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The significance of homocysteine in patients with hypertension

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Abstract

Cardiovascular disease is the most common cause of death in developed countries. Important factors leading to ischemic heart disease and strokes are hypertension and high levels of homocysteine in blood serum. The coexistence of these two factors significantly increases the risk of these diseases and premature deaths. Many studies indicate that patients with hypertension are significantly more likely to demonstrate increased blood serum homocysteine levels than those with normal blood pressure. This may be caused by a higher incidence of overweight, high intake of salt and increased uric acid levels. It has been shown that both these factors increase the prevalence of hypertension and lead to higher homocysteine levels. However, the results of some studies indicate that arterial hypertension and homocysteinemia are causally related. It was shown, among other things, that high homocysteine levels damage the endothelium and reduce nitric oxide synthesis, which may directly lead to hypertension. Serum homocysteine levels are slightly higher in patients with white coat hypertension than they are in healthy individuals and may therefore also increase the risk of cardiovascular diseases. Several authors have also shown that the levels of homocysteine in blood serum are higher in so-called non-dippers, i.e., patients with no night-time pressure drop. The lack of a 10%–20% decrease in blood pressure at night is associated with increased cardiovascular complications. Strokes occur especially frequently in older people with arterial hypertension and hyperhomocysteinemia. The administration of B vitamins and folic acid significantly reduces serum homocysteine levels. The administration of this acid also slightly, but statistically significantly, increases the effectiveness of hypotensive drugs. Large meta-analyses meta-analysis indicate that the increased supply of folic acid in patients with hypertension significantly reduces the risk of stroke. Such management is particularly effective in patients with hypertension and hyperhomocysteinemia.

Keywords

homocysteine • hypertension • non-dipper hypertension • stroke

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Introduction

Hypertension (RR > 140/90 mmHg) affects almost 30% of adult inhabitants in our country [1]. Taking into account the criteria adopted by the United States (RR > 130/80 mmHg), the percentage of people with hypertension is even higher, i.e., over 45% [2]. According to Lawes et al., hypertension causes 50% of all cardiovascular diseases and is one of the main causes of increased mortality [3].

The cause of increased mortality during the course of hypertension is related to an accelerated atherosclerotic process. In addition to hypertension, atherosclerosis has been shown to be accelerated by many other factors such as hyperlipemia, cigarette smoking, chronic inflammation [4], and increased homocysteine levels [5].

Metabolism of homocysteine

Homocysteine is a sulphuric amino acid formed from methionine supplied in food. It is metabolized into cysteine in the cells of the body as a result of a process called transsulfuration [6]. However, it can be remethylated and converted back to methionine. Excess of homocysteine in the cells is secreted into the pericellular space, including plasma. Homocysteine metabolism in the human body is regulated by B vitamins [6, 7], among other things [8]. Increased homocysteine concentration is most often caused by low dietary folic acid supply or genetic factors through the methylenetetrahydrofolate reductase (MTHFR) gene [8]. Elevated serum homocysteine levels are also found in patients with kidney failure, cigarette smokers, the elderly, obese people, as well as diabetics. Insufficient physical

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inactivity, alcoholism, and high consumption of coffee also increase the blood levels of this compound [8]. It is also worth remembering that methotrexate, diuretics and fenofibrate also increase the concentration of homocysteine in blood serum [8]. A Polish epidemiological study showed that a deficiency in folate intake (which results in increased serum homocysteine concentration) is found in 80%–90% of the subjects [9]. Vitamin B12 deficiency was found in 32%–51% of people in our country [9]. It is believed that normal serum homocysteine concentration should not exceed 15 μmol/l. However, an increasing number of authors suggest lowering this limit to 10 μmol/l [9].

Increased serum homocysteine levels are a risk factor for accelerated death [10, 11] in atherosclerotic processes (myocardial infarction, stroke), and possibly also in heart failure [12] or renal failure [13].

The important role of hyperhomocysteinemia in the development of atherosclerotic processes was first pointed out by McCully KS in 1969 [5]. Direct evidence for the atherogenic effects of homocysteine was provided by numerous clinical studies and a large meta-analysis [14, 15]. The exact mechanism of the influence of homocysyteine on the development of atherosclerosis is still unknown.

The increase in arterial pressure caused by increased homocysteine levels may be explained by impaired endothelial function, oxidative stress, the direct influence of homocysteine on diastolic function of blood vessels through, among other things, effects on the extracellular matrix, as well as inhibition of adenosine bioavailability and finally altered function of some genes [16]. Toxic effects of homocysteine on the vascular endothelium lead to reduced bioavailability and synthesis of nitric oxide, which promotes the development of hypertension [17].

It has also been demonstrated, that homocysteine increases the concentration of asymmetric dimethylarginine (ADMA) which is an inhibitor of nitric oxide synthesis [18]. Increased levels of homocysteine also damage the endothelium by inhibiting the regeneration of endothelial cells. It has been suggested that hyperhomocysteinemia inhibits the methylation of DNA and proteins, resulting in reduced cell division and the remaining endothelial cells in phase G1 of the cell cycle [18, 19]. Hyperhomocysteinemia also contributes to increased endothelial cell apoptosis [20]. Increased homocysteine concentrations at reduced NO bioavailability lead to myocyte proliferation. Excessive growth of smooth muscle cells in the vascular wall increases peripheral resistance and promotes hypertension [21]. The increased activity of some metalloproteinases favors increased collagen production, which in turn reduces the flexibility of vessel walls [22]. Increased homocysteine concentration leads to oxidative stress, and free radicals cause excess damage to structural proteins and vascular wall enzymes. A detailed analysis of the pathomechanism of endothelial damage by excessive homocysteine was presented by Baszczuk et al. [16].

Increased levels of homocysteine in blood in hypertension

The coexistence of hypertension and high homocysteine concentration significantly increases the risk of ischemic cardiac disease and stroke. Although basic studies have shown endothelial damage and decreased nitric oxide synthesis are caused by excessive homocysteine, clinical studies did not always confirm higher incidence of hyperhomocysteinemia in patients with hypertension. In several studies, usually involving smaller numbers of subjects, no correlation was found between serum homocysteine levels and arterial blood pressure [23, 24, 25]. On the other hand, numerous other studies have shown that serum homocysteine levels in patients with hypertension are significantly higher than in healthy individuals [26, 27, 28]. Thus, according to Kahleov et al., systolic blood pressure values in adolescents (mean age 19 years) significantly correlate with serum homocysteine levels [29]. On the other hand, Sutton-Tyrrell et al. showed a significant and independent correlation in the elderly between isolated systolic pressure and serum homocysteine levels [30]. The large Hordaland Homocysteine Study of 16,000 hypertensive patients showed a significant correlation between diastolic blood pressure and homocysteine levels [31].

Serum homocysteine levels were also found to be higher in patients with hypertension and simultaneously smoking cigarettes [32], diabetics [33], stroke patients [34] and dialysis patients [35] ($p < 0.05$) than in healthy subjects. In the years 1988–1994, the NHNES study examined more than 7,000 subjects and found a significant correlation between homocysteine concentration in the blood as well as in systolic and diastolic pressure [36]. One standard deviation of homocysteine concentration (5 μmol/l) is associated with an increase in systolic pressure of 0.7 mmHg and diastolic pressure of 0.5 mmHg in men and 1.2 and 0.7 mmHg in women, respectively.

Chinese researchers have conducted a detailed analysis of factors affecting homocysteine levels in patients with hypertension [37]. According to these authors, old age, high BMI, increased blood creatinine levels, smoking, high salt intake, elevated uric acid, and triglyceride levels correlate with increased homocysteine levels. Many of these elements affect both blood pressure and homocysteine levels. This argues for the important role of coexisting factors, apart from hypertension, on homocysteine serum levels.

Currently, a scientific discussion is held whether the increase in homocysteine in patients with hypertension is

statistically significant, and if is so, whether homocysteine and hypertension are causally related [38, 39]. Dinavahi et al. found a significant correlation between serum homocysteine levels and blood pressure in women only [23]. The significance of this correlation vanished after the age and BMI of the examined women were taken into account. In turn, Fakhrzadeh et al. observed higher homocysteine levels ($p < 0.031$) only in men with hypertension compared to those of healthy individuals [40]. Again, in this study, the statistical significance vanished after the interfering factors were taken into account. The already quoted study by Sutton-Tyrrell et al. showed a statistically significant correlation that is not dependent on the interfering factors between systolic pressure and serum homocysteine levels [30].

One progressive study examined whether elevated serum homocysteine levels in healthy individuals would cause more frequent development of hypertension in the future. This relationship turned out to be statistically significant in this study but vanished after taking into account the age, sex, and BMI of the subjects [25]. Other conclusions were reached by Tao et al., who observed 3,913 people without hypertension from 2012 to 2017 [41]. Baseline serum homocysteine was evaluated in all patients. After an average of 3.8 years, some of the observed people developed hypertension, with the baseline homocysteine level being most often higher.

Several researchers have demonstrated a significant relationship between serum homocysteine levels and arterial stiffness [42, 43]. A significant relationship was also found between peripheral and central systolic pressure values and serum homocysteine levels in over 3,900 healthy people. This relationship did not vanish after the interfering factors were considered. Similar conclusions were reached by Chinese researchers [44]. They also found a statistically significant correlation in 4,300 healthy subjects between central and peripheral systolic blood pressure and homocysteine serum levels. A particularly high correlation described above was observed in slim subjects [44]. The results obtained allowed the authors of this study to conclude that there is an independent relationship between the tested values. The causal relationship between homocysteine levels and arterial stiffness is also supported by the results of Wang et al., who had been observing almost 1,500 subjects for over 4 years [45]. Initially, homocysteine concentration in blood serum was determined in all patients, and at the end of the observation the pulse wave velocity was defined as a measure of arterial stiffness. The authors found a statistically significant correlation between the examined parameters, independent of interfering factors.

Serum homocysteine levels are significantly higher in the early stages of pregnancy in those women who later develop pregnancy-induced hypertension or develop pre-eclampsia. This was demonstrated by Sun et al., who observed 4,418 pregnant women with normal blood pressure, in whom serum homocysteine levels were determined between the 11th and 13th week of pregnancy [46]. In women with an average homocysteine level of 8.5 μmol/l, hypertension, or significant proteinuria developed in the later months of pregnancy, and in women with lower homocysteine levels (7.22 μmol/l) blood pressure values remained normal. Although the difference in homocysteine levels was slight, it turned out to be highly statistically significant ($p < 0.001$). Concentrations of folic acid and vitamin B12 were similar in both groups of patients studied.

Homocysteine and white coat and masked hypertension

Several authors assessed serum homocysteine levels in patients with white coat hypertension. According to Curgunl et al., homocysteine concentration in patients with white coat hypertension is 12.3 ± 1.1 μmol/l and is significantly higher than in healthy individuals, who have 5.35 ± 1.4 μmol/l ($p < 0.001$) [47]. In patients with established hypertension, homocysteine concentration is even higher, i.e., 19 ± 0.79 μmol/l, and is higher than in patients with white coat hypertension ($p < 0.001$). Similar results were obtained by Coban et al., who demonstrated that homocysteine concentration is significantly higher in patients with white coat hypertension than in healthy individuals ($p = 0.02$) but also significantly lower than in patients with established hypertension ($p = 0.03$) [48]. These data indicate that white coat hypertension may also be a risk factor for cardiovascular complications but much less than established hypertension.

According to Pierdomenoco et al., serum homocysteine concentration in patients with white coat hypertension does not differ significantly from that in healthy subjects (8 ± 2.0 and 7.6 ± 1.9 μmol/l, respectively) and is statistically significantly lower than in patients with established hypertension, who have 12.6 ± 3.9 μmol/l ($p < 0.0003$) [49].

Serum homocysteine concentration in patients with masked hypertension was evaluated by Yocel et al. [50]. According to these authors, homocysteine levels are higher in doctor's office (established) hypertension than in latent hypertension ($p = 0.02$). In addition, the authors have shown a higher homocysteine concentration in cigarette smokers (more commonly found in latent hypertension) than nonsmokers. The authors cited also found a small but statistically significant correlation between homocysteine levels and systolic blood pressure.

Administration of folic acid and blood pressure drop

Folic acid added to food significantly reduces serum homocysteine concentration. The addition of 0.5 to 5 mg of folic acid to food products reduces homocysteine levels by 25%. Vitamin B12 at a dose of 0.02 to 1 mg per day added to folic acid reduces homocysteine concentration by a further 7% [51].

The first studies suggested that a decrease in homocysteine concentration after folic acid administration is accompanied by a reduction in arterial pressure [52, 53], while a subsequent meta-analysis showed only a slight decrease of 2 mmHg in systolic blood pressure on the border of statistical significance [54]. However, it was demonstrated that high serum homocysteine concentration slightly but statistically significantly decreases the hypotensive efficacy of enalapril. In the CSPPT study involving 20,000 patients with hypertension, after 3 weeks of enalapril administration, systolic pressure decreased by 1.39 mm Hg in patients with homocysteine concentration above 10 μmol/l, and by 3.25 mm Hg in patients with homocysteine concentration below 10 μmol/l. This difference in enalapril efficacy persisted also after 15 weeks of therapy and 4.5 years of enalapril administration [55]. Subsequent studies have shown that concomitant administration of folic acid and hypotensive drugs reduces blood pressure more than hypotensive drugs without folic acid. This relationship was confirmed by Wang et al. in a meta-analysis [56], according to which simultaneous administration of folic acid with hypotensive drugs decreases blood pressure slightly more, but statistically significantly, than hypotensive drugs alone.

Homocysteine and night-time blood pressure drop

The majority of healthy and hypertensive patients demonstrate a decrease in blood pressure at night. In those patients whose night-time blood pressure drop is less than 10% compared to daytime pressure, the risk of cardiovascular complications is significantly higher [57].

The reason for lack of adequate reduction of night-time blood pressure is not fully explained. Several authors believe that elevated serum homocysteine levels contribute to this situation. Korkimaz et al. pointed out that patients with diabetes are more likely to experience a lack of adequate reduction of blood pressure at night, and at the same time, diabetes is more likely to result in elevated serum homocysteine levels than is the case in healthy individuals [58]. These researchers compared serum homocysteine levels in 50 patients with diabetes and hypertension and in 35 healthy subjects. In all subjects, daily blood pressure measurements were taken using the ABPM method, and in the morning serum homocysteine levels were determined. The patients with diabetes and hypertension included 72% of non-dipper patients (i.e., without a decrease in blood pressure at night), and 57% of non-dippers were in the control group. Homocysteine concentration in the non-dipper patients was 13.4 ± 8.1 μmol/l, and in healthy dipper patients it was lower, i.e., 11.8 ± 5 μmol/l. Although the difference in homocysteine concentration was not statistically significant, the authors of the study believe that it should be repeated in more patients to explain the effect of homocysteine on blood pressure variability.

The Italian authors tried to explain this issue. To this end, they administered 15 mg of active folates (to lower homocysteine levels) in 15 healthy menopausal women for 3 weeks, and another 15 women were given placebo [59]. Blood pressure was measured in all patients using the ABPM method; homocysteine, insulin, glucose, and triglycerides were measured at the beginning and end of the study. Increased folate supply caused a statistically significant decrease in systolic and diastolic blood pressure at night (4.5 mm ± 1.8 mm Hg and 5.3 ± 1.3 mm Hg, respectively). Blood pressure during the day did not change significantly. The difference between systolic pressure during the day and night increased by 6.9 ± 4.81 mm, the corresponding difference for diastolic pressure was 5.7 ± 6.0 mm Hg. All these differences turned out to be statistically significant. In addition, the pressure difference between day and night was greater in non-dippers (6.1 ± 2.3 than in dippers (0.35 ± 0.88 mm Hg, p = 0.012). Folate therapy also caused a decrease in insulin concentration, and insulin resistance (assessed by the HOMA method).

In the next work, the authors cited tried to explain the reasons for the drop in blood pressure described after an increased supply of folates [60]. For this purpose, they determined free oxygen radicals (free oxygen radicals test FORT) and the ability of the system to remove them (free oxygen radicals defense FORD). After folate administration, the FORT value dropped from 397 ± 74 to 326 ± 82 (p = 0.008), while the FORD value increased from 0.85 ± 0.32 to 1.35 ± 0.94 (p = 0.07). The authors showed a statistically significant positive correlation between a decrease in the amount of free oxygen radicals and a reduction in diastolic pressure at night (r = 0.777, p = 0.002). Thus, a large amount of free oxygen radicals inhibits the pressure drop at night, while the reduced amount caused by folate administration correlates to the reduction of pressure at night. The high correlation (r = 0.777) between the parameters tested is noteworthy.

The results of these studies have been confirmed in the work of Dong Yi-Fey et al. [61]. These authors randomly selected 244 patients with normal nighttime blood pressure drop (blood pressure drop greater than 10%, dippers) and 249

patients with abnormal nighttime blood pressure drop (non-dippers) from 5,223 hypertensive patients. Moreover, from the group of 1,858 patients with hypertension, 390 patients with CT/CC genotype of MTHFR gene and 79 patients with TT genotype of this gene were randomly selected. In all patients, the 24 h blood pressure profile was assessed using the ABPM method. The group of non-dipper patients was characterized by a significantly higher homocysteine concentration than in patients with normal night pressure drop $p < 0.0001$). Moreover, the authors showed a significant negative correlation between homocysteine concentrations and the systolic and diastolic night-time blood pressure drop ($p = 0.001$ and $p = 0.002$, respectively). Multidimensional logistic regression showed that the relationship between homocysteine and blood pressure variability is independent of many other interfering factors. With a homocysteine concentration of 10 micromoles as a limit, 36% of non-dippers are below this value and 54.24% of non-dippers at a concentration above 10 µmol/l. Homocysteine concentrations are higher in patients with the TT MTHFR gene polymorphism than in other patients with CC and CT polymorphism of this gene. The percentage of patients with the CC/CT genotype is significantly lower in dippers than in non-dippers ($p < 0.024$).

On the basis of the studies presented, it can be concluded that serum homocysteine concentrations are probably among the factors influencing daily blood pressure fluctuations.

Patients with obstructive sleep apnea are characterized by frequent hypertension, especially at night (non-dippers) and simultaneously elevated homocysteine levels (36). Treatment of obstructive sleep apnea with an air denture (CPAP) reduces blood pressure, especially at night, along with homocysteine levels [62]. It cannot be ruled out that the increased serum homocysteine levels of these patients, in addition to other factors, may interact with nighttime increases in blood pressure.

Administration of folic acid in the preventions of strokes

Although the frequency of cardiovascular complications is much higher in patients with high serum homocysteine levels, the first studies did not show that lowering the concentration of this compound in the blood resulted in a lower risk of cardiovascular complications. The results of large prospective studies in which vitamin B was administered and a significant reduction of homocysteine concentration was achieved were disappointing; the number of cardiovascular complications did not decrease or even increased slightly and insignificantly [63, 64]. However, subsequent large randomized trials showed that the reduction of homocysteine in serum significantly reduces the risk of stroke but does not reduce the risk of myocardial infarction. In the HOPE 2 study, which included patients with a history of cardiovascular events, administration of folic acid in a dose of 2.5 mg, vitamin B6 in a dose of 50 mg and vitamin B12 in a dose of 1 mg resulted in a 25% reduction in stroke but did not affect the risk of heart disease [65]. The largest of these studies, the China Stroke Primary Prevention, covering 20,000 hypertensive patients without other cardiovascular disease, showed that daily administration of 0.8 mg/day of folic acid significantly reduced the risk of stroke [66]. In patients with high cholesterol levels, the administration of folic acid reduced the risk of stroke by 30% [67]. In recent years several large meta-analyses have been published, all of which stated that folic acid therapy and possibly with the addition of other B vitamins reduces the risk of stroke by 10%–15% [56, 68, 69]. A meta-analysis by Wanga et al. assessed the efficacy of folic acid supplementation among patients with hypertension and hyperhomocysteinemia (homocysteine >10 µmol/l) [56]. The authors included RCTs, examining the effects of folic acid plus antihypertensive therapy compared with the therapy alone. The meta-analysis showed that folic acid supplementation significantly reduced the risk of cardiovascular and cerebrovascular events by 12.9% compared with the control group. A bigger beneficial effect was seen in those RCTs with treatment duration longer than 12 weeks, and a decrease in the concentration of total homocysteine of more than 25%. Similar results are presented by Li et al. [68]. In this meta-analysis involving more than 80,000 people, the authors showed that the administration of folic acid reduces the risk of stroke by 10% and cardiovascular complications by 4% compared with controls ($p = 0.002$).

Zhao's meta-analysis confirmed that the use of vitamin B statistically significantly reduces the risk of stroke by 11% [70]. Interestingly, lower doses of folic acid (< 0.8 mg/day or low baseline vitamin B_{12} levels <384 pg/ml) were more effective than higher doses. This observation requires confirmation in subsequent studies.

The meta-analyses mentioned concerned patients with uncomplicated arterial hypertension as well as with arterial hypertension and other cardiovascular diseases.

Strokes are more common in patients with hypertension and diabetes than in patients with hypertension alone [71]. Folic acid supplementation in patients with diabetes and hypertension in the study of Xu et al. decreased the risk of stroke by 34% [71]. In Meng et al., on the other hand, such therapy significantly reduced atherosclerotic changes in the retina compared to those in patients without this supplementation [72].

Folic acid and kidney diseases

Arterial hypertension often damages the kidneys and may lead to kidney failure. According to Li et al., folic acid supplementation in patients with hypertension significantly reduced the occurrence of proteinuria [73]. In 20,000 hypertensive patients observed during 4.5 years proteinuria occurred in 213 (3.9%) of patients treated with enalapril and in 188 (3.5%) of patients treated with enalapril and additionally with folic acid. In the subgroup of patients with hypertension and diabetes, proteinuria occurred in 7.4% of patients treated with enalapril and in 3.7% of patients treated with enalapril with folic acid. The authors also observed significant slowdown in progression of renal failure in patients receiving folic acid (p = 0.002). Simultaneous addition of folic acid to enalapril significantly reduced mortality in patients with hypertension and severe proteinuria (6.4% vs 10.8%) [74]. However, two meta-analyzes examining the effects of folic acid administration in kidney disease have produced conflicting results [75, 76]. First, meta-analysis indicates that folic acid supplementation may be effective for CVD prevention in patients with kidney disease [76]. Second, meta-analysis concluded folic acid supplementation does not reduce the risk of myocardial infarction or stroke in patients with chronic kidney disease, and might have no effect on mortality [75].

Knowledge of the interactions between hypertension and serum homocysteine levels is growing and may be important not only for understanding the pathomechanisms of these diseases but may also be useful in the clinical practice.

Conclusions

The high concentration of homocysteine in the blood serum is associated with arterial hypertension.

Higher levels of homocysteine were also found in patients with white coat hypertension and without physiological blood pressure drop in the night hours.

Folic acid supplementation reduces the concentration of homocysteine in blood serum and can, therefore, reduce the risk of stroke, which is why it should be more widely used in clinical practice.

Most of the studies on blood homocysteine levels in patients with hypertension come from China. Large prospective studies in Europe on the efficacy of folic acid in the prevention of stroke are desirable.

Authors' Contribution

J.G.: Research concept and design, supervising the project, writing the manuscript, drafting the article critically for important intellectual content, final proofreading, and approval of the version for publication; T.K.: Drafting the article critically for important intellectual content, literature review, final proofreading, and approval of the version for publication.

Conflict of Interest

The authors have no potential conflicts of interest to declare.

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