UDC 616-005.4:616-007.271:577.112.85+616.198:616-055:616-053
DOI: http://doi.org/10.31928/2664-4479-2024.2.5360

Gender, clinical and instrumental parallels of Lp(a) levels in patients with very high cardiovascular risk

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In recent years it has been established that elevated levels of Lp(a) are an independent genetic risk factor for the development of atherosclerotic cardiovascular diseases and aortic stenosis, however, issues of gender and age characteristics remain controversial.

The aim of study was to analyze the gender characteristics of the relationship between Lp(a) levels and atherogenic changes in the lipid spectrum of the blood, clinical and instrumental characteristics, taking into account damage to the aortic valve and the results of coronary angiography in patients with stable coronary heart disease.

Materials and methods. The 106 patients with chronic coronary heart disease (CAD) were examined. The average age of the subjects was 55.00±1.0 years (95% CI 51.11-58.89), among them: 78 men and 28 women.

The entire cohort of patients was divided depending on the Lp(a) levels: 1group (n=58) with a Lp(a) level less than 50 mg/dl; 2 group (n=20) with Lp(a) level 50-100 mg/dl; 3 group (n=8) with Lp(a) level 101-150 mg/dl and 4 group (n=20) with Lp(a) level more than 150 mg/dl.

Research methods included: 1. General clinical examination; 2. Laboratory characteristics of lipid (with determination of Lp(a)) and carbohydrate metabolism, as well as standard biochemical parameters; 3. Instrumental examination (electrocardiography, echocardiography, ultrasound peripheral vessels examination, coronary angiography); 4. Mathematical and statistical processing of the results obtained.

Results and conclusions. In patients with CAD verified by clinical-instrumental and coronary angiographic criteria, it is noted that Lp(a) levels in women are on average significantly higher ($p<0.05$) than in men and increase with the onset of menopause.

Close correlations have not been recorded between Lp(a) in mg/dL and total cholesterol, LDL cholesterol and non-HDL cholesterol, as well as the concentrations of glucose, glycosylated hemoglobin, serum creatinine, and the concentration of thyroid-stimulating hormone (TSH).

Determined that in patients with documented atherosclerotic lesions of the coronary arteries against the Lp(a) levels above 100 mg/dl, there is a greater need for coronary revascularization. A close relationship is observed between the increase in Lp(a) levels and the percentage of detection of aortic stenosis, which confirms the pathogenetic role of this lipoprotein in the formation of this acquired aortic valve disease.

Key words: Lipoprotein(a), coronary heart disease, lipids, revascularization, aortic stenosis.

Lipoprotein(a) (Lp(a)) consists of low-density lipoprotein (LDL) associated with apolipoprotein(a). In recent years it has been established. that elevated Lp(a) levels are an independent genetic risk factor for the development of both atherosclerotic cardiovascular disease and aortic stenosis [1]. In addition, increased Lp(a) levels are associated with increased systemic inflammation, leading to vascular endothelial dysfunction, initiating the occurrence and growth of atherosclerotic lesions. There is still controversy regarding the units of its measurement [2] and although there is increasing evidence regarding the advisability of

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Стаття надійшла до редакції 16 квітня 2024 року

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Received 16.04.2024

defining the concentration of Lp(a) in nmol/l versus defining its mass in mg/dl, although there are still references in the latest EAS Consensus, 2022, to determine its mass in mg/dL [1]. Specific targeted therapy aimed at reducing Lp(a) levels is still under development, and standard lipid-lowering therapies such as statins, fibrates and ezetimibe have little effect on Lp(a) levels. At the same time, it has been noted that drugs affecting the proprotein convertase subtilisin kesin type 9 (PCSK9) lead to a decrease in its concentration, although the prevalence of such drug use is currently low [3]. Most authors note that Lp(a) levels are genetically determined and do not change throughout life, although recent work has noted that there are gender differences, with Lp(a) concentrations usually higher in women than in men, as in blacks, and white faces [4-6]. Additionally, in men, Lp(a) levels remain relatively constant throughout life, whereas in women it is indicated that levels may tend to increase during menopause [7-10].

Aim of the study was to analyze the gender characteristics of the relationship between Lp(a) levels and atherogenic changes in the blood lipid spectrum, clinical and instrumental characteristics, taking into account damage to the aortic valve and the results of coronary angiography in patients with stable coronary heart disease.

MATERIALS AND METHODS

A contingent of 106 patients with chronic coronary heart disease (CAD) were examined in 2023. Average age was 55.00±1.0 years (95% CI 51.11-58.89), among them: 78 average age men was 53.85±1.74, who made up 73.58% of the examined and 28 average age women was 58.07±2.61 years, which amounted to 26.42% of those examined, that is, the age of women was significantly higher ($p<0.05$), which is due to the fact that only patients with confirmed CAD were included in the study and this disease usually occurs 10 years later in women.

All patients underwent a general clinical and laboratory examination with determination of blood lipids, glucose, glycated hemoglobin and pituitary thyroid-stimulating hormone (TSH), echocardiography and ultrasound examination of peripheral arteries (carotid arteries and peripheral arteries of the legs), stenting or coronary artery bypass grafting, as well as determination of Lp(a) immunoturbidimetric method. Given that Lp(a) levels are not recommended to be converted from nmol/L to mg/dL or vice versa, since all conversion coefficients are inherently isoform dependent (2), only patients with Lp(a) mass measurements were included in the analysis. in mg/dL, which were currently more quantity in our clinic. Of the examined patients, 28.3% suffered a myocardial infarction, arterial hypertension was found in 94.3% of patients, diabetes mellitus – in 26.4% of patients. The average body weight of the subjects was 30.30±0.79 kg/m^2, which indicates the presence of overweight and obesity of the first degree. No thyropathies were found in the examined patients.

Taking into account the recommendations of the EAS Consensus, 2022 (1) regarding Lp(a) standards in mg/dl, in which Lp(a) parameters <30 mg/dl are the norm, and the range of 30-50 mg/dl is a «gray zone», the entire contingent of patients was divided depending on the detected Lp(a) mass in the blood samples: 1group (n=58) with Lp(a) level less than 50 mg/dl; 2 group (n=20) with Lp(a) level 50-100 mg/dl; 3 group (n=8) with Lp(a) level 101-150 mg/dl and 4 group (n=20) with Lp(a) level more than 150 mg/dl.

According to defined Lp(a) ranges, the study groups had the following gender and age characteristics *(Table 1)*:

1 group (n=58) with Lp(a) level less than 50 mg/dl (n=29), average age 53.76±2.70 years, consisted of 48 men (82.76%), average age 54.00±2.35 years and 10 women (17.24%), average age 52.60±3.21 years;

2 group (n=20) with Lp(a) level from 50 to 100 mg/dl (n=10), average age 55.09±2.51 years, consisted of 16 men (80.00%), average age 53,40±2.38 years and 4 women (20.00%), average age 60.00±1.00 years;

3 group (n=8) with Lp(a) level from 101 to 150 mg/dl, average age 64.50±4.11 years, consisted of 4 men (50.00%), average age 62.00±8.00 years and 4 women (50.00%), average age 62.00±5.00 years;

4 group (n=20) with Lp(a) level more than 150 mg/dl, mean age 54.52±4.04 years, consisted of 10 men (50.00%), mean age 50.00±5.38 years and 10 women (50.00%), average age 59.20±5.0 years.

Methods included:

1. General clinical examination.

2. Laboratory characteristics of lipid and carbohydrate metabolism:

a) lipid profile (total cholesterol (C), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-high-density lipoprotein cholesterol (non-HDL-C);

Table 1
Gender and age characteristics of patients depending on Lp(a) levels

Groups	Age, years	1 group Lp(a) <50 mg/dL, years	2 group Lp(a) 50-100 mg/dL, years	3 group Lp(a) 101-150 mg/dL, years	4 group Lp(a) >150 mg/dL, years
All patients	54.96±1.00 (n=106)	53.76±2.70 (n=58)	55.09±2.51 (n=20)	64.50±4.11 (n=8)	54.52±4.04 (n=20)
Men	53.85±1.74 (n=78)	54.00±2.35 (n=48)	53.40±2.38 (n=16)	62.00±8.00 (n=4)	50.00±5.38 (n=10)
Women	58.07±2.40 (n=28)	52.60±3.21 (n=10)	60.00±1.00 (n=4)	62.00±5.00 (n=4)	59.2±5.0 (n=10)

* Lp(a) – Lipoprotein(a). p_{2-3}<0,05.

c) glycemic status (diabetes history, fasting glucose level, glycemic profile, glycosylated hemoglobin (HbA1c));

c) biochemical profile (liver enzymes, creatinine, α-amylase).

3. Instrumental (electrocardiography, echocardiography, daily ECG monitoring, daily blood pressure monitoring, ultrasound peripheral vessels examination, coronary angiography, stenting, coronary artery bypass grafting (CABG)).

4. Mathematical and statistical processing of the obtained results. Qualitative items were presented as n (%) and quantitative item was presented as mean ± standard error of mean (SEM). Independent sample t-test was used to determine the difference between quantitative items in different groups. Pearson correlation analysis were conducted to determine the relation between Lp(a) and LDL-C. All statistical analysis was performed with statistical packages Microsoft Excell 2010 and STATISTICA for Windows 10/11 by TIBCO Software Inc. It was considered statistically significant as $p<0.05$.

RESULTS AND DISCUSSION

According to the results obtained, the first thing to note is the fact that while the percentage of male patients examined and treated (73.58%) was higher than female patients (26.42%), the average age of women (58.07±2.61 years) with coronary artery disease is significantly higher than men (53.85±1.74 years) in the examined cohort. This may find its natural explanation in the fact that coronary heart disease in women usually begins to develop 10 years later against the background of hypoestrogenism in menopause *(Table 1)*.

The second point, also noted in women, was that the age of women in group 1 with Lp(a) levels less than 50 mg/dl, was 52.60±3.21 years, which is significantly lower than among women with elevated Lp(a) levels, which in groups 2,3 and 4 was about 60 years old, that is, corresponding to the age of menopause as noted earlier in the EAS Consensus in 2022 (1). Among men, such a dependence on the increase in Lp(a) levels with age was not observed.

At the same time, in accordance with the analysis of the main clinical and biochemical parameters presented in *Table 2*, it was noted that there was no parallelism between the increase in Lp(a) levels and the levels of total cholesterol (C) and low-density cholesterol (LDL-C) in the examined groups. Thus, taking into account the increase in Lp(a) ranges by 50 mg/dl in each of the subsequent 1-4 study groups, which was inclusion criteria for patients in the study, the highest total cholesterol level of 7.04±1.87 mmol/l was observed in 1 group with the lowest Lp(a) concentration less than 50 mg/dl. The lowest concentrations of total cholesterol, which amounted to 4.86±0.78 mmol/l, were found in 3 group with Lp(a) 101-150 mg/dl, as well as 5.29±0.69 mmol/l in 4 group. with Lp(a) more than 150 mg/dl. Understanding that the level of LDL-C in the first group may not be calculated correctly by the calculation method against the background of an increase in the level of triglycerides to an average of 4.41±2.12 mmol/l, we analyzed a more reliable indicator of non-HDL cholesterol. Here, too, there was no parallelism between the increase in Lp(a) levels along with the values of non-HDL cholesterol in the groups. It was noted that the highest levels of non-HDL cholesterol were indicated in the 1 group – 4.03±0.64 mmol/l and in the 2 group – 4.23±0.45 mmol/l, against the background of lower concentrations of lipoprotein(a), amounting to on

Table 2
Lipid and biochemical characteristics of patients depending on the level of Lp(a)

Indicator	All patients (n=106)	1 group Lp(a) <50 mg/dL (n=58)	2 group Lp(a) 50-100 mg/dL (n=20)	3 group Lp(a) 101-150 mg/dL (n=8)	4 group Lp(a) >150 mg/dL (n=20)
Age, years	55.0±1.0	51.0±2.7	55.09±2.51	64.54±4.12	54.52±4.04
Body mass index	30.30±0.79	31.08±0.86	30.93±2.61	31.09±1.68	27.16±1.88
Lp(a), mg/dL	68.33±10.67	14.48±1.75	65.69±4.03	110.26±3.50	210.34±13.66
C, mmol/l	6.19±1.83	7.04±1.87	5.16±0.38	4.86±0.78	5.29±0.69
LDL, mmol/l	3.50±0.27	3.42±0.42	3.71±0.33	3.01±0.91	3.73±0.61
HDL, mmol/l	1.14±0.05	1.13±0.07	1.13±0.11	1.08±0.15	1.19±0.10
Non-HDL, mmol/l	3.47±0.39	4.03±0.64	4.23±0.45	2.99±0.37	2.95±0.28
TG, mmol/l	3.15±1.17	4.41±2.12	1.78±0.27	1.60±0.22	1.51±0.22
ApoA, mmol/l	1.16±0.08	1.29±0.07	1.13±0.06	1.20±0.32	1.25±0.15
ApoB, mmol/l	1.04±0.08	1.04±0.14	1.27±0.13	0.96±0.13	1.01±0.09
HbA1c, %	6.02±0.16	5.93±0.22	5.89±0.39	6.03±0.28	6.42±0.23
Glucose, mmol/l	5.72±0.19	5.57±0.26	5.73±0.34	5.85±0.64	6.10±0.23
Creatinine, ml/l	85.42±2.62	85.03±3.70	89.60±4.76	95.25±14.06	78.40±5.00
TSH, mIU/l	2.75±0.35	2.91±0.54	2.31±0.34	4.48±0.88	1.63±0.24

* Lp(a) – Lipoprotein(a); C – total cholesterol; LDL-C – low-density lipoprotein cholesterol; HDL-C – high-density lipoprotein cholesterol; TG –triglycerides; non-HDL-C – non- high-density lipoprotein cholesterol; HbA1c – glycosylated hemoglobin; TSH – thyroid-stimulating hormone.

average 14.48±1.75 mg/dl in 1 group and 65.69±4.03 mg/dl in 2 group.

Along with this, the highest concentrations of Lp(a) in the other two groups, namely 110.26±3.50 mg/dl in 3 group and 210.34±13.66 mg/dl in 4 group, were not associated with an increase in LDL-C, the levels of the latter were approximately 1.0 mmol/l lower, as 2.99±0.37 mmol/l in 3 group and 2.95±0.28 mmol/l in 4 group. That is, there was no parallelism between the increase in Lp(a) levels in patients with clinically and angigraphically confirmed CAD with the main lipid components of the blood. Significant correlations between the growth of Lp(a) and the concentration of HbA1c, glucose, creatinine and the values of thyroid-stimulating hormone of the pituitary gland are also not indicated *(Table 2)*.

The most interesting were the results of comparison of angiographic examination of the coronary and peripheral arteries, revascularizations performed and determination of the number of detections of aortic stenosis in the examined groups, according to national and international criteria [11–14], collectively considered as moderate (average gradient 25-40 mm), and severe (average gradient more than 40 mm Hg) degree, presented in *Table 3*.

Coronary atherosclerosis to varying degrees was detected in all 100% of the examined patients according to the results of coronary angiographic examination. The percentage of single-vessel lesions of the coronary arteries in the examined patients was insignificant on average 9.43%, its largest proportion was observed in patients of group 1 with Lp(a) less than 50 mg/dl and reached 18.37%, at the same time as in the vast majority patients were found to have multi-vessel lesions – in 90.57%. Taking into account the fact that all patients were transferred from the cardiac surgery clinic after undergoing planned coronary angiography, almost all patients were recommended for planned revascularization. However, 18 patients (16.98%) refused to undergo it for financial reasons, which did not exclude indications for its implementation.

Revascularization was carried out in the vast majority of patients, on average in 83.02% of cases, however, it was noted that in 3 and 4 groups, 85.00% and 100% of patients needed revascularization, while in 1 and 2 groups the need for revascularization was slightly less and amounted to 80.00% and 81.03%. That is, the need for revascularization due to hemodynamically significant stenoses increased along with an increase in Lp(a) concentration. Atherosclerosis of the

Table 3

Detection of angiographically affected arteries, performed revascularizations and total counted aortic stenosis of moderate (average gradient 25-40 mm Hg) and severe (average gradient more than 40 mm Hg) degree

	All patients (n=106)		1 group Lp(a) <50 mg/dL (n=58)		2 group Lp(a) 50-100 mg/dL (n=20)		3 group Lp(a) 101-150 mg/dL (n=8)		4 group Lp(a) >150 mg/dL (n=20)	
	n	%	n	%	n	%	n	%	n	%
One-vessel lesion	10	9,43	11	18.97	0	0	0	0	3	15,00
Multivascular lesion	96	90,57	47	81,03	20	100,00	8	100	17	85,00
Stenting	35	33,02	18	31,03	5	25,00	8	100	6	30,00
CABG	63	59,43	36	62.07	15	75,00	4	50	11	55,00
All revascularization	88	83,02	47	81.03	16	80,00	8	100	17	85,00
No revascularization	18	16,98	11	18,97	4	20,00	0	0	3	15,00
Aortic stenosis	18	16,98	4	6,90	4	20,00	2	25	8	40,00
Atherosclerosis of carotid arteries	70	66,04	36	62,07	18	90	4	50	12	60
Atherosclerosis of the arteries of the legs	36	33,96	22	37,93	6	30,00	2	25	8	40

* Lp(a) – Lipoprotein(a); CABG – coronary artery bypass grafting.

carotid arteries was also recorded in the overwhelming number of patients in the groups, reaching an average of 66.04%, although no parallelism was noted between the percentage of its detection and the concentration of Lp(a).

According to ultrasound of the carotid arteries, atherosclerosis was recorded in an average of 66.04%, and atherosclerosis of the arteries of the legs was detected in an average of 33.96% and did not demonstrate a direct relationship with the concentration of Lp(a) in the groups of patients examined. At the same time, ultrasound recording of the structural and functional characteristics of the heart revealed a close relationship between the increase in Lp(a) concentration and the percentage of detection of aortic stenosis *(Table 3)*. We found that the percentage of total aortic stenosis of moderate (average gradient 25-40 mm Hg) and severe (average gradient more than 40 mm Hg) degrees averaged 16.98%. However, in parallel with the increase in Lp(a) concentration, the percentage of detection of aortic stenosis also increased from 6.90% in 1 group of patients with Lp(a) less than 50 mg/dl to 20.00% in 2 group with Lp(a) 50-100 mg/dl, 25% – in 3 group with Lp(a) concentration 101-150 mg/dl and up to 40% in 4 group with Lp(a) concentration more than 150 mg/dl.

This fact is clearly visible in *Figure* in the progressive growth of the dark sector on the pie charts, which indicates the percentage of detected total counted moderate and severe aortic stenosis. An increase in the percentage of atherosclerosis of the carotid arteries and atherosclerosis of the vessels of the lower extremities was also recorded in parallel with the increase in the levels of Lp(a) in the blood of patients.

The data obtained confirm the information available in the literature about the atherogenicity of Lp(a) and the fairly powerful ability of this lipoprotein to provoke the development of atherosclerotic lesions and aortic stenosis. Of course, larger population-based studies such as the Copenhagen General Population Study and the Iranian Patient Cohort [16-18] may provide more reliable data when analyzing larger groups of patients. At the same time, it is possible that the lack of close clinical and laboratory correlations with cholesterol and LDL is due to the fact that in our study we analyzed only the Lp(a) mass in mg/dL, and not the

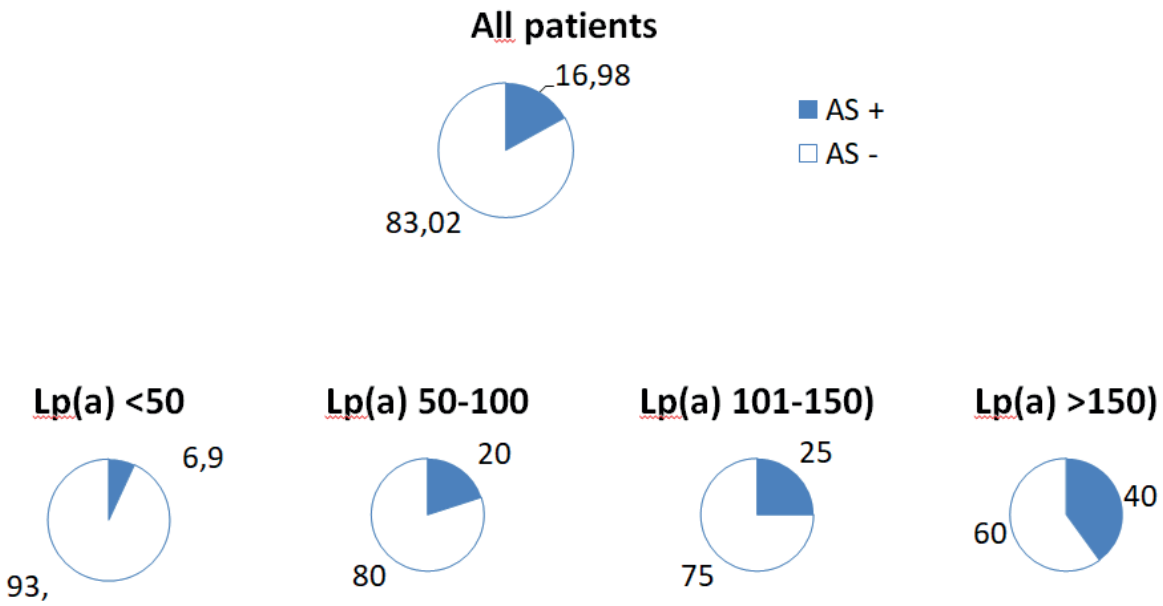

Figure. **Detection of a total moderate and severe degree of aortic stenosis (AS) in % of all patients. *AS – aortic stenosis; Lp(a) – Lipoprotein(a).**

concentration in nmol/l. With such a calculation, it is impossible to take into account the contribution of small Lp(a) isoforms with a small number of structural repeats in the apo(a) protein, which have the most pronounced proatherogenic potential.

CONCLUSIONS

As was assigned to the beginning of this publication, the principle of division into groups in the conducted research was the mass value of Lp(a) in mg/dL. In this case, no significant differences were found in the values of lipid characteristics, other biochemical indicators between groups, or correlations between Lp(a) and the studied parameters. This, based on the similar atherosclerotic process of coronary vessels in groups, can further confirm the thesis about the independence of Lp(a) as a known factor in atherogenesis.

But the main result of the investigation was the identification of a progressive increase in aortic stenosis from 6.9% against a background of Lp(a) less than 50 mg/dL, which is recognized as a «gray zone 30-50 mg/dl» (1), up to 40% with Lp(a) more than 150 mg/d. None of the lipid and biochemical characteristics analyzed in this study demonstrated such persistence. Therefore, against the background of the recognized atherogenicity of Lp(a) for the vascular bed, this work emphasizes the need for measuring Lp(a) for verification of the patients with the threat of developing aortic stenosis

It can be concluded that based on the results obtained, the following gender and clinical-instrumental parallels of Lp(a) content in patients with very high cardiovascular risk were registered. In patients with CAD, verified by clinical, instrumental and coronary angiographic criteria, it was noted that Lp(a) levels in women are on average significantly higher ($p<0.05$) than in men, and tend to increase with the onset of the menopause. There were no close correlations between the concentration of Lp(a) and indicators of total cholesterol, LDL cholesterol and non-HDL cholesterol, as well as the concentration of glucose, glycosylated hemoglobin, serum creatinine, as well as the concentration of pituitary thyroid-stimulating hormone. In patients with registered atherosclerotic lesions of the coronary arteries, the need for revascularization increases against the background of Lp(a) concentration above 100 mg/dl (groups 3 and 4 of those examined). There is a close relationship between an increase in Lp(a) concentration and the percentage of detection of aortic stenosis, which confirms the pathogenetic role of this lipoprotein in the formation of acquired heart defects. All identified dependencies require observation on a larger contingent of patients and analysis in accordance with the latest publications regarding the desirable study of Lp(a) concentration in nmol/l instead of studying Lp(a) mass in mg/dl (2), which may not allow hiding or reducing important connections with the characteristics of lipid and carbohydrate profiles, as well as with coronary angiographic parameters.

None of the authors has a conflict of interest.

Participation of the authors in the preparation of the article: collection of material – Y.B., O.M.; processing of the material – Y.B., D.B.; writing the article – O.M., Y.B.; discussion of results and formulation of conclusions – O.M., Y.B., D.B.

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Статеві та клініко-інструментальні паралелі рівнів ліпопротеїн(а) в пацієнтів з дуже високим серцево-судинним ризиком

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Встановлено, що підвищений рівень ліпопротеїн(а) [Lp(a)] є самостійним генетичним фактором ризику розвитку атеросклеротичних серцево-судинних захворювань і стенозу аорти, однак питання статево-вікових особливостей залишаються дискусійними.

Мета дослідження – проаналізувати гендерні особливості зв'язку рівня Lp(a) з атерогенними змінами ліпідного спектра крові, клініко-інструментальних характеристик з урахуванням ураження аортального клапана та результатів коронароангіографії в пацієнтів зі стабільною ішемічною хворобою серця (ІХС).

Матеріали і методи. Обстежено 106 хворих із хронічною ІХС. Середній вік обстежених становив (55±1) рік (95 % довірчий інтервал 51,11–58,89), серед них: 78 чоловіків і 28 жінок.

Всю когорту пацієнтів було розподілено залежно від рівня Lp(a): 1-ша група (n=58) – пацієнти з рівнем Lp(a) менше ніж 50 мг/дл; 2-га група (n=20) – з рівнем Lp(a) 50–100 мг/дл; 3-тя група (n=8) – з рівнем Lp(a) 101–150 мг/дл; 4-та група (n=20) – з рівнем Lp(a) більше ніж 150 мг/дл.

Застосовували такі методи дослідження: 1) загальний клінічний огляд; 2) лабораторна характеристика ліпідного (з визначенням Lp(a)) та вуглеводного обміну, а також стандартні біохімічні показники; 3) інструментальне обстеження (електрокардіографія, ехокардіографія, ультразвукове дослідження периферійних судин, коронарографія); 4) математична та статистична обробка отриманих результатів.

Результати та висновки. У хворих з ІХС, верифікованою за клініко-інструментальними та коронароангіографічними критеріями, відзначено, що рівні Lp(a) у жінок у середньому значущо вищі ($p<0,05$), ніж у чоловіків, і підвищуються з настанням менопаузи.

Не було зареєстровано тісних кореляцій між Lp(a) в мг/дл і загальним холестерином, холестерином ліпопротеїнів низької щільності і холестерином не-ліпопротеїнів високої щільності, а також концентраціями глюкози, глікозильованого гемоглобіну, креатиніну в сироватці крові та концентрацією тиреотропного гормону.

Визначено, що в пацієнтів із задокументованим атеросклеротичним ураженням коронарних артерій на тлі рівня Lp(a) вище ніж 100 мг/дл існує більша потреба у коронарній реваскуляризації. Спостерігали тісний зв'язок між підвищенням рівня Lp(a) і відсотком виявлення стенозу аорти, що підтверджує патогенетичну роль цього ліпопротеїну у формуванні цієї набутої вади аортального клапана.

Ключові слова: ліпопротеїн(а), ішемічна хвороба серця, ліпіди, реваскуляризація, аортальний стеноз