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Impact of administration of folic acid on selected indicators of inflammation in patients with primary arterial hypertension

Ocena wpływu podawania kwasu foliowego na wybrane wskaźniki stanu zapalnego u chorych na pierwotne nadciśnienie tętnicze

Authors' Contribution:
A Study Design
B Data Collection
C Statistical Analysis
D Data Interpretation
E Manuscript Preparation
F Literature Search
G Funds Collection

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Summary

The results of epidemiological and clinical tests have shown that in patients with primary arterial hypertension, a chronic mild inflammation develops. The purpose of the study was to determine whether administration of folic acid to patients with primary arterial hypertension influences concentrations of indicators of inflammation: hsCRP, sICAM-1 and sVCAM-1.

Material & methods

The examination was carried out in 41 patients with primary arterial hypertension, aged 19–65 (21 men and 20 women), without complications of hypertension and/or coexisting diseases. The examined patients were administered 15 mg of folic acid once a day for 45 days. Before and after administration of folic acid, concentrations of folic acid, homocysteine, hsCRP, sICAM-1 and sVCAM-1 in serum were assessed.
Concentrations of folic acid and homocysteine were determined using the immunoenzymatic method (Abbott) on an AxSYM analyzer. The level of C-reactive protein (CRP) was determined with an ultra-sensitive turbidimetric assay on a Dimension analyzer (Siemens). Next, concentrations of adhesion particles sICAM-1 and sVCAM-1 were assessed with the ELISA technique (R&D).

Results

After the administration of folic acid in patients with primary arterial hypertension, a significant decrease in median concentrations of homocysteine in blood was observed. Simultaneously, the median hsCRP, ICAM-1 and VCAM-1 concentrations in serum in patients with primary arterial hypertension were significantly reduced.

Conclusions

Administration of folic acid to persons with primary arterial hypertension in a dose of 15 mg/day for 45 days caused a decrease in the concentration of homocysteine in serum. That could indirectly result in the decrease in concentrations of the indicators of inflammation (hsCRP, ICAM-1 and VCAM-1), as it is apparent from previous studies that hyperhomocysteinemia stimulates the synthesis of CRP and the expression of adhesion molecules.

Key words: **hypertension • inflammation • hsCRP • sICAM-1 • sVCAM-1**

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Introduction

Inflammation in vessel walls develops as a response to the damage of vascular endothelium. In the case of the long-term influence of factors damaging vessel walls, inflammation turns into a chronic state which does not lead to improvement, but additionally increases the dysfunction of the endothelium. Immune cell migration is a crucial phenomenon characteristic for the inflammation in injured tissues in response to chemotactic stimuli [22]. The activation of leucocytes causes the expression of integrins on their surface containing α4 or β2 families. Integrins of the β2 family are connected with adhesion particles belonging to the superfamily of immunoglobulins: ICAM-1 (intercellular adhesion molecule-1, CD54) and ICAM-2 (intercellular adhesion molecule 2, CD102) present in endothelial cells. Both types of intercellular adhesion particles are present on non-stimulated endothelium cells. However, after their activation, the expression of ICAM-1 grows greatly, although the ICAM-2 expression remains at the same level. In the case of chronic inflammation, also the expression of VCAM-1 (vascular cell adhesion molecule 1, CD106) grows [10].

In the course of arterial hypertension, coronary disease and heart failure, an increase in concentration of adhesion particles as well as other indicators of inflammation – interleukins (e.g. IL-1, IL-6), E-selectin, fibrinogen, A-amyloid and C-reactive protein (CRP) – was observed [7]. The production of CRP is influenced by non-specific stimulation of cytokines: interleukin 6 (IL-6), interleukin 1β (IL-1β) and tumor necrosis factor α (TNF-α). This protein plays a substantial role in the regulation of inflammation. Its participation in this process consists mainly of binding and neutralization of bacteria, endotoxins and tissue decomposition products as well as activation of the complement system and phagocytosis. At present, it is believed that CRP can adversely affect functions of blood vessels by reducing the production of nitric oxide in vascular endothelium, increasing the production of endothelin-1, and participating in detection of low density lipoprotein (LDL) molecules by macrophages [31].

The cause-and-effect relationship of hypertension and increase in the process of inflammation was not precisely defined. It is assumed that this process is a defensive response to numerous factors damaging vessel walls, including hypertension, diabetes, infections, free radicals, modified LDL particles, and hyperhomocysteinemia. Increased concentrations of homocysteine which cause the damage of blood vessels often appear in patients with primary arterial hypertension [4]. However, modification of the level of homocysteine is possible by the administration of folic acid, which is a relatively easy and inexpensive method [12].

The purpose of the study was to determine whether administration of folic acid to patients with primary arterial hypertension has an influence on concentrations of parameters of inflammation: hsCRP, sICAM-1 and sVCAM-1.

Material and methods

The examination was carried out in 41 patients with primary arterial hypertension, aged 19–65 (21 men and 20 women) undergoing their treatment at the Department of Internal Medicine, Metabolic Disorders and Hypertension, Poznań University of Medical Sciences.

Patients included in the trial had a mean blood pressure on the arm artery equal to 140/90 mmHg or higher. In these persons, complications such as diabetes, nephropathies, heart diseases, cancers, psoriasis, endocrine diseases and inflammation were not observed in the last six months. Selected parameters of clinical and laboratory characteristics of examined patients with primary arterial hypertension are presented in table 1.

After written permission concerning their participation in this test, concentrations of folic acid, homocysteine, hsCRP, ICAM-1 and VCAM-1 in serum were assessed. Subsequently, 15-mg of folic acid was administered in these persons once a day for 45 days. After this time, the same laboratory parameters were assessed again. Concentrations of folic acid and homocysteine were determined using the immunoenzymatic method (Abbott) on an AxSYM analyzer. The level of CRP was determined with an ultra-sensitive turbidimetric assay on a Dimension analyzer (Siemens). Next, concentrations of adhesion particles ICAM-1 and VCAM-1 were assessed with the ELISA technique (R&D). During the administration of folic acid, patients with primary arterial hypertension continued their hypotensive treatment, but did not receive anti-inflammation medications and/or statins.

Table 1. Selected parameters of clinical and laboratory characteristics of patients with primary arterial hypertension

PARAMETER/ UNIT	MEAN ± SD	MEDIAN	MIN-MAX
AGE (years)	45.22±13.39	48.00	19.00-65.00
SYSTOLIC BLOOD PRESSURE (mmHg)	152.98±15.23	150.00	130.00-215.00
DIASTOLIC BLOOD PRESSURE (mmHg)	95.32±9.36	95.00	66.00-120.00
PULSE (min)	73.92±9.68	74.50	58.00-94.00
BMI (kg/m2)	27.09±4.37	27.00	18.60-34.90
GLUCOSE (mmol/l)	5.50±0.53	5.51	4.39-6.57
TOTAL CHOLESTEROL (mmol/l)	5.57±1.27	5.46	4.03-10.36
HDL CHOLESTEROL (mmol/l)	1.430 ±0.43	1.40	0.77-2.78
LDL CHOLESTEROL (mmol/l)	3.56±1.44	3.30	2.00-8.50
TRIGLYCERIDES (mmol/l)	1.35±0.72	1.18	0.34-3.22
FOLIC ACID (mg/ml)	6.89±2.72	6.20	2.18-15.20

Table 2. Concentration of homocysteine (Hcy) and hsCRP in serum of patients with primary arterial hypertension after administration of folic acid

	Patients with primary arterial hypertension before administration of folic acid N=41	Patients with primary arterial hypertension after administration of folic acid N=41
HOMOCYSTEINE (µmol/l)		
Mean ±SD	10.14±2.95	7.95±1.96
Median	9.42	*7.72
Min-max	6.27-19.72	5.01-13.90
Hcy 5.00-12.0 (µmol/l)	N=30 (73%)	N=38 (93%)
Hcy > 12.00 (µmol/l)	N=11 (27%)	N=3 (7%)
hsCRP (mg/l)		
Mean±SD	2.50±1.63	1.93±1.79
Median	2.22	*1.14
Min-max	0.50-7.53	0.50-6.84
hsCRP <1 mg/l	N=8 (20%)	N=18 (44%)
hsCRP 1-3 mg/l	N=21 (51%)	N=15 (37%)
hsCRP >3 mg/l	N=12 (29%)	N=8 (19%)

N - number of patients

* statistically significant difference as compared with concentration of the parameter in serum of patients with primary arterial hypertension before administration of folic acid, $p < 0.05$.

Table 3. Concentrations of sICAM-1 and sVCAM-1 in serum of patients with primary arterial hypertension after administration of folic acid

	Patients with primary arterial hypertension before administration of folic acid N=24	Patients with primary arterial hypertension after administration of folic acid N=24
	sICAM-1 (ng/ml)	
Mean±SD	236.71±59.24	224.67±61.58
Median	230.55	* 226.40
Min-max	130.20-354.60	106.50-318.60
sICAM 115-306 ng/ml	N=21 (88%)	N=20 (83%)
sICAM >306 ng/ml	N=3 (12%)	N=4 (13%)
	sVCAM-1 (ng/ml)	
Mean±SD	569.74±165.30	531.81±134.55
Median	525.30	* 512.25
Min-max	320.00-997.70	297.30-798.10
sVCAM-1 <349 ng/m	N=1 (4%)	N=1 (4%)
sVCAM-1 349-991 ng/ml	N=22 (92%)	N=23 (96%)
sVCAM-1 >991 ng/ml	N=1 (4%)	N=0 (0%)

N - number of patients

* statistically significant difference as compared with concentration of investigated parameter in serum of patients with primary arterial hypertension before administration of folic acid, $p < 0.05$

Obtained results concerning concentrations of hsCRP, sICAM-1, sVCAM-1, folic acid and homocysteine in blood of patients with primary arterial hypertension before and after the administration of folic acid were subjected to statistical analysis. For that purpose, the Mann-Whitney-Wilcoxon U-test was applied. Also the Spearman coefficient of correlation was examined. All statistical hypotheses were reviewed at the level of statistical significance of $p<0.05$. A statistical analysis of tests was performed using STATISTICA v 8.0 software.

Results

After the administration of folic acid in patients with primary arterial hypertension, a significant decrease in the median concentrations of homocysteine in blood was observed (9.42 vs. 7.72 µmol/l), and the percentage of patients with hyperhomocysteinemia was reduced from 27 to 7% (table 2).

Next, the median of the hsCRP concentrations in serum of persons with primary arterial hypertension after the administration of folic acid decreased significantly from 2.22 mg/l to 1.14 mg/l. Simultaneously, the percentage of persons in whom the concentration of CRP was lower than 1.00 mg/l doubled. Also, the percentage of persons with primary arterial hypertension in whom the hsCRP concentration was higher than 3.00 mg/l decreased by 10% (table 2).

After the administration of folic acid also a significant decrease in the median sICAM-1 concentrations in serum of patients with primary arterial hypertension was observed (230.55 vs 226.40 ng/ml) (table 3). Similar changes were observed in the median sVCAM-1 concentrations in serum of patients with primary arterial hypertension. After the administration of folic acid, this concentration decreased from 525.30 to 512.25 ng/ml. This difference was also statistically significant (table 3).

In the next stage of the analysis of the results, a relation between the increase in the concentration of folic acid and lowering of concentrations of analyzed indicators of inflammation was examined. The Spearman test did not show a statistically significant correlation between increase in the concentration of folic acid and the change of values of parameters of inflammation (hsCRP, sICAM-1, sVCAM-1) (table 4). A similar correlation between lowering of concentration of homocysteine induced with the administration of folic acid and changes of test values of parameters of inflammation was also not demonstrated (table 4).

Discussion

The results of epidemiological and clinical tests showed that in patients with primary arterial hypertension, a chronic mild inflammation develops [11]. An accepted laboratory indicator of inflammation is the concentration of CRP, regarded as an independent risk factor of coronary dise-

Table 4. Correlation between change in concentration of folic acid and change in concentration of homocysteine and change in values of parameters of inflammation ΔhsCRP, ΔsICAM-1 and ΔsVCAM-1 in serum of patients with primary hypertension after administration of folic acid

Correlation between change in concentration of folic acid and:	R	p
Δ hsCRP	–0.089487	0.577940
Δ sICAM-1	–0.026974	0.900434
Δ sVCAM-1	–0.053078	0.805434
Correlation between change in concentration of homocysteine and:		
Δ hsCRP	–0.237519	0.134831
Δ sICAM-1	–0.142640	0.506116
Δ sVCAM-1	–0.184823	0.387263

R – Spearman correlation coefficient
p – statistical significance

ase, cerebral stroke or vascular fibrosis [3]. Some authors suggest that CRP, assessed with high-sensitive methods (hsCRP), is the strongest non-lipid prognostic factor of the risk of cardiovascular diseases [25]. According to Ridker, the stratification of the risk of cardiovascular diseases depending on the CRP concentration is as follows: a CRP concentration lower than 1 mg/l indicates low risk, CRP concentration from 1 to 3 mg/l means an average risk level, and higher than 3 mg/l is considered to be a high risk factor of cardiovascular diseases [25]. Our previous tests confirmed the clear dependence between arterial hypertension and elevated level of the CRP protein in serum. In the serum of 54 patients with arterial hypertension, the concentrations of CRP were characteristically higher than in the serum of 35 healthy individuals (2.81 vs 1.61 mg/l) [3]. Similar relations were observed in the results of other clinical research [18,27,33] including NATPOL Plus [32].

Reduction in risk factors, including the reduction in the increase of inflammation in patients with arterial hypertension and other cardiovascular diseases, seems to be clinically beneficial.

The outcomes of our own research showed that hsCRP concentration in serum of patients with primary arterial hypertension decreased significantly after the administration of folic acid. At the same time, the number of patients with primary arterial hypertension, in whom the hsCRP concentration was higher than 3 mg/l, decreased by 10%. The percentage of patients in whom the hsCRP concentration was 1–3 mg/l decreased by 14%. The percentage of persons in whom the hsCRP concentration was lower than 1 mg/l increased by half. Taking into consideration Ridker's principles of stratification, it is possible to assume that the risk of cardiovascular diseases in the examined group of patients was reduced. In their clinical research, Gariballa et al. also observed a decrease of CRP concentration after the administration of folic acid. [14]. Also, in the large population-based Augsburg Study, including 2045 women and 2172 men administered vitamins E, C, and those of B group, the administration of folic acid and microelements was correlated with a significant decrease of the concentration of CRP in the serum of women. The researchers explained that this effect is correlated with the reduction of the increase in the inflammatory process in vessel walls [26].

Further results of our research show that the administration of folic acid in patients with primary arterial hypertension resulted in lowering of concentrations of adhesion particles sICAM-1 and sVCAM-1. Experiments showed the characteristic influence of folic acid on the decrease of the expression of the adhesion molecule VCAM-1. Li et al. reported that administration of folic acid prevented hyperhomocysteinemia and inhibited the increase of the level of mRNA for VCAM-1 in aorta cells of rats [21]. The effect of lowering of the concentration of homocysteine and, among others, of concentration of VCAM-1 in the endothelium of vessels of brain after the administration of folic acid to rats with induced hyperhomocysteinemia was also demonstrated in the work of Lee et al. [20]. Also, the results of clinical research of Alian et al. showed that administration of folic acid to persons with type 1 diabetes resulted in a significant decrease in the concentration of VCAM-1 [2].

The influence of the administration of folic acid on the decrease of the concentration of homocysteine can result from the beneficial influence of this vitamin on the efficiency of the process of remethylation of homocysteine to methionine [28]. In turn, the decrease in the concentration of homocysteine can indirectly improve the function of vascular endothelium and alleviate the inflammation. This is due to the fact that one of the effects of hyperhomocysteinemia is the increase of factors promoting the development of inflammation and settlement of macrophages in the vessel wall [4]. High concentrations of homocysteine increase the expression of the MCP-1 protein responsible for the migration of monocytes towards the vessel wall [30]. The inflammatory reaction in the endothelium of vessels can also be caused by appearing proteins modified by N-homocysteinylation on the surface of cells, because in human serum,

the presence of G-class immunoglobulins directed against epitopes Nε-Hcy-Lys was observed [17]. A positive correlation between the level of homocysteine and concentration of VCAM-1 was also observed [16]. Moreover, the findings of Bogdański et al. suggest that hyperhomocysteinemia also causes an increase in the concentration of tumor necrosis factor (TNF-α), which stimulates the synthesis of CRP [6].

Based on the abovementioned data from our own tests and from the literature, it can be supposed that administration of folic acid caused a decrease in the concentration of homocysteine and, as a consequence, could influence the decrease in the concentration of indicators of inflammation: hsCRP and adhesion particles. However, this effect has not always been observed in clinical research. According to the results of the WENBIT trial (Western Norway B-vitamin Intervention Trial), the concentration of homocysteine after six months of administration of folic acid as well as with vitamins B_{12} and B_6 decreased by 33%, although a decrease in the concentration of CRP in patients with coronary disease was not observed [5]. Also Klerk et al. [19], O'Doherty et al. [24] as well as Mierzecki et al. [23] did not observe the effect of a decrease in the concentration of CRP after supplementation with folic acid. The results of our tests showed a simultaneous decrease in concentrations of homocysteine and hsCRP and of both adhesion particles ICAM-1 and VCAM-1. However, a significant correlation between changes in the concentration of homocysteine and aforementioned indicators of inflammation was not observed.

The cause of the lack of strong correlation between lowering of the concentration of homocysteine and decrease in the concentration of indicators of inflammation in clinical research is probably the fact that hyperhomocysteinemia is only one of numerous factors damaging vessel walls which provoke the general immune response. The concentration of CRP and adhesion particles in persons with cardiovascular diseases also depends on infectious agents, the ability of the organism to mount an individual immune response, oxidizing status, blood pressure, liver efficiency, smoking and the amount of body fat [15].

The effect of the administration of folic acid can also depend on its dose, time of supplementation and additional administration of vitamins. In our tests, high doses of folic acid were applied: 15 mg per day for 45 days. As a consequence, a significant decrease in hsCRP concentration in serum occurred in patients with primary arterial hypertension. Patients of Gariballa et al. were administered with 1.67 mg of folic acid a day, along with B group vitamins, for three months, and also the concentration of CRP decreased, although this decrease was not statistically significant [14]. Mierzecki et al. did not observe any decrease in the concentration of CRP after administration of low-dose folic acid (0.4 mg per day for three months) [23].

Taking into consideration literature data, one should acknowledge that the influence of administration of folic acid on the function of vessels, including the increase of inflammation, is complicated. This problem requires further clinical research performed in large populations. However, bearing in mind the results of large intervention studies which did not confirm clinical benefits of applying vitamins lowering the concentration of homocysteine in blood of persons with metabolic diseases, conducting further population trials will be difficult [1,8,13]. Spence et al. suggest that in further trials the administration of folic acid and the polymorphism of the gene for methylenetetrahydrofolate reductase should be taken into account. Such trials should be conducted in carefully selected groups of patients [29]. However, collection of such a group is difficult. In our own tests, patients with complications of hypertension and/or coexisting diseases were excluded from the group. For this reason, the examined group was small. The small number of people in this group could cause, among others, a decrease in the correlation of changes of the concentration of homocysteine and parameters of inflammation. For these reasons, these tests should be continued in a larger number of patients. Also additional experimental research in animal models and tissue cultures would be helpful.

Conclusions

Administration of folic acid to persons with primary arterial hypertension in a dose of 15 mg/day for 45 days caused a decrease in the concentration of homocysteine in serum. That could indirectly result in the decrease in concentrations of indicators of inflammation – hsCRP, ICAM-1 and VCAM-1 – as it is apparent from previous studies that hyperhomocysteinemia stimulates the synthesis of CRP and the expression of adhesion molecules.

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