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ARTYKUŁ ORYGINALNY / *ORIGINAL ARTICLE*

Influence of folic acid supplementation on coagulation, inflammatory, lipid, and kidney function parameters in subjects with low and moderate content of folic acid in the diet

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Abstract

Background: The human body requires folic acid (FA) to produce blood cells, secure cell division, and growth. Moreover, this vitamin is important in the prevention of cardiovascular disease (CVD). Because the results of studies on the use of FA in the prevention of CVD are ambiguous, it seems necessary to conduct further research, which will explain in which cases supplementation is effective.

Aim: To assess the impact of FA supplementation on the coagulation, inflammatory, lipid parameters, and kidney function in subjects with atherosclerosis risk factors, depending on the content of FA in their diet.

Methods: The study enrolled 97 young adult Caucasian individuals (34 males and 63 females) with atherosclerosis risk factors. This population was divided into two groups: A — with low content of FA in the diet (< 40% of reference daily intake) and B — with moderate content of FA in the diet (40–90% of reference daily intake). The participants were asked to take FA in the low-dose of 0.4 mg/24 h for 3 months.

Results: Low-dose FA supplementation resulted in elevation of FA concentrations (79% vs. 75.1%) in the studied groups and, concomitantly, a decrease in homocysteine concentrations (21% vs. 20.3%). Mean level of creatinine decreased after FA supplementation in both groups (0.93 ± 1.1 vs. 0.72 ± 0.15 mg/dL and 0.83 ± 0.16 vs. 0.77 ± 0.15 mg/dL). These differences were statistically significant ($p < 0.0001$). The difference in mean estimated glomerular filtration rate values before and after FA supplementation was statistically significant in group A ($p = 0.002$) and on the border of statistical significance in group B ($p = 0.06$).

Conclusions: FA supplementation has no influence on the coagulation, inflammatory and lipid parameters in subjects with atherosclerosis risk factors depending on the content of FA in their diet. However FA supplementation may have a beneficial effect on kidney function in subjects with low content of FA in the diet.

Key words: diet, folic acid, kidney function, supplementation

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INTRODUCTION

The human body requires folic acid (FA) to produce blood cells, secure cell division, and growth [1, 2]. Numerous studies have shown that this vitamin is important in the prevention of neurodegenerative diseases, cancer, and cardiovascular disease (CVD) [3, 4]. In 1996 Morrison et al. [5] published a study indicating that individuals with low folate concentration (< 25th percentile) were exposed to significantly higher

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risk of death from cardiac causes than were subjects with a concentration above the 75th percentile. This finding was confirmed by the European Concerted Action Project (ECAP), in which a significant relationship between low concentrations of folate in erythrocytes and coronary artery disease, peripheral vascular disease, and stroke was observed [6]. The Framingham Heart Study found that low folate concentration was correlated with a two-fold higher risk of carotid artery stenosis. This dependency was significant even after taking into account other risk factors, including concentrations of homocysteine (Hcy) [7]. A meta-analysis by Yang et al. [8] has shown that FA supplementation may be beneficial in the prevention of stroke. Huo et al. [9] pointed out that those benefits are significant in the population deprived of FA fortification, and thus with higher shortages of folate in the diet. However, there are reports that are not consistent with the results of earlier quoted studies. The authors of the Atherosclerosis Risk in Communities Study (ARIC) denied the impact of FA on the CVD and confirmed its correlation with low concentrations of vitamin B6 in the blood [10]. Moreover, results of three large-scale studies: 2004 Vitamin Intervention for Stroke Prevention (VISP) [11], Heart Outcomes Prevention Evaluation 2 (HOPE 2) [12], and the Norwegian Vitamin Trial (NORVIT) [13] published in 2006, are also contradictory. These long-follow-up trials investigated the effect of preventive FA use (optionally with other group B vitamins) on cardiovascular incidents. The administration of FA was not associated with lower risk of new cardiovascular incidents like recurrent myocardial infarction (MI), stroke, or death from it, and in the NORVIT study the number of incidents was even increased in subjects with recent MI or with stents. Because the results of studies on the use of FA in the prevention of CVD are ambiguous, it seems necessary to conduct further research that will explain in which cases supplementation is effective.

The aim of this study was to assess the impact of FA supplementation on the coagulation, inflammatory, lipid parameters, and kidney function in subjects with atherosclerosis risk factors, depending on the content of FA in their diet.

METHODS

The study enrolled 97 young adult Caucasian individuals (34 males and 63 females) with atherosclerosis risk factors. This population was divided into two groups: A — with low content of FA in the diet (< 40% of reference daily intake) and B — with moderate content of FA in the diet (≥ 40% and < 90% of reference daily intake). The patients' nutrition was assessed with the use of a single 24-h dietary recall method related only to days not differing from the patients' typical dietary regimens — a fact confirmed by cross-questioning of the dietary habits and product intake frequency. The FA contents were calculated with the use of the Polish computer program Dietetyk 2 developed by the National Food and Nutrition Institute. All subjects underwent a standard interview about atherosclerosis risk factors. The precise characteristics of the studied patients are presented in Table 1. The inclusion criteria for the study groups were: age ≥ 18 years, patient's written informed consent, presence of atherosclerosis risk factors: family history of premature ischaemic stroke, arterial hypertension, dyslipidaemia, overweight or obesity, cigarette smoking, and low physical activity, absence of concurrent inflammation, no hypolipidaemic or metabolism-modulating agents, no administration of B-group vitamins or vitamin preparations within the six months preceding the study (use of hypotensive agents and oral contraceptives did not constitute exclusion criteria), young age of parents at the moment of ischaemic stroke (fathers younger than 55 years, mothers younger than 65 years) confirmed by means of computed tomography or magnetic resonance. The exclusion criteria were as follows: age < 18 years, lack of consent to participate in the study, non-compliance, administration of hypolipidaemic, metabolism-modulating agents, supplements, and vitamin preparations, chronic inflammation, CVD diagnosed prior to or during the study, diabetes, chronic kidney disease, and gout. The study involved an initial assessment through medical history taking, physical examination and blood analysis. Next, the participants were asked to take FA in the low-dose of 0.4 mg/24 h for three months [14], after which a follow-up examination was performed, again through medical history taking, physical examination, and blood analysis. Initially, FA supplementation was offered to 124 subjects, 27 of which (21.8%) were excluded in the course of the study due to non-compliance — taking below 80% of pills (irregular taking of FA, stopping taking of it altogether, or not reporting for the follow-up examination at the end of the treatment period). The participants were given the drug in an amount sufficient until the end of the study. The study was approved by the

Table 1. Characteristics of studied groups

	Group A (n = 53)	Group B (n = 44)
FA intake [μg]	82.89 ± 19.73	199.9 ± 53.08
Age [years]	27.54 ± 5.4	28.0 ± 6.1
Sex (male/female)	32% male	39% male
Family history of PIS	100%	100%
BMI [kg/m²]	24.84 ± 4.3	23.3 ± 3.5
BMI > 25 [kg/m²]	35%	34%
Dyslipidaemia	72%	70%
Cigarette smoking	35%	37%
High physical activity	24%	45%
Systolic BP [mm Hg]	126.0 ± 19.1	125.0 ± 12.3
Diastolic BP [mm Hg]	85.8 ± 10.8	83.0 ± 10.3
Arterial hypertension	31%	30%

Group A — low content of FA in the diet; Group B — moderate content of FA in the diet; FA — folic acid; PIS — premature ischaemic stroke; BMI — body mass index; BP — blood pressure

Bioethics Committee of the Pomeranian Medical University in Szczecin, Poland, according to the provisions of the Declaration of Helsinki (as revised in Edinburgh 2008), and written consent was obtained from all participants.

Laboratory methods

Fasting blood for biochemistry was collected. Blood tests comprised the following: measurements of FA and Hcy concentrations, lipid profile — total cholesterol (T-C), high-density lipoprotein-cholesterol (HDL-C), low-density lipoprotein-cholesterol (LDL-C), triglycerides (TG), apolipoprotein AI (ApoAI), apolipoprotein B (ApoB), lipoprotein(a) [Lp(a)], coagulation, inflammatory parameters, and creatinine (Cr) concentrations. The FA level was determined by an Abbott test kit (Abbott Laboratories, Chicago, Illinois, USA) using the ion capture method on an IMX immunochemical analyser (by Abbott). Total Hcy was determined by high performance liquid chromatography using test kits from Bio-Rad, on a Hewlett-Packard analyser with a fluorescence detector. TG and T-C levels were determined by enzymatic methods. LDL-C and HDL-C were obtained using the precipitation method and cholesterol concentrations in each fraction were measured. Apolipoproteins B and AI were measured using a photometric method utilising antigen-antibody binding. Measurements were taken using reagents from the commercial test kits from Roche, and a Clinilab analyser from bioMérieux. Lp(a) was measured using a photometric method utilising antigen-antibody binding on a latex carrier, with the use of test kits from Dialab, and a Clinilab analyser. The von Willebrand factor (VWF) was measured by means of a miniVidas analyser (bioMérieux) and enzyme-linked immunosorbent assay. Fibrinogen (Fb) level was determined by the Clauss method on a Hemolab analyser, using bioMérieux test kits. High-sensitivity C-reactive protein (hsCRP) concentration was measured by the immunoephelometric method using a Dade-Behring BN-100 analyser (Dade Behring Holding GmbH, Liederbach, Germany). Creatinine concentration evaluation was performed with a Reflotron analyser using strip tests by Roche. The estimated glomerular filtration rate (eGFR) was calculated with the Modification of Diet in Renal Disease (MDRD) Study Group formula.

Statistical analysis

Statistical analysis was performed using the STATISTICA StatSoft Polska v.9.0 package (StatSoft Inc., Tulsa, Oklahoma, USA), and the examined parameters were first evaluated for normal distribution (Shapiro-Wilk test). The Lp(a) and hsCRP values were subjected to logarithmic transformation. All continuous variables are presented as mean ± standard deviation. Differences between biochemical parameters among the studied groups were compared using unequal variance Student's t-test for the two samples (heteroscedastic variance). The significance level was set at $p \leq 0.05$.

RESULTS

Table 2 shows a comparison of the analysed biochemical parameters between the groups with low and moderate content of FA in the diet. Low-dose FA supplementation resulted in elevation of FA concentrations (79% vs. 75.1%) in the studied groups and, concomitantly, a decrease in Hcy concentrations (21% vs. 20.3%). However, these differences were not statistically significant. A slight reduction in mean concentration of T-C was observed in both groups (5.3% vs. 5.04%) after FA supplementation. These differences were not statistically significant. The HDL-C values increased after FA supplementation in group A (2.05%), but decreased in group B (1.09%), and LDL-C values decreased in both groups (7.4% vs. 5.67%). Mean level of TG decreased in group A (7.8%) but increased in group B (1.71%). However, these differences did not reach the border of statistical significance. After FA supplementation, concentrations of apoliporoteins (ApoAI, ApoB) and Lp(a) did not change significantly between the groups. There was a decrease in VWF levels in group A (7.5%) and group B (4.97%), an increase in Fb levels in both groups (0.98% vs. 1.8%), and a decrease in CRP concentrations in group A (3.77%) followed by a decrease in group B (13.9%). These differences were not statically significant. Mean level of Cr decreased after FA supplementation in both groups (0.93 ± 1.1 vs. 0.72 ± 0.15 mg/dL in group A and 0.83 ± 0.16 vs. 0.77 ± 0.15 mg/dL in group B). These differences between the groups were statistically significant ($p < 0.0001$). Mean eGFR values increased after FA supplementation in both groups (109.94 ± 26.8 vs. 120.92 ± 30.6 mL/min/1.73 m^2 in group A and 109.45 ± 1.41 vs. 117.68 ± 4.94 mL/min/1.73 m^2 in group B). These differences were not statistically significant between the groups; however, the difference in mean eGFR values before and after FA supplementation was statistically significant in group A ($p = 0.002$) and on the border of statistical significance in group B ($p = 0.06$).

DISCUSSION

In our study, the starting point was the analysis of FA content in the diet. We evaluated the change between the baseline FA levels and after supplementation, to verify the thesis that individuals with low FA content in the diet would benefit more. For both groups, FA intake was below daily reference, but significantly much lower in group A than in group B (82.89 ± 19.73 μg vs. 199.9 ± 53.08 μg; $p < 0.00001$). This was reflected in slightly lower levels of FA, although the difference was not statistically significant. Perhaps the reason for the lack of stronger correlation between consumption and blood levels of folate is a high sensitivity to thermal processing of food. Although FA supplementation affected the coagulation, inflammatory and lipid parameters in the studied individuals, the comparison between groups divided depending on folate content in the diet revealed no significant differences. However, FA supplementation resulted in

Table 2. Comparison of analysed biochemical parameters between groups with low and moderate content of folic acid in the diet

Parameter	Group A: Low content of FA in the diet (n = 53)				Group B: Moderate content of FA in the diet (n = 44)				P*	P**
	Before supplementation	After supplementation	Change (95% CI); %	P	Before supplementation	After supplementation	Change (95% CI); %	P		
Folic acid [ng/dL]	6.7 ± 3.14	12.0 ± 4.1	5.3 (4.29–6.28); 79.0%	0.00001	6.85 ± 2.8	12.0±3.2	5.15 (4.3–6.00); 75.1%	0.00001	0.413	0.434
Homocysteine [μmol/L]	11.1 ± 3.6	8.7 ± 2.11	–2.4 [–2.98–(–1.74)]; 21.0%	0.00006	11.3 ± 5.0	9.0±2.0	–2.3 (–1.26–3.32); 20.3%	0.003	0.404	0.453
Total cholesterol [mg/dL]	195.6 ± 41.7	185.17 ± 38.6	–10.43 [–14.05–(–4.8)]; 5.3%	0.117	214.0 ± 49.3	203.2±37.7	–10,8 [–17.87–(–3.86)]; 5.04%	0.124	0.019	0.362
HDL-C [mg/dL]	53.6 ± 12.1	54.7 ± 12.2	1.1 (–0.78–3.02); 2.05%	0.321	55.0 ± 10.7	54.4±10.7	–0,6 (–2.06–0.79); 1,09%	0.391	0.264	0.077
LDL-C [mg/dL]	105.5 ± 35.2	97.6 ± 31.9	–7.9 [11.93–(–3.38)]; 7.4%	0.112	119.9 ± 41.6	113.1±37.5	–6.8 [–11.37–(–2.14)]; 5.67%	0.213	0.035	0.345
Triglycerides [mg/dL]	98.5 ± 44.7	90.8 ± 35.8	–7.7 (–16.0–0.77); 7.8%	0.170	116.3 ± 95.0	118.3 ± 76.8	2.0 (–8.94–12.90); 1.71%	0.457	0.0114	0.079
ApoI [mg/dL]	146.2 ± 19.4	148.4 ± 21.5	2.2 [–0.53–(–4.18)]; 1.5%	0.298	146.7 ± 19.6	149.2 ± 19.1	2.5 (–0.40–5.4); 1.7%	0.273	0.447	0.424
ApoB [mg/dL]	91.1 ± 20.6	90.5 ± 18.3	–0.6 (–3.56–2.44); 0.65%	0.430	94.5 ± 18.5	93.7 ± 18.8	–0.8 (–4.12–2.49); 0.84%	0.419	0.204	0.437
Lp(a) [mg/dL]	30.5 ± 25.2	31.3 ± 23.7	0.8 (–1.02–2.40); 2.6%	0.443	23.2 ± 22.5	22.4 ± 22.5	–0.8 (–2.43–1.02); 3.44%	0.441	0.060	0.127
VWF [%]	77.2 ± 22.1	71.4 ± 22.1	–5.8 [–9.72–(–1.67)]; 7.5%	0.096	74.3 ± 22.7	70.6 ± 19.9	–3.7 (–7.96–0.57); 4.97%	0.210	0.268	0.250
Fibrinogen [g/L]	3.04 ± 0.68	3.07 ± 0.76	0.03 (–0.19–0.13); 0.98%	0.413	2.65 ± 0.6	2.7 ± 0.5	0.05 (–0.09–0.21); 1.8%	0.312	0.001	0.437
C-reactive protein [mg/L]	1.06 ± 1.17	1.02 ± 1.1	–0.04 (–0.27–0.20); 3.77%	0.431	0.86 ± 1.0	0.98 ± 1.14	0.12 (–0.19–0.45); 13.9%	0.315	0.187	0.200
Creatinine [mg/dL]	0.93 ± 1.1	0.72 ± 0.15	–0.21 (–0.59–0.12); 22.5%	0.049	0.83 ± 0.16	0.77 ± 0.15	–0.06 [–0,09–(–0.02)]; 7.22%	0.351	0.297	0.0001
eGFR [mL/min/1.73 m^2]	109.94 ± 26.8	120.92 ± 30.6	10.98 (2.9–18.9); 9.91%	0.002	109.45 ± 1.41	117.68 ± 4.94	8.22 (2.4–13.9); 7.49%	0.06	0.464	0.293

*Differences between baseline values of the parameters in the studied groups.
**Differences between the changes in the mean concentrations of the parameters in the studied groups.
CI — confidence interval; HDL-C — high-density lipoprotein cholesterol; LDL-C — low density lipoprotein cholesterol; Lp(a) — lipoprotein(a); ApoB — apolipoprotein B; ApoI — apolipoprotein I; VWF — von Willebrand factor; eGFR — estimated glomerular filtration rate

significant kidney function improvement in the group with low folate content in the diet.

The role and mechanism of action of FA in the prevention of CVD is not fully known. Some studies link the FA metabolism with the Hcy level, as the main anti-atherosclerotic effect [4, 7, 15]. FA must be reduced and methylated to 5-methyltetrahydrofolate (5-MeTHF), which serves as a cofactor for Hcy methylation and reduction of dihydrobiopterin (BH_2) to tetrahydrobiopterin (BH_4), to become a metabolically active form that can be utilised by tissues [16]. Therefore, when content of FA in the diet is low, these reactions are insufficient. As a consequence, Hcy levels inside the cells increase and become a distress to the inner layer of arteries. In the presence of Hcy, free radicals inactivate the nitric oxide (NO) and damage the endothelium. This mechanism is the basis of atherosclerosis pathogenesis [17]. Many authors suggest that the potential beneficial effects of FA on vascular endothelium may be associated with pathways other than through Hcy. Verhaar et al. [18] first demonstrated that 5-MeTHF in higher concentration reduces free radicals originating from different reactions in the body. Moreover, it has been shown that 5-MeTHF can directly affect the activity of nitric oxide synthase (NOS), although this mechanism was not observed when the level of NOS was not associated with a shortage of BH_4. The beneficial effect of 5-MeTHF on NOS was noted also in healthy individuals, and some reports indicate that 5-MeTHF may stabilise BH_4 and prevent its oxidation to inactive BH_2 [19]. Many works have assessed the influence of FA on availability of NO and endothelium function; however, to explain its detailed mechanism of action, further studies are needed.

Beneficial impact of FA in regard to reducing the risk of CVD may also result from effects on the clotting mechanism. Liem et al. [20] found no association of low-dose FA supplementation with Fb concentration. Nevertheless, other reports state that FA supplementation results in a decrease of Fb concentration and an increase in plasminogen and antithrombin III levels [21]. The ARIC study confirmed that VWF is a risk factor of ischaemic stroke [10]. It was shown that FA supplementation decreases VWF concentrations. In our previous study the effect of low-dose FA supplementation (0.4 mg/24 h) on Fb, VWF, and CRP concentrations was evaluated. After FA supplementation a significant decrease in VWF concentrations in the analysed individuals was observed. Moreover, this effect was especially marked in smoking and dyslipidaemic women and in smoking, dyslipidaemic, and overweight men. FA supplementation had no effect on Fb and CRP concentrations in the studied group [22]. In this study we observed that FA supplementation resulted in significant Cr decrease in subjects with low content of FA in the diet. There are reports that administration of FA, pyridoxine, and cyanocobalamin in patients with chronic renal failure had a favourable effect on risk factors of atherosclerosis. However, authors of this report did not evaluate Cr concentrations [13]. Similar observations were made by Qin et al. [23]. The conclusion of their meta-analysis is that FA therapy can reduce CVD risk in patients with end stage renal disease by 15%. In another study, glomerular function was assessed among rats exposed to ethanol. The supplementation of FA had no effect on the Cr levels in the studied animals [24]. The results of Anti-Oxidant Therapy in Chronic Renal Insufficiency (ATIC) study indicate that Hcy-lowering therapy with use of FA, pyridoxine, and cyanocobalamin has no effect on renal function [25]. However, that study was conducted on patients with chronic kidney disease.

In the present study, there were no significant changes in the VWF serum concentrations; however, there were differences on the border of statistical significance in the group with low content of FA in the diet. Moreover, in our earlier study we found that VWF serum concentrations decreased significantly after FA supplementation, regardless of the FA content in the diet [22]. VWF is considered to be a marker of endothelial dysfunction in vascular disorders. Administration of FA improves endothelial cell function through Hcy level lowering and oxidative stress reduction. The kidneys play a crucial role in plasma Hcy clearance. Patients with kidney disease present hyperhomocysteinaemia, and markers of GFR (like serum Cr) correlate with Hcy, even in subjects with normal renal function. The association between Hcy and GFR seems linear and is present even in the hyperfiltrating range. The precise mechanism by which GFR is related to Hcy concentration is not definitively established. Nevertheless, FA supplementation through Hcy level lowering affects the serum Cr concentrations [26]. We assume that this effect can be more intensive in subjects without established kidney disease than in patients with already existing kidney failure.

CONCLUSIONS

In view of our study, FA supplementation has no impact on the coagulation, inflammatory, and lipid parameters in subjects with atherosclerosis risk factors, depending on the content of FA in their diet. However, FA supplementation may have a beneficial effect on kidney function in subjects with low content of FA in the diet.

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References

1. Masoodi I, Kakar A, Byotra SP et al. Hemorrhagic manifestation of megaloblastic anemia: report of two cases and literature review. Blood Coagul Fibrinolysis, 2011; 22: 234–235.
2. Yazdy MM, Tinker SC, Mitchell AA et al. Maternal tea consumption during early pregnancy and the risk of spina bifida. Birth Defects Res A Clin Mol Teratol, 2012; 94: 756–761.

3. Luchsinger JA, Tang MX, Miller J et al. Higher folate intake is related to lower risk of Alzheimer's disease in the elderly. J Nutr Health Aging, 2008; 12: 648–650.
4. Antoniades C, Antonopoulos AS, Tousoulis D et al. Homocysteine and coronary atherosclerosis: from folate fortification to the recent clinical trials. Eur Heart J, 2009; 30: 6–15.
5. Morrison HI, Schaubel D, Desmeules M, Wigle DT. Serum folate and risk of fatal coronary heart disease. JAMA, 1996; 275: 1893–1896.
6. Robinson K, Arheart K, Refsum H et al. Lowcirculating folate and vitamin B6 concentrations. Risk factors for stroke, peripheral vascular disease and coronary artery disease. Circulation, 1998; 97: 437–443.
7. Selhub J, Jacques PF, Bostom AG et al. Association between plasma homocysteine concentrations and extracranial carotid artery stenosis. N Engl J Med, 1995; 332: 286–291.
8. Yang HT, Lee M, Hong KS et al. Efficacy of folic acid supplementation in cardiovascular disease prevention: an updated meta-analysis of randomized controlled trials. Eur J Intern Med, 2012; 23: 745–754.
9. Huo Y, Qin X, Wang J et al. Efficacy of folic acid supplementation in stroke prevention: new insight from a meta-analysis. Int J Clin Pract, 2012; 66: 544–551.
10. Folsom AR, Nieto J, McGovern PG et al. Prospective study of coronary heart disease incidence in relation to fasting total homocysteine, related genetic polymorphism and B vitamins. The Atherosclerosis Risk in Communities (ARIC) Study. Circulation, 1998; 98: 204–210.
11. The Heart Outcomes Prevention Evaluation (HOPE) 2 Investigators. Homocysteine lowering with folic acid and B vitamins in vascular disease. N Engl J Med, 2006; 354: 1567–1577.
12. Bønaa KH, Njølstad I, Ueland PM et al. Homocysteine lowering and cardiovascular events after acute myocardial infarction. N Engl J Med, 2006; 354: 1578–1588.
13. Toole JF, Malinow MR, Chambless LE et al. Lowering homocysteine in patients with ischemic stroke to prevent recurrent stroke, myocardial infarction, and death: the Vitamin Intervention for Stroke Prevention (VISP) randomised controlled trial. JAMA, 2004; 291: 565–575.
14. Naruszewicz M, Klinke M, Dziewanowski K et al. Homocysteine, fibrinogen, and lipoprotein(a) levels are simultaneously reduced in patients with chronic renal failure treated with folic acid, pyridoxine, and cyanocobalamin. Metabolism, 2001; 50: 131–134.
15. Tighe P, Ward M, McNulty H et al. A dose-finding trial of the effect of long-term folic acid intervention: implications for food fortification policy. Am J Clin Nutr, 2011; 93: 11–18.
16. Wang X, Fenech M. A comparison of folic acid and 5-methyltetrahydrofolate for prevention of DNA damage and cell death in human lymphocytes in vitro. Mutagenesis, 2003; 18: 81–86.
17. Niki E. Do free radicals play causal role in atherosclerosis? Low density lipoprotein oxidation and vitamin E revisited. J Clin Biochem Nutr, 2011; 48: 3–7.
18. Verhaar MC, Wever RM, Kastelein JJ et al. 5-methyltetrahydrofolate, the active form of folic acid, restores endothelial function in familial hypercholesterolemia. Circulation, 1998; 97: 237–241.
19. Gori T, Burstein JM, Ahmed S et al. Folic acid prevents nitroglycerin-induced nitric oxide synthase dysfunction and nitrate tolerance: a human in vivo study. Circulation, 2001; 104: 1119–1123.
20. Liem A, Reynierse-Buitenwerf GH, Zwinderman AH et al. Secondary prevention with folic acid: effects on clinical outcomes. J Am Coll Cardiol, 2003; 41: 2105–2113.
21. Mayer O Jr, Simon J, Rosolova H et al. The effects of folate supplementation on some coagulation parameters and oxidative status surrogates. Eur J Clin Pharmacol, 2002; 58: 1–5.
22. Mierzecki A, Kłoda K, Jastrzębska M et al. Is there an effect of folic acid supplementation on the coagulation factors and C-reactive protein concentrations in subjects with atherosclerosis risk factors? Postepy Hig Med Dosw, 2012; 66: 696–701.
23. Qin X, Huo Y, Langman CB et al. Folic acid therapy and cardiovascular disease in ESRD or advanced chronic kidney disease: a meta-analysis. Clin J Am Soc Nephrol, 2011; 6: 482–488.
24. Ojeda ML, Barrero MJ, Nogales F et al. Oxidative effects of chronic ethanol consumption on the functions of heart and kidney: folic acid supplementation. Alcohol Alcohol, 2012; 47: 404–412.
25. Nanayakkara PW, van Guldener C, ter Wee PM et al. Effect of a treatment strategy consisting of pravastatin, vitamin E, and homocysteine lowering on carotid intima-media thickness, endothelial function, and renal function in patients with mild to moderate chronic kidney disease Arch Intern Med, 2007; 167: 1262–1270.
26. Guldener C. Why is homocysteine elevated in renal failure and what can be expected from homocysteine-lowering? Nephrol Dial Transplant, 2006; 21: 1161–1166.

Wpływ suplementacji kwasem foliowym na parametry krzepnięcia, zapalne, lipidowe i funkcję nerek u osób z niską i średnią zawartością kwasu foliowego w diecie

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Streszczenie

Wstęp: Ludzki organizm wymaga kwasu foliowego (FA) do produkcji krwinek oraz zabezpieczenia podziału komórek i ich wzrostu. Ponadto ta witamina jest ważna w prewencji chorób sercowo-naczyniowych (CVD). Przeprowadzono wiele szeroko zakrojonych badań klinicznych obejmujących duże populacje, w których oceniano użycie FA w prewencji przede wszystkim udaru mózgu i zawału serca. Większość tych badań dotyczyła jednak profilaktyki drugorzędowej. Ponieważ wyniki stosowania FA w profilaktyce CVD są niejednoznaczne, konieczne wydaje się prowadzenie dalszych badań, które wyjaśnią, w jakich przypadkach suplementacja jest korzystna.

Cel: Celem badania była ocena wpływu suplementacji FA na parametry krzepnięcia, zapalne, lipidowe i funkcję nerek u osób z czynnikami ryzyka miażdżycy, w zależności od wyjściowego stężenia FA w ich diecie.

Metody: Do badania włączono 97 młodych osób dorosłych (34 mężczyzn i 63 kobiety) z czynnikami ryzyka miażdżycy, takimi jak dodatni wywiad rodzinny w kierunku przedwczesnego udaru niedokrwiennego mózgu, nadciśnienie tętnicze, dyslipidemia, nadwaga i otyłość, palenie tytoniu, niska aktywność fizyczna. Populacja została podzielona na dwie grupy: A — z niską zawartością FA w diecie (< 40% zalecanego spożycia) i B — ze średnią zawartością FA w diecie (40–90% zalecanego spożycia). Uczestników badania poproszono o przyjmowanie FA w niskiej dawce 0,4 mg/24 h przez 3 miesiące. Zaproponowana dawka została ustalona na podstawie doniesień z piśmiennictwa i wcześniejszych badań autorów. We krwi badanych oznaczono stężenia: FA, homocysteiny, profilu lipidowego — cholesterolu całkowitego, frakcji HDL, frakcji LDL i triglicerydów, apolipoproteiny AI, apoliporoteiny B, lipoproteiny (a), czynnika von Willebranda, fibrynogenu, białka C-reaktywnego i kreatyniny.

Wyniki: Suplementacja niskimi dawkami FA spowodowała wzrost jego stężeń (79% *vs*. 75,1%) w obu grupach ze współtowarzyszącym obniżeniem stężeń homocysteiny (21% *vs*. 20,3%). Jednak różnice te nie były istotne statystycznie. Różnice w średnich stężeniach parametrów krzepnięcia, zapalnych i lipidowych nie były znamienne statystycznie po suplementacji FA. Średnie stężenie kreatyniny obniżyło się po suplementacji FA w obu grupach badanych (odpowiednio 0,93 ± 1.1 *vs*. 0,72 ± 0,15 mg/dl i 0,83 ± 0,16 *vs*. 0,77 ± 0,15 mg/dl). Różnice te były istotne statystycznie ($p < 0,0001$). Średnie wartości estymowanego wskaźnika filtracji kłębuszkowej przed suplementacją i po suplementacji FA różniły się znamiennie w grupie A ($p = 0,002$) i były na granicy istotności statystycznej w grupie B ($p = 0,06$).

Wnioski: Suplementacja FA nie wpływa na parametry krzepnięcia, zapalne i lipidowe u osób z czynnikami ryzyka miażdżycy w zależności od wyjściowego stężenia FA w ich diecie. Jednak podaż FA może mieć korzystny wpływ na funkcję nerek wśród osób z niską zawartością FA w diecie. Poprawa w zakresie funkcji nerek może się wiązać z korzystnym wpływem FA na śródbłonek naczyń.

Słowa kluczowe: dieta, funkcja nerek, kwas foliowy, suplementacja

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