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Association between low-dose folic acid supplementation and blood lipids concentrations in male and female subjects with atherosclerosis risk factors

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Background: Folic acid (FA) is one of the B complex vitamins. It is thought that FA deficiency promotes atherosclerosis formation in arterial endothelium. FA, acting through reducing homocysteine (Hcy) levels, may contribute to decreased cholesterol (Ch) synthesis.
The aim of this study was to analyze the association of low-dose folic acid supplementation with blood lipids concentrations in subjects with atherosclerosis risk factors.

Material/Methods: The study enrolled 124 Caucasian individuals (60 M, ages 20–39; and 64 F, ages 19–39) with atherosclerosis risk factors (family history of premature ischemic stroke, arterial hypertension, dyslipidemia, overweight and obesity, cigarette smoking, and low level of physical activity). The participants were asked to take FA at a low dose of 0.4 mg/24 h for 12 weeks.

Results: FA levels increased in females (6.3 *vs.* 12.5 ng/dL; p=0.001) and males (6.4 *vs.* 11.4 ng/dL; p=0.001) and Hcy levels decreased (10.6 *vs.* 8.3 µmol/L; p=0.001 and 11.5 *vs.* 9.3; p=0.001, respectively). A significant reduction in mean concentration of total cholesterol in females (203.4 *vs.* 193.1 mg/dL; p=0.001) and in males (209.5 *vs.* 201.9; p=0.002) was observed. The low-density lipoprotein cholesterol (LDL-C) levels decreased in females and in males (107.4 *vs.* 99.9 mg/dL; p=0.001 and 121.5 *vs.* 115.1; p=0.002, respectively). The apoAI concentrations increased in smoking women and in men with BMI ≥25 kg/m^2 (p=0.032 and p=0.024, respectively).

Conclusions: Low-dose FA supplementation has a beneficial effect on blood lipids through decreasing concentrations of total cholesterol and LDL-C and increasing concentrations of apoAI.

Key words: apolipoprotein • atherosclerosis • cholesterol • folic acid • lipoprotein

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Background

Folic acid (FA), also called folate or vitamin B_9, is one of the B complex vitamins [1]. Preventive effects of FA on developmental birth defects, Alzheimer's disease, and megaloblastic anemia have been confirmed [2,3]. Introduction of the folate food fortification program in North America resulted in coronary plaque regression through lowering of homocysteine (Hcy) [4], which is an atherosclerosis risk factor [5]. It is considered that even a slight FA deficiency promotes atherosclerosis lesions formation in arterial endothelium [6]. Deficiency of FA coexisting with hyperhomocysteinemia can be observed in healthy individuals and individuals with established cardiovascular disease [7]. However, the preventive effect of FA on cardiovascular disease remains unclear. Large-scale clinical trials failed to show a benefit from Hcy-lowering treatment in individuals with established cardiovascular disease or with history of myocardial infarction. However, those studies evaluated high-dose FA supplementation as secondary prevention and were not investigating low-dose FA supplementation as primary prevention of cardiovascular disease [8–10].

High levels of cholesterol (Ch) in the blood, especially the low-density lipoprotein cholesterol (LDL-C), have been linked to arterial damage and cardiovascular disease, because of atherosclerosis promotion [11]. Hcy activates 3-hydroxy-3-methylglutaryl coenzyme A reductase, which plays a key role in Ch biosynthesis [1]. FA, acting through reducing Hcy, may contribute to decreased Ch synthesis [13]. Therefore, folate could have a preventive effect on atherosclerosis development. Apolipoproteins are structural components of lipids and transport them through the lymphatic and circulatory systems. There are 6 classes of apolipoproteins, which differ in regard to biological function. Apolipoprotein AI (apoAI) is the major component of high-density lipoprotein (HDL); apolipoprotein B (apoB) binds with chylomicrons and LDL. Lipoprotein(a) (Lp(a)) is a lipoprotein subclass linked with atherosclerosis and is also responsible for clot generation, because of reducing plasmin generation. Numerous studies have identified Lp(a) as a risk factor for coronary heart disease, cerebrovascular disease, thrombosis, and stroke [14–16].

The aim of this study was to analyze the association of low-dose folic acid supplementation, used as primary prevention, with blood lipids concentrations in subjects with atherosclerosis risk factors.

Material and Methods

The study enrolled 124 adult Caucasian individuals (60 males ages 20–39; mean age: 28.7 years and 64 females ages 19–39; mean age: 28.3 years) with atherosclerosis risk factors. A standard interview on the environmental risk factors for atherosclerosis was performed and revealed the presence of family history of premature ischemic stroke, arterial hypertension, dyslipidemia, overweight and obesity, cigarette smoking, and low level of physical activity among study participants. Family history of premature ischemic stroke was defined as episode of ischemic stroke in parents of studied individuals – fathers younger than 55 years and mothers younger than 65 years of age confirmed by means of CT or MRI. Arterial blood pressure was measured on the right arm 3 times via a sphygmomanometer after 5 min of rest. Then a mean value was noted down. Arterial hypertension was defined as systolic blood pressure at or over 140 mmHg and diastolic blood pressure at or over 90 mmHg. Dyslipidemia was defined as abnormal amount of lipids in the blood: total cholesterol ≥190 mg/dl and/or LDL-C ≥115 mg/dl and/or HDL-C <40 mg/dl in men and <45 mg/dl in women and/or triglycerides ≥150 mg/dl. Overweight was defined as BMI ≥25 kg/m^2 and obesity was defined as BMI ≥30 kg/m^2. Confirmation of cigarette smoking was based on patients' statements. Low level of physical activity was considered as unsatisfactory activity from the primary and secondary prevention point of view and it was adopted according to the Drygas definition [17].

The inclusion criteria for the study group were: age ≥18 years, patient's informed consent granted, absence of concurrent inflammation, no hypolipidemic or metabolism-modulating agents, no administration of B-group vitamins or vitamin preparations within 6 months before the study (use of hypotensive agents and oral contraceptives did not constitute exclusion criteria), young age of parents at the time of ischemic stroke. All studied individuals were inhabitants of the urban areas of north-western Poland. The study involved an initial assessment through medical history taking, physical examination, and blood analysis. In the studied group, 11.9% of subjects had chronic diseases, none of which was associated with atherosclerosis risk factors (bronchial asthma, cardiac valve defect, peptic ulcer disease, urolithiasis) and 26.0% of all women in the study group were taking oral contraceptives. Next, the participants were asked to take low-dose (0.4 mg/24 h) FA orally for 3 months [18,19], after which a follow-up examination was performed, again, through medical history taking, physical examination, and blood analysis. Initially, FA supplementation was offered to 147 subjects, 23 of whom (15.6%) were excluded in the course of the study due to non-compliance (irregular taking of FA, stopping it altogether, or not reporting for the follow-up examination at the end of the treatment period). The study was approved by the Bioethics Committee of the Pomeranian Medical University in Szczecin, Poland and a 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

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Table 1. Subjects' characteristics.

Characteristics	Study group n=124
Age (years)	28.4±5.9
Females	51.6%
Family history of PIS	100.0%
Smokers	36.3%
Dyslipidaemia	71.7%
BMI >25 kg/m^2	38.7%
Low physical activity	70.2%

PIS – premature ischemic stroke; BMI – body mass index.

concentrations, lipid panel (total cholesterol, HDL-C, LDL-C, triglycerides [TG]), apoAI, apoB, and Lp(a). The FA level was determined by an Abbott test kit (Abbott Laboratories, Chicago, IL, USA) using the ion capture method on an IMX immunochemical analyser (Abbott). Total Hcy was determined by high performance liquid chromatography (HPLC) using test kits from Bio-Rad, on a Hewlett-Packard analyser with a fluorescence detector. TG and total cholesterol levels were determined by enzymatic methods. LDL-C and HDL-C were obtained using the precipitation method and cholesterol concentration in each fraction was measured. Apolipoproteins B and AI were measured using a photometric method using an antigen-antibody binding. Measurements were done using reagents from the commercial test kits from Roche, and a Clinilab analyser from bioMérieux. Lp(a) was measured using a photometric method using antigen-antibody binding on a latex carrier, with the use of test kits from Dialab and a Clinilab analyser.

Statistical analysis

Statistical analysis was performed by the STATISTICA StatSoft Polska v.9.0 package (StatSoft Inc., Tulsa, OK, USA) and the examined parameters were first evaluated for normal distribution (Shapiro-Wilk test). The paired t test was used for the comparison of mean values of measured parameters after structuring subjects in the study by sex. The results obtained, which suggested the occurrence of significant metabolic differences between males and females, convinced us that this division should be maintained during further analysis. Significance level was set at $p \leq 0.05$.

Results

Table 1 presents characteristics of examined subjects. Tables 2 and 3 show that low-dose FA supplementation resulted in statistically significant elevation of FA levels in studied females (6.3 *vs.* 12.5 ng/dL; p=0.001) and males (6.4 *vs.* 11.4 ng/dL; p=0.001) and, concomitantly, a decrease in Hcy levels (10.6 *vs.* 8.3 µmol/L; p=0.001 and 11.5 *vs.* 9.3; p=0.001, respectively). A significant reduction in mean concentration of total cholesterol in females (203.4 *vs.* 193.1 mg/dL; p=0.001) and in males (209.5 *vs.* 201.9; p=0.002) was observed. The LDL-C levels also decreased in females and in males (107.4 *vs.* 99.9 mg/dL; p=0.001 and 121.5 *vs.* 115.1; p=0.002, respectively). There were no significant differences in HDL-C and TG concentrations before and after FA supplementation in both sexes. However, the total cholesterol/HDL-C ratio and LDL-C/HDL-C ratio differed significantly in both females (3.6 *vs.* 3.4; p=0.001 and 1.9 *vs.* 1.8; p=0.001, respectively) and males (4.4 *vs.* 4.2; p=0.02 and 2.6 *vs.* 2.4; p=0.01, respectively). There were no significant differences in apolipoproteins concentrations before and after FA supplementation in either sex. Tables 4 and 5 show that low-dose FA supplementation resulted in statistically significant elevation of FA levels in studied females and males with dyslipidemia, overweight and obese (BMI ≥25 kg/m^2), and smokers, and, concomitantly, a decrease in Hcy levels in all those groups. The concentrations of total cholesterol, LDL-C, total cholesterol/HDL-C ratio, and LDL-C/HDL-C ratio decreased among studied subjects, except male smokers. There were no significant differences in HDL-C and TG concentrations before and after FA supplementation in either sex divided into dyslipidemia, BMI ≥25 kg/m^2, and smokers subgroups. The apoAI concentrations increased significantly among smoking women and men with BMI ≥25 kg/m^2 (154.3 *vs.* 157.6 mg/dL; p=0.032 and 140.4 *vs.* 145.0; p=0.024, respectively). There were no significant differences in apoB, apoB/apoAI ratio, or Lp(a) concentrations before and after FA supplementation in either sex divided into dyslipidemia, BMI ≥25 kg/m^2, and smokers subgroups.

Discussion

In our study, the low-dose FA supplementation used as primary prevention showed encouraging results in terms of the reduction of Hcy and beneficial change in lipoproteins profile (significant decrease of the concentrations of total cholesterol and LDL-C in the studied group, and increased apoAI in some individuals).

The 3-month low-dose FA supplementation nearly doubled the folate level and reduced Hcy to below 10 µmol/L in 80% of participants, which is considered within normal range. The increased folate and reduced Hcy achieved in our study are in agreement with results of other authors [8]. Hcy, through activation of 3-hydroxy-3-methylglutaryl coenzyme A reductase in vascular endothelial cells, increases synthesis of Ch [13]. Moreover application of a hypolipidemic drug – simvastatin – to endothelial cells reduced cellular cholesterol and inhibited the suppression of nitric oxide (NO) production by Hcy. These

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Table 2. The effect of three-month diet supplementation with folic acid on Hcy, blood lipids and apolipoproteins concentrations in females (n=64).

Factor	Before supplementation		After supplementation		p*
	Mean	SD	Mean	SD	
Folic acid (ng/dL)	6.3	3.0	12.5	3.9	0.001
Hcy (µmol/L)	10.6	3.8	8.3	2.1	0.001
Total cholesterol (mg/dL)	203.4	31.9	193.1	30.1	0.001
LDL-C (mg/dL)	107.4	27.7	99.9	27.3	0.001
HDL-C (mg/dL)	59.2	10.9	58.8	10.4	NS
Total cholesterol/HDL-C	3.6	0.9	3.4	0.9	0.001
LDL-C/HDL-C	1.9	0.8	1.8	0.7	0.001
TG (mg/dL)	89.9	32.1	88.0	33.8	NS
apoB (mg/dL)	92.5	16.8	92.3	15.7	NS
apoAI (mg/dL)	155.0	15.6	155.9	15.9	NS
apoB/apoAI	0.6	0.1	0.6	0.1	NS
Lp(a) (mg/dL)	30.9	10.5	31.1	10.8	NS

* Student's paired t-test; SD – standard deviation; Hcy – homocysteine; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; apoB – apolipoprotein B; apoAI – apolipoprotein AI; Lp(a) – lipoprotein(a).

Table 3. The effect of three-month diet supplementation with folic acid on Hcy, blood lipids and apolipoproteins concentrations in males (n=60).

Factor	Before supplementation		After supplementation		p*
	Mean	SD	Mean	SD	
Folic acid (ng/dL)	6.4	2.8	11.4	3.0	0.001
Hcy (µmol/L)	11.5	3.9	9.3	1.8	0.001
Total cholesterol (mg/dL)	209.5	53.0	201.9	47.0	0.002
LDL-C (mg/dL)	121.5	44.1	115.1	39.5	0.002
HDL-C (mg/dL)	49.1	9.6	49.5	10.2	NS
Total cholesterol/HDL-C	4.4	1.2	4.2	1.0	0.02
LDL-C/HDL-C	2.6	1.0	2.4	0.9	0.01
TG (mg/dL)	120.2	83.5	116.6	64.9	NS
apoB (mg/dL)	94.1	22.0	94.0	20.4	NS
apoAI (mg/dL)	139.7	19.5	141.6	20.0	NS
apoB/apoAI	0.7	0.1	0.7	0.1	NS
Lp(a) (mg/dL)	26.2	11.4	27.0	11.7	NS

* Student's paired t-test; SD – standard deviation; Hcy – homocysteine; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; apoB – apolipoprotein B; apoAI – apolipoprotein AI; Lp(a) – lipoprotein(a).

findings explain the proatherogenic effect of Hcy. FA, acting through reducing Hcy, may play an important role in atherogenesis prevention. A significant decrease in LDL-C and Hcy concentrations after 8 weeks of FA, fiber, and B vitamins was reported by Sprecher et al. [20]. No adverse changes of TG or HDL-C levels were noted. Results obtained in this study are consistent with our observations. However, it should be noted that, in general, the degree of the reduction in LDL-C was higher with larger initial LDL-C values.

Apart from decreasing Hcy, total cholesterol, and LDL-C levels, we found that the low-dose FA supplementation increases apoAI, the primary HDL-C apolipoprotein. We observed this effect only in smoking women and men with BMI ≥25 kg/m^2.

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Table 4. The effect of three-month supplementation with folic acid on Hcy, blood lipids and apolipoproteins concentrations depending on dyslipidaemia (n=43), BMI ≥25 kg/m² (n=19) and smoking (n=24) in females.

Parameter in females	Dyslipidaemia (n=43)			BMI ≥25 kg/m² (n=19)			Smokers (n=24)		
	Before	After	p	Before	After	p	Before	After	p
FA (ng/dL)	6.2	12.0	0.001	8.0	13.8	0.001	7.1	12.4	0.001
Hcy (µmol/L)	10.6	8.4	0.001	10.2	8.0	0.001	10.9	8.6	0.001
T.Ch. (mg/dL)	218.2	204.5	0.001	201.9	191.7	0.004	201.5	193.9	0.014
LDL-C (mg/dL)	118.2	107.7	0.001	110.2	101.8	0.002	108.8	102.5	0.009
HDL-C (mg/dL)	60.2	59.6	NS	54.4	54.7	NS	56.7	57.0	NS
T.Ch./HDL-C	3.79	3.59	0.001	3.82	3.58	0.003	3.67	3.52	0.036
LDL-C/HDL-C	2.1	1.93	0.001	2.1	1.92	0.002	2.02	1.9	0.031
TG (mg/dL)	95.2	93.4	NS	96.4	94.5	NS	91.7	83.1	NS
apoB (mg/dL)	97.1	95.6	NS	95.2	97.2	NS	95.2	96.0	NS
apoAI (mg/dL)	155.7	156.4	NS	151.9	150.7	NS	154.3	157.6	0.032
apoB/apoAI	0.63	0.62	NS	0.63	0.65	NS	0.63	0.62	NS
Lp(a) (mg/dL)	34.1	35.3	NS	34.2	33.4	NS	32.3	32.7	NS

p – evaluated with Student's paired t-test; FA – folic acid; Hcy – homocysteine; T.Ch. – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; apoB – apolipoprotein B; apoAI – apolipoprotein AI; Lp(a) – lipoprotein(a).

Table 5. The effect of three-month supplementation with folic acid on Hcy, blood lipids and apolipoproteins concentrations depending on dyslipidaemia (n=46), BMI ≥25 kg/m² (n=29) and smoking (n=21) in males.

Parameter in females	Dyslipidaemia (n=46)			BMI ≥25 kg/m² (n=29)			Smokers (n=21)		
	Before	After	p	Before	After	p	Before	After	p
FA (ng/dL)	6.5	11.2	0.001	6.9	11.4	0.001	6.0	11.1	0.001
Hcy (µmol/L)	11.7	9.3	0.001	11.4	9.2	0.001	12.6	9.7	0.001
T.Ch. (mg/dL)	225.0	213.5	0.001	223.7	209.4	0.001	209.9	206.0	NS
LDL-C (mg/dL)	135.1	125.8	0.001	132.4	118.8	0.001	116.7	114.1	NS
HDL-C (mg/dL)	48.2	48.4	NS	48.7	49.5	NS	51.2	51.2	NS
T.Ch./HDL-C	4.75	4.5	0.008	4.71	4.38	0.002	4.28	4.18	NS
LDL-C/HDL-C	2.87	2.67	0.003	2.82	2.51	0.001	2.42	2.33	NS
TG (mg/dL)	131.2	124.2	NS	129.0	122.5	NS	132.4	137.7	NS
apoB (mg/dL)	99.1	98.3	NS	99.8	98.9	NS	91.2	95.8	NS
apoAI (mg/dL)	138.6	140.3	NS	140.4	145.0	0.024	142.4	144.8	NS
apoB/apoAI	0.72	0.71	NS	0.72	0.69	NS	0.65	0.67	NS
Lp(a) (mg/dL)	32.2	32.4	NS	26.6	27.4	NS	27.4	27.6	NS

p – evaluated with Student's paired t-test; FA – folic acid; Hcy – homocysteine; T.Ch. – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG – triglycerides; apoB – apolipoprotein B; apoAI – apolipoprotein AI; Lp(a) – lipoprotein(a).

Experimental studies in mice conducted by Mikael et al. showed that an increased Hcy level decreases apoAI synthesis in the livers of mice [21]. The authors also showed a negative correlation between Hcy levels and apoAI levels in humans (males) with coronary artery disease. These results explain the inverse correlation between Hcy and HDL-C. They also suggest that the inhibition of apoA-I synthesis, induced by Hcy, is a subsequent mechanism through which Hcy is linked with lipid metabolism and atherosclerosis development. HDLs have antiatherogenic properties, associated not only with a reverse transport of

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Ch from cells in peripheral tissues, but also with their antioxidative, antithrombotic, and anti-inflammatory effects [22].

The beneficial results observed in our study are not consistent with the results of the 2004 VISP study, HOPE 2, and NORVIT studies published in 2006 [8,22,23]. These large-scale and long-follow-up studies investigated the effect of preventive FA use on cardiovascular incidents. However, these trials used FA as secondary prevention in individuals with established cardiovascular disease. In our study, FA was used as primary prevention in healthy individuals with atherosclerosis risk factors but without already existing cardiovascular disease. It should also be mentioned that there is a significant difference between those studies and ours in the dose of FA. In the HOPE2 and VISP studies (high-dose formulation group) the FA dose was 6 times higher, and in NORVIT twice as high as in our study. The lack of beneficial effects in those trials could be attributed to the fact that high doses of FA, which is a methyl group donor, not only may cause methylation of Hcy to methionine, but can also be a substrate for other methylation reactions (e.g., methylation of arginine may lead to the asymmetric dimethylarginine (ADMA) formation, which inhibits the endothelial nitric oxide synthase) [24]. Moreover, in those studies, the use of FA (optionally with other group B vitamins) was not associated with a lower risk of new cardiovascular incidents (recurrent myocardial infarction, stroke, or resultant death), and in the NORVIT study the number of incidents was even increased (in subjects with recent myocardial infarction or with stents). Among examined cardiovascular incidents, only in the HOPE2 study there was a reduction in stroke episodes in comparison to the placebo group. Another difference between those trials and our study was that the VISP and NORVIT studies investigated episodes of stroke and myocardial infarction occurrence and did not investigate the effects of preventive FA doses on the blood lipids, as our study did. Only in HOPE2 were the lipid panel values in subjects receiving the FA supplementation compared to the placebo group, but the differences were not statistically significant. However, VISP, HOPE2, and NORVIT were conducted on high-risk groups (individuals with diabetes, cardiovascular disease, and those after myocardial infarction or a stroke).

The use of low-dose FA supplementation demands further research, as it may have more beneficial effects than the use of high doses. Indeed, the most recent studies have shown that in patients with coronary artery disease, low-dose FA (400 µg/d) administered for 7 weeks improves vascular function through increases in nitric oxide-mediated endothelium-dependent vasomotor responses. On the other hand, high-dose FA (5 mg/d) did not provide any additional cardiovascular system benefits [18].

Conclusions

In view of our results, it seems that low-dose FA supplementation, used as primary prevention, has a beneficial effect on blood lipids through decreasing concentrations of total cholesterol and LDL and increasing concentrations of apoAI. To determine the value of FA in primary cardiovascular disease prevention, further studies are needed.

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