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Hyperhomocysteinemia: a variability factor of the daily blood pressure profile in patients with arterial hypertension and excess body weight

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ABSTRACT:

Introduction. Arterial hypertension in patients with excess body weight is associated with a rapid progression of cardiovascular events.

The aim. To determine the effect of homocysteine on the daily profile of blood pressure and blood glucose and its dependence on the level of anxiety.

Materials and methods. 103 patients (52 women and 51 men) with arterial hypertension and excess body weight were examined. A laboratory blood test, Holter monitoring of blood pressure were conducted, levels of personal and reactive anxiety were determined.

Results. The average level of homocysteine in patients was 14.3±6.0 μmol/l, and was 1.6 times higher than in healthy individuals. Hyperhomocysteinemia was found in 37% of patients. On average, they had a higher level of glycemia (6.2±0.9 mmol/l vs 5.7±0.8 mmol/l), average daily systolic blood pressure (128.0±10.7 mmHg vs 121.5±10.1 mmHg) and variability of both systolic (respectively, 18.9±4.4 vs 15.1±2.5) and diastolic blood pressure (16.8±3.5 vs 12.8±1.8); personal (respectively, 43.3±6.3 points vs 38±6.4 points;) and reactive anxiety (38.2±4.6 points vs 34.1±5.2). A mathematical model for forecasting hyperhomocysteinemia in overweight patients has been developed, which allows to identify a group of patients (about 62%) with a high risk of developing complications.

Conclusion. Hyperhomocysteinemia was found in 37% of patients with arterial hypertension and excess body weight. These patients were distinguished by higher anxiety, higher blood glucose levels, high variability of the daily blood pressure profile, which increases the risk of cardiovascular events..

Arterial hypertension (AH) in overweight patients is associated with a rapid progression of cardiovascular events (Chrysant)[1]. It is considered that adipose tissue acts as an independent endocrine organ and a source of fatty acids, triglycerides and low-density lipoproteins, affects the state of the vascular wall and the function of the myocardium regardless of the level of blood pressure (BP)[2,3]. Changes in carbohydrate metabolism, such as impaired carbohydrate tolerance, metabolic syndrome, and type 2 diabetes, are more common in patients with hypertension and excess body weight than in patients with normal body weight [4, 5].

Homocysteine (HC) metabolism can be considered as an epigenetic factor in the development of pathological processes in humans due to the changes in the levels of methionine, proteins and DNA methylation [6]. Metabolic disorder of HC leads to the development of hyperhomocysteinemia (HHC), which is primarily associated with an increase in the

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formation of free radicals, mitochondrial dysfunction and oxidative stress. Systemic immune inflammation occurs, which causes the development of cardiovascular diseases, in particular coronary heart disease (CHD), systemic atherosclerosis, ischemic stroke or myocardial infarction, increases the risk of thrombosis, etc. [7].

HC is formed from the essential amino acid methionine [8]. HC metabolism occurs in two ways: remethylation to methionine (requires the presence of folic acid and vitamin B12) and transulfuration to cystathion (requires the presence of vitamin B6). Homocysteine metabolism is coordinated by S-adenosylmethionine, which acts as an allosteric inhibitor of methylenetetrahydrofolate reductase (MTHFR) and an inducer of cystathion beta-synthase (CBS)
(Fig. 1).

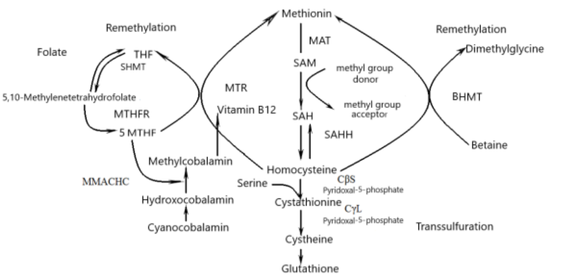

Figure 1. Metabolism of homocysteine (BHMT - Betaine homocysteine methyltransferase, CγL - Cystathionine gamma-lyase, CβS- Cystathionine beta synthase, MAT - Methionine adenosyltransferase, MMACHC - cblC complementation group, MTHFR - 5,10-methylene-THF reductase, MTR – Methyltransferase, SAH - S-adenosylhomocysteine, SAHH - S-adenosylhomocysteine hydrolase, SAM – *S*-adenosylmethionine, SHMT – serinehydroxymethyltransferase, THF – tetrahydrofolate).

Moderate HHC occurs due to metabolic disorder of HC, severe HHC is associated with genetic defects, in particular with congenital deficiency of MTHFR and CBS. HHC can be a consequence of overeating, deficiency of folic acid, vitamin B12, and to some extent, a result of vitamin B6 deficiency, which affects methionine metabolism [9].

The aim of our study was to determine the effect of homocysteine on the daily profile of blood pressure and blood glucose and its dependence on the level of anxiety.

Materials and methods. 103 patients (52 women and 51 men) with hypertension and body
mass index (BMI)>25 kg/m^2 were examined. The control group (n=30) consisted of healthy individuals, similar in terms of age and gender.

The average age of the patients was 53.5±6.0 years. The examination plan included a
laboratory blood test with the determination of the level of hemoglobin (Hb), fasting blood glucose, transaminases and a lipidogram. Holter monitoring of blood pressure was carried out using ABPM 50 device (HEACO). Using the Spielberger scale, the levels of personal (PA) and reactive anxiety (RA) were determined. Total peripheral vascular resistance (PVR) was determined using the formula PVR (dynes×sec/ml) = 1332 x BPaverage/ MBV, where MBV is the minute volume of blood circulation [10, 11].

The level of homocysteine by the method of an enzymatic cyclic reaction using a mixture of reagents (S-adenosylmethionine (SAM), 0.1 mmol/l; NADH, 0.2 mmol/l; TCEP, 0.5 mmol/l; 2-oxoglutarate, 5 mmol/l; Glutamate dehydrogenase, 10 kU/l; SAH-hydrolase, 3 kU/l; Adenosine deaminase, 5 kU/l; Homocysteine methyltransferase, 5 kU/l) (DiaSys Diagnostic Systems GmbH, Germany)[12]. Reference values for women – homocysteine level up to 14 µmol/l, for men – up to 16 µmol/l [13, 14].

The Statistica 10 program (StatSoft Inc., USA) was used for statistical processing of the obtained data. Independent samples were compared using the Mann-Whitney (U) test. In all cases of statistical evaluation, the reliability of differences was considered at a value of $p<0.05$.

Results and discussion

The level of HC in patients with hypertension and high BMI was, on average, 14.3±6.0 µmol/l vs. 8.9±1.9 µmol/l in the control group, with no significant difference ($p>0.05$).
(Fig. 2)

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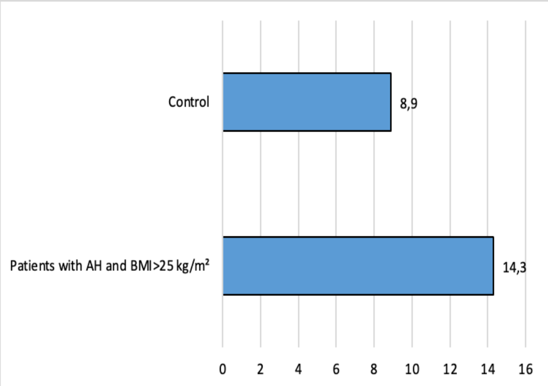

Figure 2. Homocysteine level (µmol/l) in patients with arterial hypertension and BMI>25kg/m^2 and in the control group.

Hyperhomocysteinemia was detected in 37% of patients with hypertension and BMI>25 kg/m^2.

Patients with hypertension and high BMI were divided into groups depending on the level of homocysteine. Patients with hypertension and high BMI with a normal level of homocysteine were included in the group I, and patients with hyperhomocysteinemia in the group II.

During the analysis of laboratory data indicators and the results of clinical-instrumental studies, probable differences in some parameters were revealed (Table 1).

Table 1

Examination results in patients with hypertension and high BMI depending on the level of homocysteine

Indicators	Distribution of patients by groups		P
	I	II	
Age, years	55,0±8,6	50,7±11,7	0,137
Hb, g/l	138,6±13,8	147,8±15,0	0,031
Glucose, mmol/l	5,7±0,8	6,2±0,9	0,047
SBP average, mmHg.	121,5±10,1	128,0±10,7	0,036
DBP average, mmHg.	73,9±6,5	77,1±9,7	0,176
Variability SBP	151±2,5	18,9±4,4	<0,001
Variability DBP	12,8±1,8	16,8±3,5	<0,001

The level of hemoglobin was probably higher among patients with HHC (g/l 147.8±15.0 vs. 138.6±13.8 g/l; p=0.031), the level of glucose (6.2±0.9 mmol/l vs. 5.7±0.8; p=0.047).

During daily blood pressure monitoring, it was found that patients with HHC had significantly higher levels of systolic blood pressure (128.0±10.7 mmHg vs. 121.5±10.1 mmHg; p=0.036), diastolic blood pressure – no significant difference was found, although this indicator was also a bit higher in patients of the II group (77.1±9.7 mmHg vs. 73.9±6.5 mmHg; p= 0.176). A significantly higher variability of both systolic and diastolic blood pressure was also found among patients of the II group (respectively, 18.9±4.4 vs. 15.1±2.5; p<0.001 and 16.8±3.5 vs. 12.8± 1.8; p<0.001 and p=0.00001).

It is noted the high level of anxiety in patients with arterial hypertension, which may require medication correction to achieve better control of blood pressure levels (Fig. 3).

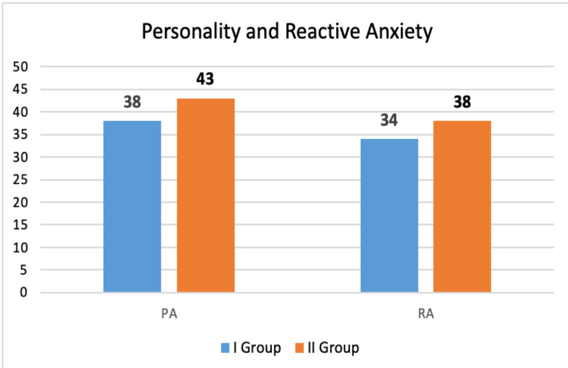

Figure 3. Level of anxiety in examined patients with arterial hypertension and BMI>25 kg/m^2 in different groups.

In all patients with hypertension and high BMI, on average, the level of personal anxiety (PA) was increased (38±6.4 and 43.3±6.3; p= 0.012), patients with HHC had significant differences. The level of reactive anxiety (RA) was also significantly higher in patients with HHC (38.2±4.6 vs. 34.1±5.2; p=0.007).

Patients with arterial hypertension often suffer from headaches (Fig. 4).

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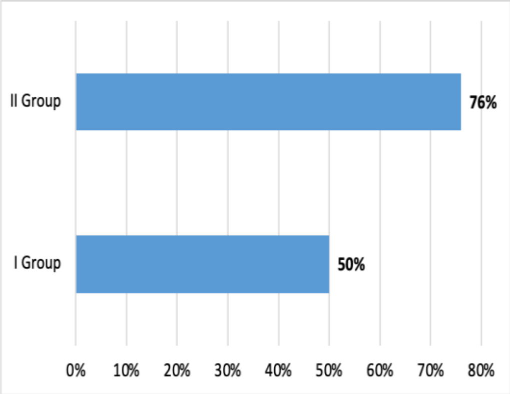

Figure 4. Frequency of headache complaints in examined patients with arterial hypertension and BMI>25 kg/m^2 in different groups.

Patients with arterial hypertension and high BMI who had HHC experienced headache 1.5 times more often than patients with normal levels of HC (76% vs. 50%; p=0.03).

Therefore, when determining the level of homocysteine in patients with arterial hypertension and obesity or excess body weight, differences in indicators of laboratory and instrumental methods of research, as well as psycho-emotional state, were found. Since it is known that HHC can independently be considered as a risk factor for complications of arterial hypertension, the determination of this indicator is relevant for the forecast of the course of the disease. However, not all patients in this category have HHC, and the method itself is not routine and requires additional financial costs. In order to identify patients with a high probability of HHC, a mathematical calculation of the forecasted high level of homocysteine was used, and a multiple logistic regression equation was applied.

As a result of multiple logistic regression, a formula for calculating the probability (forecast) of the development of a high level of homocysteine (Y) depending on 11 indicators, where Y is the theoretical probability of the development of HHC was obtained.

$$Y = 0{,}002448 \times Hb + 2{,}13429 \times Gl + 0{,}1762 \times SBPaverage + 0{,}1249 \times StandDevSBP + 0{,}7577 \times StandDevDBP + 0{,}2011 \times PA + 0{,}1613 \times RA - 1{,}2831 \times HA + 0{,}01703 \times ALT - 0{,}09893 \times Age - 0{,}2312 \times DBPaverage - 38{,}74$$

where:

Hb – hemoglobin, g/l;
Gl – blood glucose, mmol/l;
SBP average - the average daily level of systolic blood pressure level, mmHg;
StandDevSBP – standard deviation of systolic blood pressure;
StandDevDBP – standard deviation of diastolic blood pressure;
PA - level of personal anxiety;
RA – level of reactive anxiety;
HA - complain of headache;
ALT – alanine transferase, U/L;
Age of the patient, years;
DBPaverage - the average daily level of diastolic blood pressure level, mmHg;

The accuracy of the model is 94%. Belonging to group 0 - "low HC" is determined by the model with 97% accuracy, and belonging to group 1 - "high HC" - with 89% accuracy, area under the curve AUC = 0.956 (0.859 - 0.994), chi-square = 42,6, P < 0.001. The model has a very high predictive power.

When applying the HHC forecast formula for patients with hypertension and a high body mass index, it was found that in 60% of cases, patients have a high probability of HHC, in 2% - received a dubious result, and in 38% - probably a normal level of HHC (Fig. 5).

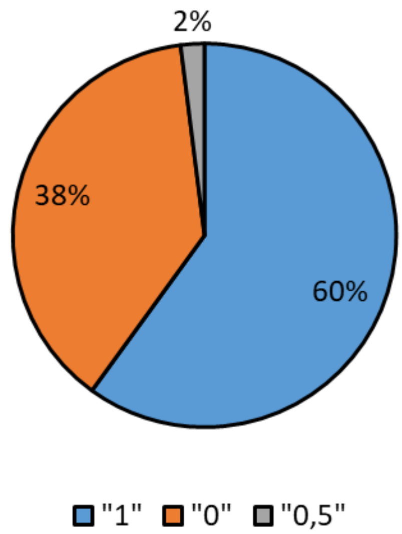

Fig. 5. Probability of developing hyperhomocysteinemia in patients with arterial hypertension and excess body weight based on the results of mathematical forecasting.

After applying mathematical forecasting to identify the high probability of the presence of hyperhomocysteinemia, it is possible to identify patients for laboratory confirmation or to use the data in order to consider in the therapy of hypertension and prevention of complications.

It is known that HHC is associated with unstable atherosclerotic plaques, which is the cause of the development of thrombosis. Although nowadays, the question of the contribution of HC as a risk factor and the need for routine research of its levels in patients remains problematic [15]. However, a meta-analysis on the association between HC and subtypes of ischemic stroke in the TOAST study showed that serum homocysteine level can be considered a risk factor for ischemic stroke.

Hyperhomocysteinemia in our patients was associated with increased blood pressure variability, which is known [16] to be a risk factor for cardiovascular events in patients with arterial hypertension.

Conclusions.

1. Patients with hypertension and BMI>25kg/m^2 have hyperhomocysteinemia in 37% of cases, which is, on the average, 1.6 times more often than reference values.
2. Patients with hypertension and BMI>25kg/m^2 with hyperhomocysteinemia have a higher level of glycemia (6.2±0.9 mml/l vs. 5.7±0.8; p=0.047), which points to an association of hyperhomocyteinemia with disorder of carbohydrate metabolism.
3. Higher levels of average daily systolic blood pressure, variability of systolic and diastolic blood pressure in patients with hypertension and BMI>25kg/m^2 with hyperhomocysteinemia point to worse blood pressure control and increased risks of developing cardiovascular events.
4. Increased reactive and personal anxiety in patients with hypertension and BMI>25kg/m^2 with hyperhomocysteinemia, headache worsen the quality of life, reduce compliance to treatment and require therapeutic correction with dietary recommendations for this contingent of patients.
5. Applying of mathematical forecast of the presence of hyperhomocysteinemia for patients with hypertension and BMI>25kg/m^2 allows to identify a group of patients (about 62%) with a higher risk of developing complications for primary or secondary prevention.

Conflict of Interest

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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