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PECULIARITIES OF LIPID METABOLISM DISORDERS IN NORMOTENSIVE PERSONS WITH BURDENED HEREDITY FOR HYPERTENSION AND PATIENTS WITH STAGE II HYPERTENSION

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The article presents the results of a study of lipid metabolism in healthy individuals with a burdened heredity for arterial hypertension and patients with stage II hypertension. Lipid metabolism was studied using standard lipidogram parameters, with additional determination of apolipoproteins B100 and A-1 and lipoprotein (a). It was noted that in the blood serum of healthy individuals with a burdened heredity for arterial hypertension, proatherogenic changes in lipid fractions occur, similar to those of patients with stage II hypertension. It is noteworthy that the level of Lp(a) in individuals with a hereditary predisposition to hypertension was 67.0 % higher than in the control group ($p<0.001$) and almost reached the "critical" level, at which the probability of developing cardiovascular disease increases. However, the levels of apolipoproteins B100 and A-1 in this group did not differ from those of the control group. Thus, our data indicate that people with hereditary hypertension experience unfavorable shifts in the lipid spectrum of the blood even earlier in the onset and development of hypertension, which suggests that they are genetically determined.

Key words: hypertension, genetic predisposition, heredity for hypertension, lipid metabolism disorders, dyslipidemia, lipoprotein (a), apolipoprotein A-1, apolipoprotein B100.

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ОСОБЛИВОСТІ ПОРУШЕНЬ ЛІПІДНОГО ОБМІНУ В ОСІБ ЗІ СПАДКОВІСТЮ ПО АРТЕРІАЛЬНІЙ ГІПЕРТЕНЗІЇ ТА У ХВОРИХ НА ГІПЕРТОНІЧНУ ХВОРОБУ ІІ СТАДІЇ

У статті відображені результати дослідження показників ліпідного обміну у здорових осіб з обтяженою спадковістю по артеріальній гіпертензії та пацієнтів з гіпертонічною хворобою ІІ стадії. Ліпідний обмін вивчали за стандартними показниками ліпідограми з додатковим визначенням аполіпопротеїдів В100 і А-1 та ліпопротеїну (а). Відмічено, що в сироватці крові здорових осіб з обтяженою спадковістю по артеріальній гіпертензії відбуваються проатерогенні зміни в ліпідних фракціях, які є аналогічними показникам хворих на гіпертонічну хворобу ІІ стадії. Звертає увагу, що рівень Лп(а) в осіб зі спадковою схильністю до артеріальній гіпертензії був на 67,0 % вищий за групу контролю ($p<0,001$) і практично досягав «критичного» рівня, при якому зростає ймовірність розвитку серцево-судинних захворювань. Проте, рівні аполіпопротеїнів В100 і А-1 в цій групі не відрізнялись від показників контролю. Таким чином, отримані нами дані свідчать, що у людей зі спадковістю по артеріальній гіпертензії ще до виникнення і становлення гіпертензії, відбуваються негативні зсуви в ліпідному спектрі крові, що дає підстави думати про їх генетичну обумовленість.

Ключові слова: гіпертонічна хвороба, генетична схильність, спадковість по артеріальній гіпертензії, порушення ліпідного обміну, дисліпідемії, ліпопротеїн (а), аполіпопротеїн А-1, аполіпопротеїн В100.

The work is a fragment of the research projects: "Metabolic risk factors, cardiovascular remodeling and functional state of kidneys in patients with cardiovascular pathology. Possibilities of pharmacological correction", state registration No. 0119U101849, and "Cardiovascular remodeling, structural and functional state of the liver and kidneys and their relationship with cardiometabolic risk factors in patients with cardiac pathology and comorbidities. Possibilities of treatment optimization", state registration No. 0124U002036.

Despite the significant scientific advances in modern medicine, cardiovascular disease (CVD) has remained the leading cause of death worldwide including in Ukraine for decades, accounting for more than a third of all deaths, according to WHO [1, 9, 11].

Arterial hypertension (AH) is not just a pathological condition with a persistent increase in blood pressure, but also the most common cause of complications such as myocardial infarction, cerebral stroke, and chronic heart failure. It makes this pathology one of the most pressing health problems worldwide [9, 11]. According to the WHO, one in four men and one in five women in the world suffer from hypertension, a total of more than a billion people. According to the STEPS study (STEPwise approach to noncommunicable disease risk factor Surveillance), one-third of the population of Ukraine (34.8 % of respondents) had hypertension or took antihypertensive drugs. The proportion of the population with high blood pressure increased sharply with age: from 12.7 % in the 18–29 age group to 71.1 % in the 60–69 age group [2].

Hypertension is an important factor in the formation and progression of systemic atherosclerosis, the complications of which are mostly associated with cardiovascular mortality. Searching for new markers and predictors of atherosclerosis onset and progression lasts for many years. Recently, much attention has been paid to the study of lipoprotein (a) (Lp(a)) and apolipoproteins B100 and A-1 (apoB100 and apoA-1) as the markers of the development and progression of the atherosclerotic process. Despite the established cause-and-effect relationship between lipid metabolism disorders and atherosclerosis-related CVD, the role of such disorders in the genesis of hypertension itself is not fully understood.

The purpose of the study was to evaluate the peculiarities of lipid metabolism in normotensive persons with burdened hypertension heredity and patients with stage II hypertension.

Materials and methods. The patients included in the study sought consultations with cardiologists at Vinnytsia Clinical City Hospitals No. 1 and No. 2, Vinnytsia Regional Clinical Hospital named after M.I. Pirogov, and Central Clinical Hospital No. 5 of the Southern Ukrainian Railways in Kharkiv.

We examined 231 patients with stage II hypertension (105 men and 126 women), whose average age was 52.3±1.2 years. The mean arterial hypertension (AH) duration in patients was 9.7±0.45 years. In 121 of 231 patients, concomitant stable coronary heart disease (CHD) was diagnosed – functional class (FC) II–III angina pectoris. The mean duration of CHD was 4.21±1.6 years. In addition to the control group, which included 30 practically healthy individuals of comparable age and sex without a family history of hypertension, a comparison group was created, which included 23 practically healthy individuals of similar age and sex without hypertension and CHD, but with a burdened heredity for hypertension: close relatives (first line) had a proven myocardial infarction due to hypertension or cerebral stroke in history.

The study did not include patients with AH of I and III stages, severe cardiac rhythm and conduction disorders, kidney or liver disease with impaired function, diabetes mellitus, obesity of the III-degree, heart disease, severe chronic heart failure (II-B–III stages according to the classification of M.D. Strazhesko and V.H. Vasilenko), chronic respiratory diseases, or respiratory failure. After the examination, patients with established symptomatic hypertension were excluded.

Blood sampling from the cubital vein for clinical and biochemical examination was performed on the first day of admission to the hospital. At the beginning of the study, in addition to general clinical examinations, all patients underwent blood analysis of glucose, electrolytes (K+, Na+), urea and creatinine, prothrombin index or INR, total protein, fibrinogen, total bilirubin and its fractions, alanine, and aspartate aminotransferase activity.

All patients underwent determination of total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), and triglycerides (TG) using the enzymatic colorimetric method. The level of very-low-density lipoprotein cholesterol (VLDL- C) was determined by the formula: TG x 0.45; low-density lipoprotein cholesterol (LDL-C): LDL-C = TC – HDL-C – VLDL-C. The atherogenicity index (AI) was calculated as the ratio of the cholesterol level in proatherogenic lipoproteins to HDL-C: AI = (TC – HDL-C) / HDL-C.

The level of lipoprotein (a) (Lp(a)) was determined by enzyme-linked immunosorbent assay (ELISA) using a reagent kit from Cormay Diagnostic Automation, Inc. The levels of apolipoprotein B100 and apolipoprotein A-1 were studied using a turbidimetry method using reagent kits “Dialab” (Austria).

Statistical calculations were performed using Microsoft Excel and Statistica for Windows 10.0. Statistical processing of the results was performed using parametric and nonparametric statistics. The study results are presented as the median and interquartile range Med (Q1; Q3), where Med is the median, and Q1 – Q3 are the 1st and 3rd quartiles and percentiles, respectively. Comparison of discrete values (%) between groups was performed using the χ^2 criterion. Comparison of sample sizes was performed using the nonparametric method with the Mann-Whitney test. Kendall's nonparametric correlation analysis determined the relationship between individual parameters.

Results of the study and their discussion. The analysis of blood lipid spectrum parameters in patients with a burdened heredity for hypertension and patients with stage II hypertension revealed proatherogenic changes in both groups of the study, characterized by a significant increase in total cholesterol levels compared to the control group, mainly due to LDL-C and the atherogenicity index (AI), an integral index reflecting the ratio of proatherogenic lipoprotein classes to antiatherogenic ones ($p<0.001$). It should be noted that there was no significant difference in these parameters between the groups of patients with existing hypertension and those with normal blood pressure and a genetic predisposition to AH ($p>0.05$) (Table 1).

Table 1

Indices of the blood lipid spectrum in the examined groups

Index	Control group (n=30)	Comparison group (n=23)	Patients with stage II hypertension (n=231)	P
Cholesterol, mmol/l	5.08 (4.22; 5.78)	6.47* (5.83; 7.19)	6.42* (5.72; 7.25)	ns
HDL-C, mmol/l	1.60 (1.48; 1.86)	1.54 (1.23; 1.82)	1.45* (1.25; 1.72)	ns
TG, mmol/l	1.02 (0.78; 1.20)	0.99 (0.79; 1.22)	1.00 (0.74; 1.33)	ns
LDL-C, mmol/l	0.45 (0.31; 0.50)	0.45 (0.36; 0.57)	0.46 (0.33; 0.60)	ns
LDL-C, mmol/l	3.01 (2.42; 3.26)	4.52* (3.51; 5.18)	4.63* (3.78; 5.26)	ns
IA, univ.	2.16 (1.92; 2.35)	3.19* (2.56; 3.98)	3.38* (2.65; 4.17)	ns
Lp (a), mg/dL	17.9 (14.2; 21.7)	29.92* (24.5; 32.1)	36.65* (29.7; 50.3)	<0.0001
apoA-1, mg/dL	130.43 (118.5; 145.3)	124.89 (117.8; 133.5)	100.51* (95.4; 107.0)	<0.001
apoB100, mg/dL	100.36 (82.3; 112.6)	96.03 (88.6; 105.6)	133.16 * (118.5; 143.1)	<0.0001

Notes: * – The significance of differences compared to the control group ($p<0.001$); P – the significance of differences between the comparison group and patients with essential hypertension; ns – the difference is not significant ($p>0.05$).

The levels of triglycerides and VLDL-C did not differ significantly in all three groups of subjects ($p>0.05$). The level of HDL-C was significantly lower in patients with hypertension than in the control group ($p<0.05$) but without a significant difference compared to the comparison group ($p>0.05$).

The levels of apolipoproteins apoB100 and apoA-1 in practically healthy normotensive subjects with hypertension heredity did not differ significantly from those of the control group ($p>0.05$), while in the presence of hypertension, an increase in apoB100 by an average of 32.7 % ($p=0.004$) and a decrease in apoA-1 by 22.8 % ($p<0.0001$) was found compared with controls. The detected changes indicate significant disorders of lipid metabolism, which may become additional risk factors for the incidence of cardiovascular events.

The level of Lp(a) in the blood serum of healthy individuals with hereditary hypertension increased to 29.9 (24.5; 32.1) mg/dL, which is 67.0 % higher than the level in the control group ($p=0.0005$). In patients with stage II hypertension, an increase in Lp(a) level to 36.65 (29.7; 50.3) mg/dL was found, which was significantly higher than in the control group and the comparison group ($p=0.0001$).

Since a significant portion of patients with stage II hypertension had concomitant CHD (52.4 %), we compared lipid metabolism indices depending on the presence of this condition (Table 2).

The analysis of lipid parameters in patients with stage II hypertension depending on the presence of concomitant CHD (stable angina II–III FC) did not reveal significant differences between the groups, except for a tendency to increase the level of Lp(a) (by 24.4 %; $p=0.06$): from 35.7 (29.7; 43.1) mg/dL in the group with AH without CHD to 44.4 (29.8; 54.1) mg/dL in the group with AH and CHD.

In addition, a significant positive correlation was found between the level of Lp(a) and the presence of CHD and the sum of SCORE scores ($r=0.35$, $p=0.0002$ and $r=0.25$, $p=0.002$, respectively), which confirms the relationship between an increase in Lp(a) and the presence of CHD and an increase in overall cardiovascular risk. Thus, an increase in Lp(a) levels contributes to the development of CHD, and its determination and assessment can be used as an additional risk factor for the development of CHD and cardiovascular complications, which is consistent with the results of other researchers [6, 10].

There are some speculations in the literature on the relationship between lipid profile parameters and blood pressure [3, 7, 14], but in our study, no significant differences in serum lipid profile parameters

were found depending on the degree of hypertension. Patients with both 2nd and 3rd degrees of hypertension had significantly higher levels of TC, LDL-C, Lp(a), apo-B100, and lower apo-A1 than the control group, reflecting the general proatherogenic changes in patients with hypertension. Therefore, we assume that changes in lipid metabolism are not highly dependent on blood pressure values, but only reflect metabolic processes that occur in parallel with hypertension.

Table 2

Indices of the blood lipid spectrum in patients with stage II hypertension depending on the presence of concomitant coronary heart disease

Indices	Stage II hypertension without CHD (n=110)	Stage II hypertension with CHD (n=121)	P
Cholesterol, mmol/l	6.60* (5.76; 7.60)	6.55* (5.67; 7.44)	ns
HDL-C, mmol/l	1.47* (1.29; 1.79)	1.43* (1.22; 1.66)	ns
TG, mmol/l	1.05 (0.73; 1.35)	0.98 (0.75; 1.31)	ns
LDL-C, mmol/l	0.47 (0.33; 0.61)	0.45 (0.34; 0.59)	ns
LDL-C, mmol/l	4.70* (3.88; 5.42)	4.62* (3.78; 5.33)	ns
IA, univ.	3.51* (2.66; 4.10)	3.49* (2.64; 4.20)	ns
Lp (a), mg/dL	35.7* (29.7; 43.1)	44.4* (29.8; 54.1)	0.06
apoA-1, mg/dL	100.9* (95.1; 109.2)	100.0* (95.5; 105.2)	ns
apoB100, mg/dL	134.2* (121.4; 144.5)	132.8* (118.5; 139.7)	ns

Notes: * – The significance of differences compared to the control group ($p<0.001$); P – the significance of differences between different groups; ns – the difference is not significant ($p>0.05$).

The association between atherosclerosis and hypertension has been confirmed by many clinical studies, and the main cause of atherosclerosis progression is lipid metabolism disorders, primarily changes in lipoprotein metabolism. Apolipoproteins, which are components of lipoproteins, are involved in the pathological process at the very early stages of atherogenesis and significantly contribute to the manifestation of endothelial dysfunction, proinflammatory activation, atheroma formation, and growth [12], which, in combination with high blood pressure, contributes to a more rapid progression of the disease and the incidence of cardiovascular catastrophes.

On the one hand, endothelial dysfunction is a consequence of the negative impact of cardiovascular risk factors, including hypertension, on the vascular endothelium. On the other hand, it causes an increase in blood pressure due to an imbalance in the ratio of vasodilators (primarily nitric oxide) and vasoconstrictors in favor of the latter, proliferation of smooth muscle cells, and increased vascular wall stiffness [4, 8].

The study found that proatherogenic lipid metabolism disorders are detected in HD, as evidenced by a significant increase in the levels of VLDL, LDL-C, IA, Lp(a), apoB100, and a decrease in the level of apoA-1, which has antiatherogenic properties, as reported by other researchers [5, 7, 8].

An interesting fact is the detection of lipid profile abnormalities in practically healthy individuals with a burdened heredity for hypertension. Not only an increase in the levels of VLDL and LDL-C but also an increase in the value of Lp(a), which practically reached the “critical” level, at which the probability of developing CVD increases [12].

In a prospective study of the relationship between blood lipid profile and the risk of developing hypertension conducted by S. Chen and W. Cheng (2022), a multivariate analysis established a relationship between CVD, LDL-C, and non-LDL-C on the one hand and the risk of hypertension on the other [5]. Similar results were obtained by other researchers [10, 13]. In these studies, the authors pay particular attention to LDL-C, an integral indicator of plasma proatherogenic activity, and its impact on the prognosis of individuals with both elevated and normal blood pressure.

Thus, our data indicate that people with hereditary hypertension, even before the onset and formation of AH, have unfavorable shifts in the blood lipid spectrum, which gives reason to think about their genetic predisposition. At the same time, the "traditional" blood lipid profile in such patients does not differ significantly from that of patients with established stage II hypertension, while such a difference has

been established for apolipoproteins A-1 and B100 and Lp(a). That is why the determination of apolipoprotein A-1 and B100 and Lp(a) levels can help to assess the risk of complications and should be included as an additional criterion for cardiovascular risk stratification.

Conclusion

The abnormalities of the blood lipid spectrum detected in individuals with a burdened heredity for hypertension may indicate that lipid metabolism disorders in people with established hypertension can start even earlier than the increase in blood pressure and are genetically determined.

The data indicate a high prognostic significance of Lp(a) in practically healthy individuals with a burdened heredity for hypertension and patients with stage II hypertension in the incidence and progression of hypertension, as well as in terms of the onset and progression of CHD in patients with hypertension and an increased cardiovascular risk.

Further studies in this area will improve cardiovascular risk stratification, and early diagnosis of lipid metabolism disorders in patients with determined hypertension and patients with uncomplicated hypertension to initiate or intensify antilipidemic therapy and improve the prognosis of such patients.

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