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BLOOD LIPIDS VARIATIONS OF PERSONS WITH FAMILY HISTORY OF SEVERE ARTERIAL HYPERTENSION

Zmeny krvných lipidov u osôb s rodinnou anamnézou závažnej artériovej hypertenzie

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SUMMARY

Background: Despite large research on impact of lipoprotein (a) and apolipoprotein B100 on the development of atherosclerosis and its effect on the human body, the problem of the onset of their variations in blood serum has not yet been clarified.

Aim: To compare the variations of parameters of lipid metabolism in hypertension-diseased patients and in persons with family history of severe arterial hypertension.

Patients and methods: Ninety subjects were examined. Group 1 comprised 41 patients with arterial hypertension disease, grade 2, 22 men and 19 women aged from 35 to 70 (the average age 52.4 ± 0.6 years). The comparison Group 2 comprised 23 practically healthy persons, but with family history of severe arterial hypertension. The control Group 3 consisted of 26 practically healthy subjects of comparable age and gender. Apart from full clinical examination, all the 90 persons under research were tested for overall cholesterol level, high density lipoproteins cholesterol, triglycerides, lipoprotein (a), apolipoprotein B100, apolipoprotein A-1. The statistical calculations were carried out applying the set of programs Microsoft Excel, Statistics for Windows 6.0.

Results: The patients in Group 1 affected by hypertension disease, grade 2 have shown lipid metabolic disorder manifested by the increase of overall cholesterol levels, proatherogenic lipoprotein classes low density lipoproteins and very low density lipoproteins, lipoprotein(a), apolipoprotein B100, and decrease of high density lipoproteins cholesterol and apolipoprotein A-1 which significantly differ from the related levels in the control Group 3. Persons in Group 2 with family history of severe arterial hypertension have shown similar proatherogenic changes in lipid fractions of blood serum as the patients with arterial hypertension i. e., remarkable ($p < 0.001$) rise of overall cholesterol levels, low density lipoproteins cholesterol and lipoprotein (a), as compared to the control Group 3, which can testify a genetic cause of the detected lipid metabolic disorder. The lipoprotein (a) level by 67.0 % exceeded the values in the control Group 3 ($p = 0.0005$), but was reliably lower ($p < 0.05$) than in hypertension disease-affected patients (Group 1).

Conclusions: The detected changes in lipid metabolism in persons with family history of arterial hypertension testify the possible relation of these disorders to a genetic susceptibility. The increased lipoprotein (a) level can be regarded as an additional high risk marker of onset of both ischemic heart disease and arterial hypertension in this population, as well as their unfavorable outcome.

Key words: arterial hypertension, blood lipids, lipoprotein (a), apolipoprotein B100, apolipoprotein A-1.

Lek Obzor (Med Horizon), 2016, 65(), p.

SÚHRN

Východisko: Napriek množstvu štúdií v posledných rokoch venovaných vplyvu lipoproteínu(a) a apolipoproteínu B100 vo vývoji aterosklerózy a jej následkov, problematika skorých zmien týchto parametrov v sére doteraz nie je úplne objasnená.

Cieľ práce: Porovnanie zmien v metabolizme lipidov u pacientov s artériovou hypertenziou a u osôb s rodinnou anamnézou závažnej artériovej hypertenzie.

Súbor a metódy: Do štúdie bolo zapojených 41 pacientov s esenciálnou hypertenziou etapy II, 22 mužov a 19 žien vo veku 35 až 70 rokov, priemerný vek 52,4 ± 0,6 rokov. V porovnávacej skupine bolo zahrnutých 23 prakticky zdravých osôb, ale zaťažených dedičnosťou na hypertenziu. Kontrolnú skupinu tvorilo 26 zdravých darcov podobného veku a pohlavia. U všetkých 90 osôb zaradených do štúdie sme okrem úplného klinického a laboratórneho vyšetrenia určili koncentrácie celkového cholesterolu, HDL-cholesterolu, triacylglycerolov, lipoproteínu(a), apolipoproteínu B100, apolipoproteínu A-1. Štatistické výpočty boli vykonané pomocou softvérových balíkov Microsoft Excel, Statistics for Windows 6.0.

Výsledky: Zistili sme, že u pacientov s artériovou hypertenziou v štádiu II sa prejavujú zmeny lipidového metabolizmu zvýšenou koncentráciou celkového cholesterolu, lipoproteínu(a), proaterogénnych tried lipoproteínov s nízkou a veľmi nízkou hustotou lipoproteínu(a), apolipoproteínu B100, cholesterolu a znížením HDL a apolipoproteínu A-1, ktorý bol významne odlišný od koncentrácie v kontrolnej skupine. Jedinci, ktorí sú zaťažení dedičnosťou na artériovú hypertenziu mali podobné orientačné proaterogénne zmeny v lipidových frakciách krvného séra, významné ($p < 0,001$) zvýšenie koncentrácie celkového cholesterolu, cholesterolu v lipoproteínoch s nízkou hustotou a lipoproteínu(a) v porovnaní s kontrolou, čo môže naznačovať genetickú podmienenosť. Koncentrácia lipoproteínu(a) v 67,0 % prekročila výkonnosť s kontrolnou skupinou ($p = 0,0005$), ale bola významne nižšia ($p < 0,05$) ako u pacientov s artériovou hypertenziou.

Závery: Odhalenie zmien krvných lipidov u príbuzných s dedičnou artériovou hypertenziou poukazuje na označenie možných porúch s genetickým determinovaním. Zvýšené koncentrácie lipoproteínu(a) sa môžu považovať za ďalší marker vysokého rizika artériovej hypertenzie a nepriaznivej prognózy u starších osôb.

Kľúčové slová: artériová hypertenzia, profil lipidov v krvi, lipoproteín(a), apolipoproteín B100, apolipoproteín A-1.

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Numerous experimental, epidemiological and clinical researches conducted during the last decades attest the relation of blood lipids spectrum disorders with the development of atherosclerosis, morbidity and mortality caused by ischemic heart disease (IHD). Nowadays, hypercholesterolemia is regarded as a common risk factor of developing atherosclerosis and ischemic heart disease. Nevertheless, over 1/3 of patients with IHD retain the normal overall cholesterol levels (OCL) and low density lipoproteins cholesterol (LDL-cholesterol) (2). Since many years research has been done into the new markers and predictors of development and progression of atherosclerosis.

The lipoprotein metabolic disorder plays and important role in the pathogenesis of atherosclerosis (18). Apoproteins are known to enter the pathologic process at very early stages of atherogenesis and to greater extent promote the manifestation of endothelin dysfunction, anti-inflammatory activation, formation and development of atheroma (20). The experimental data studying the pathophysiology of interrelation of blood lipoproteins with the vascular wall showed that the interaction between apolipoproteins and cell receptors in endothelium occurs at earlier stages, than endothelium damage (11). Apolipoprotein I-100 (Apo-I) level in blood plasma reflects the total number of atherogenic fractions of lipoproteins and, according to some authors, can be considered as a high cardiovascular risk factor, as well as an alternative target of anti-hyperlipidemic therapy (8, 10). A remarkable role in the process of atherogenesis is played by apolipoprotein A-I (apo A-I), which is a marker of antiatherogenic capacity of blood plasma, the shortage of which can serve as an additional criterion of cardiovascular risk (20). It has been stated that the reduction of apo A-I has a more important prognostic significance in the risk of cardiovascular disorders than the decrease in cholesterol of high density lipoproteins (HDL-cholesterol). In addition, it has been shown that A-1 possesses anti-inflammatory and antioxidation properties (3).

In the early 1980s, studies were focused on the relation of lipoprotein (a) (Lp(a)) levels with the increased risk of developing myocardial infarction (21). Since, many researchers have scrutinized the role of Lp(a) as a participant in atherosclerotic process (1, 4, 14, 18, 19, 21). There is a belief that Lp(a) and apolipoprotein B-100 (Apo-B) are prognostic markers of ischemic heart disease. It has been proved that the presence of a high level of Lp(a) increases twice the risk of IHD. The prognostic value of significant Lp(a) increase in blood serum as an important predictor of cardiovascular (CV) failure is proved in the studies focused on patients with dyslipidemia, AH and diabetes mellitus (DM) (9, 15). Valid straight correlations between the level of Lp(a) and triglycerids (TG) were found (17). At the same time, the role of Lp(a) as an inherited risk factor of developing cardiovascular diseases (CVD) is highlighted and its value can be associated with the level of cholesterol in low-density lipoproteins (LDL-cholesterol) (11). However, up to now the role of Lp(a) and apoB as independent factors of risk of various forms of IHD and myocardial infarction has not been identified (1). A number of questions remain, concerning the role of Lp(a) and apolipoproteins in the onset and development of arterial hypertension (AH). The relation between the Lp(a) levels and the presence of AH in patients with IHD has been detected. However, the level of Lp(a) in patients with AH without IHD and in healthy persons in the control group has not showed a significant difference (7). It has been proved, that coupled with AH, ischemic heart disease leads to the increase of apoB value as a risk factor of developing IHD and instable stenocardia, as compared to the IHD patients without arterial hypertension (1). The information about the Lp(a) level of patients with AH is very contradictory. Some authors have not detected a valid difference between the Lp(a) level in women with hypertension disease (HD) depending on the presence of IHD. However, the Lp(a) levels in men affected by both HD and IHD were remarkably higher than in the HD group without concomitant ischemic heart disease (6). There is evidence that the increase of Lp(a) levels in patients affected by both AH and IHD enhanced the risk of developing ischemic heart disease (1).

Thus, despite a great number of recent studies on the impact of Lp(a) and ApoB100 on the development of atherosclerosis and its consequences, the issues concerning the effect of these parameters on the prognosis and development of complications in patients with AH have not been clarified yet. There are only few works dedicated to the lipoprotein metabolic disorders in patients with HD, and the data obtained are extremely disputable and sometimes contradictory. Therefore, defining the role of Lp(a) and apolipoproteins in the genesis of the development of HD is very topical and of high interest.

The aim of our study was to compare the variations of parameters of lipid metabolism in HD patients and in persons with family history of severe arterial hypertension.

Patients and methods

Ninety persons were included to the study. In Group 1, forty-one patients affected by HD grade 2, twenty-two men and 19 women aged from 35 to 70 (the average age 52,4±0,6 years) have been examined. Twenty-seven patients were diagnosed with AH grade 2, fourteen patients with AH grade 3. The diagnosis was set according to the Recommendations of the European Society of Hypertension (ESH) and the European Society of Cardiology (ESC) (2007) (13). We have not included patients with secondary AH, with whom at the moment of examination the following diseases were detected: liver and kidney diseases with function disorders, diabetes mellitus, cardiac failure, chronic obstructive lung disease, respiratory failure. In order to conduct the research we have created a comparison Group 2 consisting of 23 practically healthy

persons without the signs of AH or IHD, but with family history of severe AH: close relatives had history of complications of HD such as myocardial infarction caused by HD or brain stroke. The control Group 3 included 26 practically healthy persons of the similar age and gender.

Prior to the research, patients' agreement has been obtained to participate in the research according to the ethic norms of the Helsinki Declaration. Screening, thorough acquisition of complaints and history has been performed.

All 90 persons participating in the research underwent clinical laboratory and instrumental examinations to confirm or deny the diagnosis of HD, and to exclude the patients with the diseases that have been part of elimination criteria.

The determination of the overall cholesterol level (OCL), cholesterol of high density lipoproteins (HLD-cholesterol) and triglycerides (TG) was performed by the enzymatic colorimetric method with the set of reagents produced by «Olvex Diagnosticum» (Russia). The cholesterol level in very-low-density lipoproteins (VLDL-cholesterol) was calculated by the formula: TG x 0.45; cholesterol in low-density lipoproteins (LDL-cholesterol) was determined in the following way: LDL-cholesterol = OCL – HDL-cholesterol – VLDL-cholesterol. The atherogenicity index (AI) *was calculated as correlation of cholesterol amount in proatherogenic lipoproteins to HDL cholesterol:* AI = OCL – HDL-cholesterol / HDL-cholesterol (8).

The lipoprotein Lp(a) levels were determined by enzyme immunoassay (EIA) and a set of reagents (Cormay, Diagnostic Automation, Inc, Poland). Apolipoprotein B100 and apolipoprotein A-1 levels were studied by the turbidimetric method with the set of reagents ("Dialab", Austria).

The statistical calculations were done with the help of applied programs Microsoft Excel, Statistica for Windows 6.0. The average values were demonstrated like Me (II), where Me stood for mediana, II - inter-quartile interval. The assessment of the validity of variations between groups was performed with the help of the test Wilcoxon-Mann-Whitney and nonparametric method Kruskall-Wallis. The comparative analysis of variations was conducted according to the criterion c^2 Pearson. The correlation analysis was carried out by Pearson and Spearman method, the differences in certain parameters in separate groups were defined by the method of linear contrasts (16).

Results

The conducted analysis of the lipid spectrum parameters in the patients with grade 2 HD without signs of chronic cardiac failure and concomitant IHD, revealed pro-atherogenic changes in the blood serum as compared to the control group, which manifested in the valid increase of OCL at the account of LDL and VLDL cholesterol, increased level of TG without remarkable deviations of HDL level cholesterol (***table 1***).

The validation of negative shifts in the lipid spectrum of HD-affected patients in Group 1 was a remarkable increase of the atherogenicity index (AI) as an integral value reflecting the correlation of pro-atherogenic lipoproteins with antiatherogenic ones. There was an incre-

Table 1. The parameters of lipid metabolism of HD-affected patients (Group 1), **of persons with family history of AH** (Group 2), **and healthy subjects** (Group 3)
Tabuľka 1. Biomarkery metabolizmu lipidov u pacientov s artériovou hypertenziou (Group 1), **u osôb s rodinnou anamnézou artériovej hypertenzie** (Group 2) **a u zdravých osôb** (Group 3)

Lipid spectrum parameters	Group 1 (n = 41)	Group 2 (n = 23)	Group 3 (n = 26)	P G1-G3 (Z/χ^2)	P G2-G3 (Z/χ^2)	P G1-G2 (Z/χ^2)
OCL, mmol/L	6.60* (6.10; 7.56)	6.47* (5.83; 7.19)	5.08 (4.22; 5.78)	<0.0001	<0.0001	0.31
HDL cholesterol, mmol/L	1.57 (1.28; 1.79)	1,54 (1.23; 1.82)	1.60 (1.48; 1.86)	0.64	0.12	0.94
TG, mmol/L	1.22* (0.79; 1.54)	0.99 (0.79; 1.22)	1.02 (0.78; 1.20)	0.002	0.82	0.13
VLDL-cholesterol, mmol/L	0.55* (0.36; 0.69)	0.45 (0.36; 0.57)	0.45 (0.31; 0.50)	0.025	0.65	0.24
LDL-cholesterol, mmol/L	4.72* (4.05; 5.64)	4.52* (3.51; 5.18)	3.01 (2.42; 3.26)	<0.0001	<0.0001	0.16
IA, units	3.52* (2.66; 4.37)	3.19* (2.56; 3.98)	2.16 (1.92; 2.35)	<0.0001	0.0003	0.48
Lp(a), mg/dL	35.7* (30.3; 53.0)	29.9* (24.5; 32.1)	17.9 (14.2; 21.7)	0.0001	0.0005	0.042
Apo-A1, mg/dL	100.6* (96.2; 109.1)	124.9 (117.8; 133.5)	130.4 (118.5; 145.3)	<0.0001	0.11	<0.0001
Apo-B100, mg/dL	133.3* (109.2; 149.6)	96.0 (88.6; 105.6)	100.4 (82.3; 112.6)	0.004	0.26	0.001

Notes: 1 – * probability of changes in indices as compared to the control Group 3 at (p<0,05); 2 - P1-2, P1-3, P2-3 – probability of divergence of indices among the groups under research.

ase in the level of lipoproteins Lp(a) to 35.7 (30.3; 53.0) mg/dL in patients affected by grade 2 HD, which truly exceeded the indices in the control Group 3 (p=0.0001). There were simultaneous changes in apolipoprotein levels in blood serum: increase of Apo-B100 on the average by 32.7% (p=0.004) and a remarkable decrease of ApoA-1 by 22,8% (p<0.0001), as compared to the control Group 3. The defined changes testify to the remarkable lipid metabolic disturbances, which can become additional risk factors, apart AH, for developing of cardiovascular failures.

In order to determine the stage at which pro-atherogenic changes in lipid metabolism come up – prior to the rise of arterial pressure AP or after its onset – and which other factors influence this process, we have analyzed the parameters of the lipid spectrum and apolipoproteins levels of practically healthy people without AH and IHD, but with family history of AH (Group 2). The obtained data show that these persons have undesired pathological changes in lipid spectrum: the increase in OCL and LDL-cholesterol levels, which credibly differed from the parameters in the control Group 3 (p<0.0001), but without considerable changes in HDL-cholesterol and TG (p>0.05). Suffice it to recall the remarkable increase in Lp(a) value up to 29.9 (24.5; 32.1) mg/dL, which is by 67.0 % higher than those in the control Group 3 (p=0.0005) and exceeds the so called tipping level 27 mg/dL with high risk of developing cardiovascular disease (1). The apolipoproteins levels in the comparison Group 2 did not differ greatly from those in the control Group 3. Comparing the lipid spectrum in Group 2 with Group 1, no remarkable differences in the main indices (OCL, VLDL-cholesterol, TG and HDL-cholesterol) were detected. However, they have shown the distinct increase of Lp(a) to 35.7 (30.3; 53.0) mg/dL (p<0.05) and ApoB100 to 133.3 (109.2; 149.6) mg/dL (p=0.001), as well as remarkable decrease of ApoA-1 up to 100.6 (96.2; 109.1) mg/dL (p<0.0001) in Group 1, as compared to Group 2. The detected changes attest to the more significant lipid metabolic disorder with presence of AH and consequently, worse prognosis when HD develops.

Discussion

The relationship between atherosclerosis and AH has been proved by numerous clinical studies and atherosclerosis suggests occurrence of lipid metabolic disorder in which changes of lipoprotein metabolism play a key role. In the recent years, a lot of attention has been focused on the research of Lp(a) and apolipoproteins B-100 and A-1 as markers of atherosclerotic process (4, 9, 11, 12, 14, 19, 20).

Our study has shown that patients in Group 1 with HD without concomitant disease of cardiovascular system have lipid metabolic disorders, which results in significantly higher levels of pro-atherogenic lipoprotein classes, mainly of LDL-cholesterol, as compared to the healthy persons of the control Group 3. The level of TG has not remarkably changed. In general, most of HD-affected patients have dyslipidemia of type II (according to *Friderikson*, 1967), which in itself associates with the risk of coronary failures (8, 10, 11). Besides, there are records of increase in Lp(a) and Apo-B100 levels as well as decline in blood serum antiatherogenic ability, which reflects in the distinct decrease of Apo-A1 amount. The detected changes in lipid metabolism can increase the risk of complications in AH-affected patients and coincide with the data of other researchers (3, 8, 9). Thus, the increase in concentration of Lp(a) and Apo-B100 in blood serum correlates with the accelerated atherosclerotic lesion of coronary, carotid, cerebral and peripheral arteries (14, 19, 20). The relation of the increased Lp(a) level to thickening of intima-media layer of carotid arteries has been proved (1, 2, 6, 18, 21). According to the research conducted by SHEP, the persons with systolic AH showed the relation of Lp(a) level to the severity of coronary atherosclerosis irrespective of other factors (4). There is also a belief, that certain types of lipid disorders are directly connected with the nature of arterial pressure increase under AH, which is proved by the additional decrease of arterial pressure by hypolipidemic therapy (5). Thus, found negative deviations in the lipid spectrum of blood serum under uncomplicated HD can lead to the increase of arterial pressure and onset and developing of atherosclerosis and remodeling of vessels.

It is interesting to mention the failures in lipid profile of practically healthy people who have family history of severe AH, in Group 2. They have shown not only an increase of OCL, cholesterol and LDL-cholesterol levels, but also the increase of Lp(a) value, which exceeded the "critical" level (27 mg/dL), which will probably lead to cardiovascular diseases (1, 2, 6, 18, 21). It has been shown that Lp(a) can directly stimulate the growth of smooth muscular fibers of arterial vessels in vitro (1). However, suffice it to mention, that the amount of apolipoproteins (ApoB100 and Apo-A1) in blood serum in Group 2 did not differ from that of control Group 3. It means that the deviations in levels of apolipoproteins which can be involved in atherosclerotic process at its early stages and promote the onset and development of atheroma and manifestation of endothelial dysfunction, occur later and probably when coupled with the increased arterial pressure. The detected failures of blood lipid spectrum in persons with severe hereditary HD history can testify to the fact, that lipid metabolic disorder of people susceptible to AH starts prior to the growth of arterial pressure, and is genetically predetermined. At the same time, concomitant AH contributes to further development of lipid metabolic disorders leading to the growth of cardiovascular risk.

Thus, the obtained data enable the suggestion that people with hereditary history of AH manifest negative deviations in the blood lipid spectrum prior to the onset of HD. The reliable increase of Lp(a) level in blood serum in Group 2, as compared to the control Group 3, testifies to the threat of onset of atherosclerotic process and development of overall cardiovascular risk. It

enables to suggest that the lipid metabolic disorder and the increase of Lp(a) level in persons with family history of severe AH are conditioned by genetic susceptibility.

Conclusions

Patients affected by hypertonic disease of grade 2 show pro-atherogenic changes in lipid metabolism parameters, such as: increase of overall cholesterol level due to LDL and VLDL, apolipoprotein B100, Lp(a), and decrease of HDL-cholesterol and apolipoprotein A-1 which considerably ($p<0.05$) differ from the parameters in the control group and testify to the remarkable lipid metabolic disorder.

Practically healthy persons with family history of severe AH showed not only remarkable ($p < 0.05$) increase of OCL, LDL-cholesterol levels which equaled to those of patients affected by HD grade ≤ 2, but also considerable increase of Lp(a) value by 67% as compared to the control value ($p = 0.0005$), however its level was reliably ($p < 0.05$) lower than that of HD-affected patients. The amount of apolipoproteins (Apo-B100 I Apo-A1) in blood serum of these persons did not differ from that of control group. The detected deviations in blood lipid spectrum of persons with family history of severe HD can testify to the fact that lipid metabolic disorder of people susceptible to AH start before the increase of arterial pressure and are genetically preconditioned. The increased Lp(a) level can be regarded as an additional high risk marker of onset of both IHD and arterial hypertension.

Further research in this direction will make it possible to detect the significant markers of unfavorable cardiovascular prognosis, their relation to the peculiarities of the disease flow and development of various complications, which in turn can deepen the understanding the pathogenesis of hypertonic disease, define adequate preventive measures and improve treatment.

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