted overnight for 12 hours at the start (baseline) and the end of the study. The tubes were immediately centrifuged to obtain either plasma or serum, which were stored at -20°C until analysis. Routine enzymatic methods were used to analyze for hemoglobin, creatinine, lipid profiles, glucose, and insulin levels. Plasma homocysteine was determined by using fluorescence polarization immunoassay method (ABBOT IMx Analyzer, Axis-shield, Dundee, UK). Serum folate and vitamin B12 were measured using

electrochemiluminescence immunoassay method (Roche Diagnostics, Mannheim. Germany). The homeostasis model for assessment of insulin resistance (HOMA-IR) was calculated using the following equation: [fasting glucose (mmol/L) x fasting insulin (mIU/mL)]/22.5[20].

Dietary intakes of folate and vitamin B12 were assessed at every visit from a 3-day dietary record and a validated semi-quantitative food frequency questionnaire for dietary folate intake[10]. Physical activity was also assessed at every visit by using The International Physical Activity Questionnaire (short form)[21].

All participants were called once a week to ensure their compliance with the dosing regimen. During the follow-up visits, they were also asked to return the remaining tablets that were counted and calculated for the percentage of compliance. Eighty percent of compliance was considered acceptable.

Statistical analysis

Demographic data were described as mean and standard deviation or percentage according to the type of data. One-sample Kolmogorov-Smirnov test was used to evaluate normally distributed data. Independent samples t-test was used to compare the difference in the mean change of homocysteine level between groups. Subgroup analyses were performed from baseline serum folate levels (below or above median). Multiple linear regression analysis was applied to adjust the effects of baseline homocysteine and vitamin B12 on the change in homocysteine levels between treatment groups. Pearson's correlation analysis was used to determine the association between baseline homocysteine and independent variables including insulin, lipid profiles, folate, vitamin B12 levels and dietary factors. The analyses were performed using Social Package of Social Sciences (SPSS) for Windows statistical software (version 16, SPSS Inc., Chicago, USA).

Results

Fifty participants were recruited and randomly allocated into 2 groups: 26 receiving folic acid (folic acid group) and 24 receiving placebo (control group). Three participants in the folic acid group and one in the control group withdrew their consent during the follow-up due to time constraints (Fig. 1). The demographic data and baseline characteristics of both groups were compared and are presented in Table 1. The mean age of the participants was 10.9±1.6 years

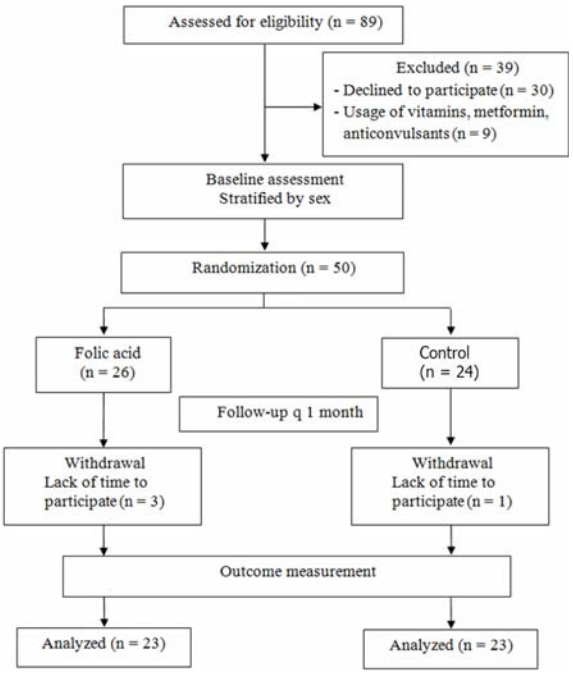


Fig. 1 Protocol flow chart.

(range 9-14.5 years) and 62% were boys. Their mean BMI Z score was 3.41±0.69. The hemoglobin and creatinine were within normal range. According to the International Diabetes Federation criteria[22], metabolic syndrome risk factors diagnosed were: (i) hypertension, 12%; (ii) hypercholesterolemia, 32%; (iii) high LDL cholesterol, 32%; (iv) low HDL cholesterol, 30%; (v) hypertriglyceridemia, 22%; (vi) impaired fasting glucose, 8%. There were no significant differences in the baseline anthropometry and clinical characteristics, except for systolic blood pressure (SBP), high density lipoprotein cholesterol (HDL- C) and serum vitamin B12, which were higher in the placebo group. Baseline homocysteine were comparable in both groups (range 4.47-13.31 μmol/L). There was no significant difference of baseline homocysteine between boys and girls (8.08±1.69 and 8.14±2.01 μmol/L). Prevalence of hyperhomocysteinemia was found to be 10% using the more than 95th percentiles age specific reference cut-off values[23]. None of the participants had low serum folate or vitamin B12 according to the reference range of 4-20 nmol/L and 96-579 pmol/L, respectively[24]. The average dietary folate intakes were similar between the two groups (78.46±24.96 and 91.27±42.24 μg per day in folic acid group and control group, respectively), but these values were much lower than the recommended intake of Thai DRI, which is 300-400

Table 1. Demographic and baseline characteristics[1]

	Folic acid (n = 26)	Placebo (n = 24)
Age (years)	11.08±1.57	10.73±1.64
Gender (male)	16 (61.5%)	15 (62.5%)
Weight (kg)	74.99±17.06	72.98±18.86
Height (cm)	152.29±10.91	148.79±9.66
BMI (kg/m^2)[2]	31.96±4.15	32.57±5.62
BMI Z score[3]	3.32±0.61	3.52±0.77
Waist circumference (cm)	96.47±10.18	96.06±10.38
SBP (mmHg)	112.12±8.10	118.46±9.10
DBP (mmHg)	67.69±11.40	67.38±7.65
Hemoglobin (g/dl)	12.94±1.23	13.0±0.80
Creatinine (mg/dL)	0.48±0.93	0.47±0.78
Total cholesterol (mg/dL)	161.58±40.44	181.25±37.54
HDL-C (mg/dL)	42.08±10.72	49.12±10.58
LDL-C (mg/dL)	104.45±31.80	116.40±31.55
Triglyceride (mg/dL)	116.04±62.68	128.13±68.83
FPG (mg/dL)	88.96±8.59	87.63±7.02
Insulin (μIU/mL)	26.80±16.56	21.44±9.48
HOMA-IR[4]	6.02±4.37	4.67±2.12
Homocysteine (μmol/L)	8.02±2.12	8.18±1.39
Serum folate (nmol//L)	18.26±6.62	20.47±7.79
Serum vitamin B12 (pmol/L)	438.98±124.34	530.79±137.40
Average dietary folate (μg/day)	78.46±24.96	91.27±42.24
Average dietary vitamin B12 (μg/day)	3.40±1.10	3.56±1.00
Average physical activity score (Met-minutes/week)	920±543.76	1,417±1,646.13
Compliance (%)	83.85±16.90	84.30±12.94

[1] Data are presented in mean ± SD or number (%), [2] Calculated from weight in kilograms divided by the square of height in meters, [3] Standard deviation score of BMI according to the WHO reference 2007, [4] Calculated from fasting glucose (mmol/L) x fasting insulin (μIU/mL)]/22.5

BMIZ score = body mass index standard deviation score; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; FPG = fasting plasma glucose; HOMA-IR = homeostasis model for assessment of insulin resistance

μg per day. On the contrary, average dietary vitamin B12 intake was above the Thai DRI recommendation, at 1.8-2.4 μg per day[25]. There were no differences in the level of physical activity between the two groups. The compliance rate was similar at around 84%, which was acceptable. No adverse side effects were reported.

Changes in plasma homocysteine

After completion of the intervention, there were no significant changes in the clinical characteristics between the two groups, except for plasma homocysteine and serum folate (Table 2). As expected, serum folate significantly increased in the folic acid group while there was no change observed in the placebo group. In the folic acid group, the mean change of homocysteine was -1.35±1.32 μmol/L, or decreased by 15.75%, which was significantly different from the magnitude of change in the control group (decreased by 6.99%, mean difference 8.76; 95%CI: 0.26%, 17.25%, $p = 0.044$). As a result, plasma homocysteine after the intervention was significantly lower in the folic acid group (6.37±1.37 μmol/L) when compared to the placebo group (7.50±1.17 μmol/L, $p = 0.004$; data not shown). Interestingly, this difference was more pronounced in boys where plasma homocysteine significantly decreased more in the folic acid than in the placebo group (19.46% vs. 5.52%, mean difference 13.93%; 95% CI: 3.48%, 24.03%, $p = 0.009$). On the other hand, the difference between the groups was not statistically significant in girls (mean difference 0.23%; 95% CI: -15.78%, 16.24%, $p = 0.98$).

Since there were the differences of baseline SBP, HDL-C and serum vitamin B12 between the two groups, multiple linear regression analysis was applied

Table 2. Comparison of changes in clinical characteristics after the intervention period[1-3]

	Folic acid (n = 23)	Placebo (n = 23)	Mean difference (95%CI)	*p*-value
BMIZ score	-0.22±0.20	-0.17±0.20	0.05 (-0.07, 0.17)	0.43
Waist circumference (cm)	-1.40±2.66	-1.33±2.52	0.70 (-1.47, 1.60)	0.93
SBP (mmHg)	-1.52±9.76	-3.52±9.83	-2.00 (-7.68, 3.68)	0.48
DBP (mmHg)	-4.78±14.64	-0.26±9.96	4.48 (-2.96, 11.92)	0.23
Total cholesterol (mg/dL)	5.26±16.47	-0.39±21.37	-5.65 (-16.99, 5.96)	0.32
HDL-C (mg/dL)	1.23±4.79	-1.60±7.29	-2.83 (-6.51, 0.85)	0.12
LDL-C (mg/dL)	1.89±13.89	0.03±16.34	-1.81 (-10.87, 7.15)	0.68
Triglyceride (mg/dL)	1.30±44.69	-15.13±47.11	-16.43 (-43.72, 10.85)	0.23
Insulin (μIU/mL)	-2.90±10.78	-1.13±8.71	1.77 (-4.05, 7.59)	0.54
HOMA-IR	-0.83±2.81	-0.22±1.96	0.61 (-0.83, 2.04)	0.40
Homocysteine (μmol/L)	-1.35±1.32	-0.68±1.25	0.68 (-0.09, 1.44)	0.08
Homocysteine (%)	-15.75±14.46	-6.99±14.12	8.76 (0.26, 17.25)	0.044
Serum folate (nmol//L)	87.28±65.23	0.27±6.61	-87.0 (-114.55, -59.45)	<0.001
Serum vitamin B12 (pmol/L)	-8.55±74.96	-8.26±105.51	0.29 (-54.09, 54.69)	0.99
Dietary folate (mg/day)	-28.99±68.83	-33.14±53.94	-4.43 (-39.55, 30.69)	0.80
Dietary vitamin B12 (mg/day)	-0.13±1.81	-0.17±3.03	-0.04 (-1.61, 1.52)	0.96
Physical activity score (Met-minutes/week)	9.74±1,020.59	-54.13±1,129.65	-63.87 (-703.6, 575.9)	0.84

[1] Data are presented in mean ± SD, [2] The value of changes were calculated from parameter at the end of the study- baseline parameter, [3] *p*-value from independent samples t-test

BMIZ score = body mass index standard deviation score; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; HOMA-IR = homeostasis model for assessment of insulin resistance

to assess the effects of treatment groups after adjusting for these covariates. The results showed that the change of homocysteine levels was dependent on treatment groups after adjusting for baseline homocysteine, SBP, HDL-C and vitamin B12. The reduction of homocysteine at 11.04% was observed in folic acid group ($p = 0.012$). An elevation of 1 mmol/L in baseline plasma homocysteine decreased plasma homocysteine levels by 4.35% ($p = 0.001$).

Subgroup analyses were performed by baseline serum folate levels using the median folate level at 17.88 nmol/L as the cut-off value (Fig. 2). In the low folate group, there was a greater reduction in homocysteine levels in the folic acid than in the placebo group (21.2% vs. 9%, mean difference 12.24%; 95% CI: 1.39%, 23.09%, $p = 0.029$). On the contrary, there was no statistically significant difference in the high folate group (mean difference 5.27%; 95% CI: -7.66%, 18.19%, $p = 0.40$).

Factors affecting plasma homocysteine in obese children

The correlation between plasma homocysteine and other clinical parameters were shown in Table 3. Plasma homocysteine level positively correlated with age (r = 0.284, $p = 0.046$) and negatively correlated with serum folate (r = -0.397, $p = 0.004$) and serum vitamin B12 (r = -0.392, $p = 0.005$). There was no linear correlation between plasma homocysteine and BMI Z score, waist circumference, as well as diet and physical activity, although there was a trend towards a positive association with serum creatinine, systolic blood pressure, and fasting insulin.

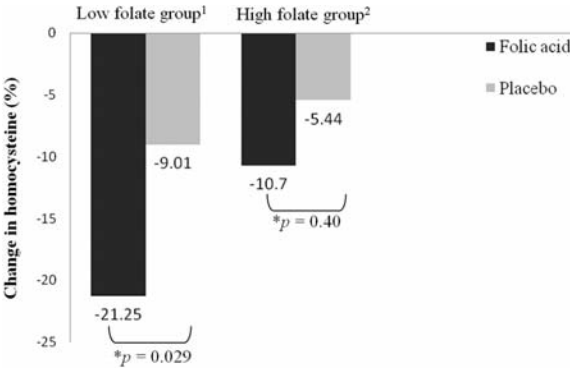
Discussion

Hyperhomocysteinemia is one of the potential risk factors for CVD. The treatment of hyperhomocysteinemia by folic acid supplementation with or without vitamin B12, or vitamin B6, is generally accepted in populations at risk for CVD. Obese children are at high risk for developing CVD in later life. We presumed that they are susceptible to folate deficiency due to inadequate dietary folate intake. Thus, folic acid supplementation may be beneficial to these children in order to reduce plasma homocysteine.

From the present study, the mean plasma homocysteine was at 8.10±1.79 μmol/L, which is in the normal range and comparable to that of obese children

in the previous studies[7,8]. The prevalence of hyperhomocysteinemia in the present study (10%) was higher than those in a previous study (5%)[12]. Larger studies in Thai pediatric population are needed to explain whether the prevalence rate should be concerned or not.

The obese children in the present study had much lower dietary folate intake (84.87±34.91 µg per day) than the recommended level (approximately only one-fourth of the Thai DRI, which is around 300-400 µg per day). Our finding was consistent with the results of Gillis L and Gillis A, that obese youth consumed significantly lower folate than their non-obese peers (122 vs. 146 µg of dietary folate/1,000 kcal)[9]. According to this information, folate-rich foods such as leafy green vegetables, fruits and cereals should be recommended for obese children. Nevertheless, their serum folate remained within normal limits. This might be due to the fact that serum folate is not an ideal indicator for long-term body storage of folate compared to RBC folate.



[1] Low folate group, serum folate level ≤17.88 nmol/L
[2] High folate group, serum folate level >17.88 nmol/L
* *p*-value from independent sample t-test

Fig. 2 Comparison of the percentage change in homocysteine levels between two groups.

Changes in plasma homocysteine levels

After two months of folic acid supplementation, serum folate considerably increased and plasma homocysteine decreased in the treatment group. After adjusting the baseline homocysteine and other different baseline parameters (SBP, HDL-C and vitamin B12), we confirmed that plasma homocysteine levels were significantly reduced in the folic acid group compared to placebo regardless of baseline homocysteine levels. The slight decrease of homocysteine levels in the placebo group might be partly due to the routine dietary and physical activity

Table 3. Correlations of baseline homocysteine and other clinical parameters

	Pearson's correlation (r)	*p*-value
Age (years)	0.284	0.046
BMI Z score	0.080	0.578
WC (cm)	0.225	0.117
Creatinine (mg/dL)	0.261	0.067
SBP (mmHg)	0.242	0.091
DBP (mmHg)	0.166	0.248
Total cholesterol (mg/dL)	0.117	0.417
HDL-C (mg/dL)	0.111	0.444
LDL-C (mg/dL)	0.103	0.476
Triglyceride (mg/dL)	0.005	0.973
FPG (mg/dL)	0.052	0.719
Insulin (µIU/mL)	0.265	0.063
HOMA-IR	0.244	0.088
Serum folate (nmol/L)	-0.397	0.004
Serum vitamin B12 (pmol/L)	-0.392	0.005
Dietary folate intake (µg/day)	0.001	0.999
Dietary vitamin B12 intake (µg/day)	0.153	0.310
Physical activity score (Met-minutes/week)	0.148	0.328

BMIZ score = body mass index standard deviation score; SBP = systolic blood pressure; DBP = diastolic blood pressure; HDL-C = high density lipoprotein cholesterol; LDL-C = low density lipoprotein cholesterol; FPG = fasting plasma glucose; HOMA-IR = homeostasis model for assessment of insulin resistance

counseling in our weight management program. In addition, there were no differences in the other potential confounding factors, such as dietary intake and physical activity during the intervention period between the two study groups. Therefore, the homocysteine lowering effects in our study should be more likely due to folic acid supplementation than these potential confounders should.

Several studies have assessed the homocysteine lowering effect of folic acid supplementation in children with hyperhomocysteinemia[11], type 1 diabetes[15], chronic renal failure[14], and more recently, obese children with endothelial dysfunction[16]. The magnitude of homocysteine reduction in our study was 15.75%, which was close to 17% reduction in obese children with endothelial dysfunction[16], but lower than the 41.2% reduction seen in hyperhomocysteinemia children[11]. Meta-analysis from the Homocysteine Lowering Trialists' Collaboration found that 0.5-5 mg of folic acid supplementation is estimated to reduce plasma homocysteine levels by about 25-33%[18,26]. This might be explained by the normal initial homocysteine level of the obese children in the present study. Subgroup analysis showed that the effects of folic acid supplementation was more apparent in children with lower baseline serum folate, which is consistent with the Homocysteine Lowering Trialists' Collaboration[18] which showed that homocysteine lowering effect of folic acid was greater at lower pretreatment serum folate (p for trend <0.001). However, in the present study, serum folate levels in the low folate group were still within normal reference range. Therefore, the authors postulate that folic acid administration could reduce plasma homocysteine levels in obese children with normal baseline folate and homocysteine levels. Moreover, we found that a daily dose of 5 mg folic acid had the same homocysteine lowering effect when compared with 0.5 mg[18]. Additionally, Wald DS et al and Homocysteine Lowering Trialists' Collaboration also showed evidence that only 0.8 mg of folic acid daily appears to achieve the maximum reduction in plasma homocysteine[26,27].

Intriguingly, although no gender difference between baseline homocysteine levels was found in the present study, the homocysteine lowering effects of folic acid supplementation was demonstrated in obese boys but not girls. This is contrary to a meta-analysis of randomized control trial which showed evidence that folic acid supplementation was associated with greater proportional reduction in homocysteine concentrations in women than in men. The discrepancy could be due to the fact that the trials in the meta-analysis were done in elderly with various diseases[26]. To our knowledge, no study has explored the difference in homocysteine lowering effects between genders in obese children. The possible explanation of our findings might be that boys tend to have more muscle mass than girls have, which is related to larger amount of homocysteine formation in connection with the creatine-creatinine synthesis[28]. The authors were unable to demonstrate the gender differences of homocysteine concentrations in this study. Not all available studies observed higher levels of homocysteine in normal weight boys during and after puberty[28-31]. Therefore, homocysteine concentration differences between genders in obese children remain controversial.

In the context of metabolic syndrome risk factors, we were unable to demonstrate any significant changes in BMI Z scores, waist circumference, blood pressure, insulin resistances and lipid profiles between the two treatment groups after completion of folic acid supplementation. On the other hand, other studies on children with hyperhomocysteinemia demonstrated that folic acid supplementation did not only reduce homocysteine levels, but also reduced blood pressure and total cholesterol levels[12,13]. It has also been demonstrated that folic acid supplementation is able to improve glycemic control and insulin resistance, in overweight and type 2 diabetes adults[32]. The possible explanation was that most of our participants were obese children who still had normal homocysteine levels and other metabolic syndrome parameters. They were different from previous studies where adults or children with various diseases had higher homocysteine levels and abnormal metabolic syndrome parameters. The alternative explanation is the short duration of our intervention. A longer duration of supplementation might be able to demonstrate a beneficial effect on these metabolic syndrome risk factors in these obese children.

Factors affecting plasma homocysteine in obese children

The authors' small cross-sectional analysis from the baseline parameters showed a positive association between plasma homocysteine levels with age and a negative association with serum folate and serum vitamin B12. These findings are consistent with the results of other studies[11,30,31]. However, the authors did not find an association between dietary folate and dietary vitamin B12 intake, contradicting a previous

study[11]. Moreover, in context of obese children, the authors did not find any significant relationship between plasma homocysteine and the determinants for obesity, such as BMI Z score, waist circumference, and obesity related co-morbidities such as glucose and lipid profiles. Although, a trend towards a positive association with serum creatinine, systolic blood pressure, and fasting insulin was observed in our study. This could be due to the small sample size, leading to insufficient power to detect these associations. Larger studies are required to evaluate the clinical significance of plasma homocysteine levels and its association with these co-morbidities in the obese children.

Conclusion

The homocysteine lowering effect of folic acid supplementation was found in obese children, especially in boys and those with low baseline serum folate. The authors did not find beneficial effects of folic acid supplementation on the metabolic syndrome risk factors. Further larger and long-term interventional studies are required to determine the effects of the lowered plasma homocysteine on the cardiovascular outcomes in obese children since hyperhomocysteinemia has been found to be an independent risk factor for atherosclerosis and cardiovascular disease. In the meantime, due to their low dietary folate intake, folate-rich food should be encouraged and folic acid supplementation may be considered in obese children.

Acknowledgement

The authors would like to thank Assistant Professor Dr. Chulaluk Komoltri for statistical analysis and very good suggestions, and Dr. Suchada Nilkumhang Wilkinh and Miss Raviwan Wittawassamrankul for placebo tablets production and packaging. This study was supported by The 90th Anniversary of Chulalongkorn University Fund (Ratchadaphiseksomphot Endowment Fund).

Potential conflict of interest

None.

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ผลของการให้กรดโฟลิคต่อระดับโฮโมซีสเตอีนในเลือดในผู้ป่วยเด็กอ้วน: การวิจัยเชิงทดลองแบบสุ่มปกปิดและมีกลุ่มควบคุม

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ภูมิหลัง: เด็กอ้วนมีแนวโน้มที่จะได้รับวิตามินโฟเลตจากอาหารไม่เพียงพอ ซึ่งโฟเลตเป็นปัจจัยร่วมที่สำคัญในการเปลี่ยนโฮโมซีสเตอีนเป็นเมไธโอนีน การขาดวิตามินโฟเลตจะทำให้ระดับโฮโมซีสเตอีนในเลือดสูงได้

วัตถุประสงค์: เพื่อศึกษาผลของการให้กรดโฟลิคต่อระดับโฮโมซีสเตอีนในเด็กอ้วน

วัสดุและวิธีการ: เป็นการวิจัยเชิงทดลองแบบสุ่มปกปิดและมีกลุ่มควบคุมในเด็กอายุ 9-15 ปี ซึ่งได้รับการวินิจฉัยว่าเป็นโรคอ้วนและได้รับการสุ่มเป็น 2 กลุ่ม กลุ่มศึกษาเป็นกลุ่มที่ได้รับกรดโฟลิคขนาดเม็ดละ 5 มิลลิกรัม ส่วนกลุ่มควบคุมได้รับยาหลอกที่มีลักษณะภายนอกและรสชาติเหมือนกรดโฟลิค ผู้เข้าร่วมวิจัยได้รับยาวันละ 1 ครั้ง เป็นระยะเวลาติดต่อกัน 2 เดือน การศึกษานี้มีการตรวจเลือดเมื่อก่อนเริ่มและสิ้นสุดการให้ยาเพื่อวัดระดับโฮโมซีสเตอีน วิตามิน บี12 โฟเลต ไขมัน น้ำตาล อินซูลิน รวมทั้งมีการใช้แบบสอบถามเพื่อประเมินค่ากิจกรรมการเคลื่อนไหวทางร่างกายปริมาณวิตามิน 12 และโฟเลตที่ได้รับจากอาหาร

ผลการศึกษา: มีผู้เข้าร่วมวิจัยทั้งหมด 50 ราย เป็นเด็กชาย 31 ราย มีอายุเฉลี่ย 10.9 ปี และมีคะแนนค่าเบี่ยงเบนมาตรฐานของดัชนีมวลกายเฉลี่ยเท่ากับ 3.41 เมื่อสิ้นสุดการได้รับยา กลุ่มทดลองมีการลดลงของระดับโฮโมซีสเตอีนร้อยละ 15.75 ส่วนกลุ่มควบคุมลดลงร้อยละ 6.99 ซึ่งมีความแตกต่างกันอย่างมีนัยสำคัญทางสถิติหลังจากมีการควบคุมตัวแปรระดับโฮโมซีสเตอีนเมื่อเริ่มต้นและตัวแปรอื่น ๆ แล้ว นอกจากนี้ยังพบการลดลงของโฮโมซีสเตอีนในเด็กชายมากกว่าเด็กหญิง และยังพบการลดลงของโฮโมซีสเตอีนในกลุ่มที่มีระดับโฟเลตในเลือดต่ำได้มากกว่ากลุ่มที่มีระดับโฟเลตในเลือดสูง

สรุป: การให้กรดโฟลิคสามารถลดโฮโมซีสเตอีนได้ในเด็กอ้วนโดยเฉพาะอย่างยิ่งในเด็กชายและกลุ่มที่มีโฟเลตต่ำ ในอนาคตควรมีการศึกษาเพิ่มเติมระยะยาวเพื่อประเมินผลของโฮโมซีสเตอีนที่ลดลงต่อการเกิดโรคหัวใจและหลอดเลือดในเด็กอ้วน