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"THE ROLE OF HOMOCYSTEINE IN THE DEVELOPMENT OF TARGET ORGAN DAMAGE IN ARTERIAL HYPERTENSION AND ITS ASSOCIATION WITH METABOLIC AND INFLAMMATORY MARKERS"

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Revised English version (scientific style, IMRAD abstract):

Relevance. Arterial hypertension (AH) is a leading cause of cardiovascular morbidity, while target organ damage largely determines its prognosis. Homocysteine is considered a potential marker of vascular injury; however, its role in clinical risk stratification in AH remains insufficiently studied.

Aim. To evaluate the association between homocysteine levels and target organ damage in arterial hypertension, as well as its relationship with metabolic, inflammatory, and coagulation parameters.

Materials and Methods. A prospective cohort study was conducted involving 111 participants (60 patients with AH and 51 without AH). Serum homocysteine levels, inflammatory markers, lipid profile parameters, oxidative stress indicators, and indices of vascular damage were assessed. Statistical analysis included Pearson correlation with adjustment for confounders.

Results. Homocysteine levels were significantly higher in patients with AH. Significant correlations were found between homocysteine and hs-CRP ($r = 0.70$; $p < 0.01$), total cholesterol ($r = 0.58$; $p < 0.01$), LDL cholesterol ($r = 0.46$; $p < 0.01$), triglycerides ($r = 0.33$; $p < 0.05$), atherogenic index ($r = 0.50$; $p < 0.01$), fibrinogen ($r = 0.49$; $p < 0.01$), and glucose ($r = 0.30$; $p < 0.05$), as well as a negative correlation with the ankle–brachial index ($r = –0.52$; $p < 0.01$). These associations remained significant after multivariate adjustment.

Conclusion. Homocysteine is associated with a spectrum of metabolic, inflammatory, and vascular alterations in arterial hypertension and may serve as a potential biomarker of target organ damage and cardiovascular risk stratification.

Keywords: arterial hypertension, homocysteine, target organ damage, endothelial dysfunction, inflammation, atherosclerosis, vascular stiffness

Relevance. Vascular alterations resulting from long-term elevation of arterial blood pressure are a hallmark of arterial hypertension and represent one of the earliest manifestations of target organ damage. Arterial stiffness is regarded as an important indicator of vascular health, while

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early detection of target organ damage in hypertension has additional prognostic value for adverse cardiovascular outcomes both in hypertensive patients and in the general population.

Homocysteine is a sulfur-containing amino acid first described in 1932. It is formed from methionine and is metabolized through three main pathways: transsulfuration (vitamin B6-dependent), remethylation (folate- and vitamin B12-dependent), and release into plasma, which determines its circulating concentration. Mendelian randomization studies have shown that homocysteine levels are higher in patients with arterial hypertension than in normotensive individuals, suggesting a potential causal relationship. [1]

Homocysteine has been associated with measures of arterial stiffness, including pulse pressure and aortic stiffness, both in the general population and in elderly individuals with multiple cardiovascular risk factors. In addition, homocysteine is linked to impaired circadian blood pressure patterns, which represent an important predictor of cardiovascular mortality. Elevated homocysteine levels are also correlated with the incidence of cardiovascular, cerebrovascular, and peripheral arterial diseases, as well as with atherosclerotic vascular damage.

Hyperhomocysteinemia is associated with microvascular endothelial dysfunction, and homocysteine levels above 10 μmol/L have been linked to increased all-cause mortality and a higher risk of cardiovascular events in elderly patients with obesity and arterial hypertension.

Several mechanisms have been proposed to explain the relationship between homocysteine and target organ damage. These include direct toxic effects on the vascular wall, interaction with lipoprotein(a), enhanced cholesterol synthesis, oxidative modification of LDL, and impaired endothelium-dependent vasodilation due to reduced nitric oxide bioavailability.

An important role is also attributed to activation of the renin–angiotensin–aldosterone system. It has been shown that aldosterone stimulates homocysteine production, forming a positive feedback loop. Aldosterone exerts direct vascular damage and promotes fibrosis independently of hemodynamic effects.

Experimental studies have demonstrated that homocysteine impairs shear stress–induced vasodilation and reduces nitric oxide production by activating angiotensin II signaling pathways via AT1 receptors. Conversely, blockade or genetic deletion of AT1 receptors attenuates vascular injury and pathological myocardial hypertrophy.

Homocysteine is an independent risk factor for cardiovascular and cerebrovascular diseases and is considered a contributor to vascular dysfunction.

Aim. The aim of this study was to determine, in real-world clinical practice, whether homocysteine levels are associated with target organ damage in arterial hypertension and whether this parameter can be used to guide hypertension treatment strategies.

A cross-sectional analysis of prospectively collected data was performed in 60 patients with arterial hypertension and 51 patients without arterial hypertension. The association between homocysteine levels, target organ damage, and the status of the renin–angiotensin–aldosterone system (RAAS) was assessed.

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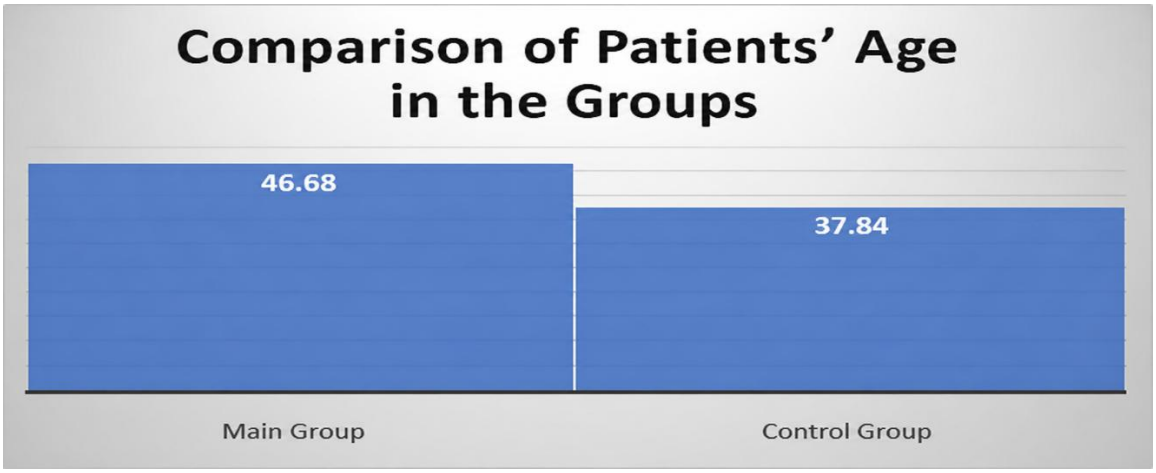
Materials and Methods. The study was conducted in three stages.
At the first stage, 1,495 employees of "UZAGROTEHMASH" aged 25 to 65 years were examined. Among all examined individuals, 598 had elevated blood pressure; of these, 60 were newly diagnosed with arterial hypertension, accounting for 10%. The mean age of patients with newly diagnosed hypertension was 46.68±1.12 years, and the mean work experience was 16.9±0.7 years.

The second stage involved an in-depth comprehensive examination of patients with newly diagnosed arterial hypertension based on the initial screening. The diagnosis of hypertension was established using combined clinical, laboratory, and instrumental methods.

The third stage evaluated the effectiveness of an algorithm for early detection of arterial hypertension and measures of its primary and secondary prevention in primary healthcare settings.

Effectiveness was assessed in two groups: the main group included 60 patients who underwent the proposed primary and secondary prevention strategy for hypertension, while the comparison group consisted of 51 patients who did not receive preventive intervention.

Results and Discussion. The mean age of participants was 46.68±1.12 years. Comparative analysis showed that patients in the main group were significantly older than those in the control group (46.68±1.12 vs. 37.84±1.68 years, respectively; $p<0.001$).



Correlation analysis showed that homocysteine levels were significantly associated with indicators of vascular damage and the homocysteine-to-cholesterol ratio. These associations remained significant after adjustment for age, sex, blood pressure level, inflammation, smoking, diabetes mellitus, and dyslipidemia.

Table: Pearson correlation coefficients (significance based on number of correlated pairs)

indicator	Pearson correlation coefficients (significance based on the number of

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	correlated pairs)				
Groups/ Correlation	**Age (main/control groups)**	**Correlation with BMI**	**Correlation with homocysteine**	**Correlation with MDA (malondialdehyde)**	**Correlation with CRP (C-reactive protein)**
Age	-	-	-	-	-
BMI	0,12 0,45**	-	-	-	-
Gomosisten	0,16 0,18	0,47** 0,43**	-	-	-
MDA	-0,10 -0,33**	0,04 -0,27*	-0,07 -0,01	-	-
Total cholesterol (TC)	0,04 0,24	0,22 0,27*	0,58** 0,11	-0,10 -0,07	-0,03 0,57**
HDL	-0,15 0,04	-0,10 -0,09	-0,23 -0,14	0,15 0,00	0,05 -0,12
LDL	0,21 0,18	0,28* 0,01	0,46** 0,13	-0,08 -0,12	0,02 0,41**
Triglycerides (TG)	-0,02 0,14	0,23 -0,12	0,33* -0,27*	-0,13 -0,35**	0,17 0,23
Atherogenic index	0,09 0,06	0,19 0,21	0,50** 0,18	-0,14 -0,02	-0,03 0,40**
High-sensitivity C-reactive protein (hs-CRP	0,04 0,23	0,51** 0,38**	0,70** 0,14	-0,03 -0,22	0,24 -0,17

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Apolipoprotein A-I	-0,03 -0,08	-0,26 0,15	-0,17 0,16	0,08 -0,07	0,25 0,02
Apolipoprotein B	-0,07 0,06	0,07 0,01	0,41** -0,16	0,02 0,08	-0,10 0,00
Fibrinogen	0,14 0,35**	0,28* 0,23	0,49** -0,02	-0,08 -0,16	-0,02 0,46**
Fibrinogen	0,00 -0,36**	-0,44** -0,03	-0,52** 0,06	0,14 -0,16	-0,11 -0,30*

In the main group, BMI demonstrated strong positive correlations with homocysteine ($r=0.47$; $p<0.01$), high-sensitivity C-reactive protein (hs-CRP) ($r=0.51$; $p<0.01$), glucose ($r=0.49$; $p<0.01$), fibrinogen ($r=0.28$; $p<0.05$), and bilirubin ($r=0.42$; $p<0.01$), as well as a negative correlation with the ankle-brachial index (ABI) ($r=-0.44$; $p<0.01$).

A moderate positive correlation was observed between BMI and homocysteine levels ($r=0.47$; $p<0.01$). This reflects an association between increased body mass and elevated homocysteine levels. In overweight patients, endothelial dysfunction is more pronounced, creating conditions for vascular remodeling.

This relationship supports the involvement of hyperhomocysteinemia in the cardiometabolic continuum in patients with arterial hypertension (AH). In the main group of patients with AH, correlation analysis revealed statistically significant positive associations between body mass index (BMI) and several metabolic and inflammatory parameters.

These findings indicate that increased body weight is closely associated with enhanced systemic inflammation, impaired glucose metabolism, activation of the coagulation pathway, and deterioration of vascular function.

In the main group, homocysteine showed strong positive correlations with malondialdehyde (MDA) ($r=0.04$ — weak, but negative in the control group), total cholesterol ($r=0.58$; $p<0.01$), low-density lipoprotein cholesterol (LDL-C) ($r=0.46$; $p<0.01$), triglycerides (TG) ($r=0.33$; $p<0.05$), atherogenic index ($r=0.50$; $p<0.01$), hs-CRP ($r=0.70$; $p<0.01$), glucose ($r=0.30$; $p<0.05$), apolipoprotein B (ApoB) ($r=0.41$; $p<0.01$), fibrinogen ($r=0.49$; $p<0.01$), and a negative correlation with ABI ($r=-0.52$; $p<0.01$).

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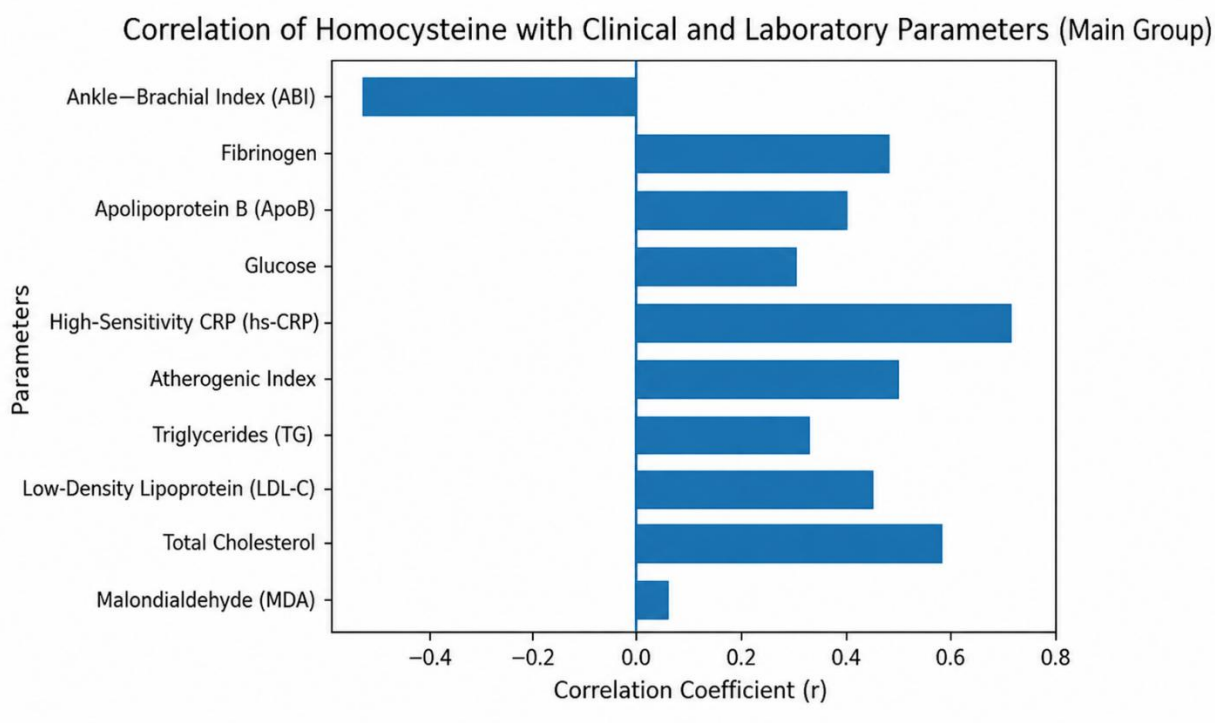

The identified correlation relationships indicate that homocysteine is an integrative biomarker reflecting the combined influence of inflammatory, metabolic, lipid, and coagulation disorders in patients with arterial hypertension. Its elevation is associated with the progression of atherosclerosis and vascular remodeling.

A weak positive correlation with MDA ($r = 0.04$) was observed, whereas an inverse correlation was noted in the control group. This may indicate a transition from physiological balance to pathological activation of oxidative stress, as well as the involvement of homocysteine in the generation of free radicals.

Significant positive correlations were found:
- with total cholesterol ($r = 0.58$; $p < 0.01$)
- with LDL ($r = 0.46$; $p < 0.01$)
- with triglycerides ($r = 0.33$; $p < 0.05$)
- with the atherogenic index ($r = 0.50$; $p < 0.01$)
- with apolipoprotein B ($r = 0.41$; $p < 0.01$)

These findings indicate a close association between hyperhomocysteinemia and atherogenic dyslipidemia, enhanced atherosclerotic processes, and an increased number of atherogenic lipoprotein particles.

A strong positive correlation was identified with hs-CRP ($r = 0.70$; $p < 0.01$), the most pronounced among all parameters. This relationship reflects the association of homocysteine with chronic inflammation, activation of pro-inflammatory cytokines, and its involvement in the development of atherosclerotic processes. This allows us to conclude that homocysteine is not only a metabolic but also an inflammatory marker.

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A positive correlation was also found with glucose levels ($r = 0.30$; $p < 0.05$), suggesting an association between hyperhomocysteinemia and insulin resistance, as well as its role in the development of metabolic syndrome and a potential contribution to endothelial dysfunction via hyperglycemia.

A moderate positive correlation was observed with fibrinogen ($r = 0.49$; $p < 0.01$), indicating activation of the coagulation pathway and the development of a prothrombotic state. Thus, homocysteine increases the risk of vascular complications through its effects on hemostasis.

A moderate negative correlation was identified with the ankle–brachial index (ABI) ($r = -0.52$; $p < 0.01$).

A negative correlation indicates impaired peripheral blood flow with increasing homocysteine levels and the presence of subclinical atherosclerosis. Thus, the higher the homocysteine level, the lower the ABI and the poorer the vascular patency.

The obtained data demonstrate that homocysteine is a central nodal factor integrating multiple pathogenetic mechanisms. These linear associations between homocysteine levels and markers of target organ damage remained significant after adjustment for age, sex, ambulatory blood pressure parameters, inflammatory status, smoking, diabetes mellitus, and lipid profile (Fig. 1).

Our results indicate that homocysteine levels are clearly associated with well-established markers of target organ damage in arterial hypertension. Importantly, these associations persisted independently of age, sex, ambulatory blood pressure, inflammation, smoking, diabetes mellitus, and dyslipidemia. In addition, the study demonstrated that homocysteine levels are associated with arterial stiffness.

In current clinical guidelines, homocysteine is not considered a tool for cardiovascular risk stratification. However, prospective studies have shown that elevated homocysteine levels predict adverse cardiovascular events independently of the Framingham risk score, suggesting its potential role as an emerging biomarker of risk.

From a pathophysiological perspective, several mechanisms of homocysteine-related vascular dysfunction have been proposed, including its direct toxic effects as well as indirect effects mediated through activation of the renin–angiotensin–aldosterone system (RAAS). Elevated homocysteine levels inhibit endothelium-dependent vasodilation via inactivation of nitric oxide [3,4]. In addition, homocysteine inactivates calcium-dependent potassium channels in resistance vessels and impairs endothelium-dependent hyperpolarization [5]. It also activates metalloproteinases, stimulates collagen synthesis, and alters the elastin/collagen ratio, leading to reduced vascular wall elasticity [2]. Furthermore, homocysteine has been shown to attenuate bradykinin-mediated changes in blood flow, vascular resistance, and arterial pressure [7].

Positive associations between homocysteine levels and atherosclerosis in patients with type 2 diabetes mellitus [8], as well as increased aortic stiffness in patients with arterial hypertension [9,10], have been reported. Our study also demonstrated that even within physiological

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concentrations, homocysteine is significantly associated with both macrovascular and microvascular damage.

Homocysteine plays an important role in vascular metabolism, as methionine is required for the formation of S-adenosylmethionine and for DNA and protein methylation. Homocysteine is metabolized via cystathionine-γ-lyase with the formation of hydrogen sulfide (H_2S), a potent vasodilator and endogenous inhibitor of endothelial ACE activity [2,6]. In contrast, cysteine serves as a substrate for enzymes involved in H_2S synthesis (cystathionine-β-synthase and cystathionine-γ-lyase), which also inhibit endothelial ACE activity [2].

In hyperhomocysteinemia, damage and inactivation of modified cystathionine-γ-lyase occur, leading to reduced H_2S production [6]. This may explain the attenuated antihypertensive effect of ACE inhibitors at high homocysteine concentrations [3].

Conclusion: Thus, it is suggested that homocysteine levels may influence RAAS signaling pathways and modify the effectiveness of antihypertensive therapy, particularly RAAS-blocking agents. From a clinical perspective, homocysteine may be considered not only as a marker of vascular damage but also as a potential tool for selecting first-line antihypertensive therapy, with angiotensin receptor blockers (ARBs) potentially being preferable in patients with homocysteine levels above 10 μmol/L.

However, further prospective studies are required to confirm these hypotheses and to evaluate the impact of homocysteine on the effectiveness of antihypertensive treatment.

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