KAPITEL 6 / *CHAPTER 6* [6]
THE ROLE OF LEPTIN AND C-REACTIVE PROTEIN BIOMARKERS IN PATIENTS WITH STABLE ANGINA: THE RELATIONSHIP WITH CLINICAL MANIFESTATIONS AND PROGNOSIS

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The metabolic role of leptin in the emergence and progression of cardiovascular pathology

Adipose tissue is an active endocrine and paracrine organ and exhibits a high level of metabolic activity, synthesis and secretion of biologically active mediators (adipocytokines) associated with energy metabolism. Among them, adiponectin, resistin, visfatin, retinol-bound protein-4 and leptin are distinguished, which, in addition to regulating body weight, influence inflammation, insulin resistance and diabetes, regulate metabolism and the immune response, and also have a direct effect on epitheliocytes , the structure and functions of the heart and the cardiovascular system as a whole [7].

In addition to subcutaneous adipose tissue, epicardial adipose tissue is an important part of visceral fat and has a high metabolic rate [10], and it also locally interacts with coronary arteries and may locally potentiate the development of coronary heart disease (CHD). Local and systemic concentrations of adipocytokines are correlated with the presence of coronary artery disease, and may be promising markers for monitoring cardiovascular risk in patients. In patients with CAD, the level of pro-inflammatory cytokines, such as interleukin-1β, -6, as well as leptin, neurohumoral factors and their receptors is significantly higher in epicardial adipose tissue, regardless of the plasma level of these molecules [7, 12].

Leptin primarily regulates food intake and energy homeostasis through a unique mechanism. Activation of leptin receptors leads to inhibition of orexigenic pathways with the participation of neuropeptide Y and simultaneous activation of anorexigenic pathways. The effect of this biomarker is implemented at the level of the hypothalamus, where it binds to receptors, suppressing the urge to eat and increasing energy

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expenditure. A high level of this mediator is also associated with the occurrence of metabolic syndrome [10].

Leptin activates immune cells and stimulates the cellular immune response, affects the production of pro-inflammatory cytokines or by direct action on the vascular wall and is a mediator of proatherogenic mechanisms with the possibility of influencing the onset and progression of atherosclerosis, stimulates the activity of the sympathetic nervous system, and induces the activity of atherosclerotic plaque [11]. Clinical studies indicate a correlation of leptin levels with cardiovascular risk factors such as lipid concentrations and blood pressure (BP) levels, as well as with endothelial dysfunction and inflammation.

Obesity is caused by an imbalance between calorie intake and energy expenditure, which causes excessive accumulation of triglycerides in adipose tissue in various parts of the body. An increase in visceral adipose tissue is associated with diabetes, while pericardial adipose tissue is associated with cardiac pathology. Adipose tissue can increase either through cellular hypertrophy or hyperplasia, with the former correlating with decreased metabolic health in obesity [5].

Leptin resistance or a deficiency in leptin signaling leads to an increased risk of cardiac dysfunction and heart failure, which is a major cause of morbidity and mortality associated with obesity and T2DM [9].

However, some studies did not demonstrate a statistically significant association between leptin levels and the risk of coronary heart disease, the relationship between leptin and the progression of coronary heart disease was considered to be moderate and more dependent on body mass index [11].

According to other researchers, adiponectin and leptin play an important pathogenetic role not only in the occurrence, but also in the severity and scale of the complexity of coronary artery damage in patients with CAD. Independent predictors of the severity of atherosclerosis are a low level of adiponectin and a high level of leptin, as well as a high level of LDL cholesterol [3].

The role of C-reactive protein in the progression of cardiovascular diseases, the relationship with leptin

It has been established that leptin induces the production of C-reactive protein (CRP), and its level is positively correlated with the level of such markers of atherosclerotic plaque activation as CRP and troponin I [1].

CRP is the most widely studied reactant of the acute phase and a sensitive marker of inflammation associated with several stages of atherogenesis, from the beginning to the appearance of clinical manifestations. Inflammation in atherosclerotic plaque can cause unstable angina by promoting rupture and erosion. The size of the atherosclerotic plaque and its destabilization due to inflammatory processes are the main determinants of ischemia and acute coronary syndrome (ACS).

Elevated CRP after acute myocardial infarction (MI) is associated with adverse outcomes, including cardiac rupture, left ventricular (LV) aneurysm development, and cardiac death, with alterations in LV structure and function. Elevation of CRP exacerbates LV dysfunction and contributes to adverse post-infarction LV remodeling, which may be associated with increased apoptosis, macrophage infiltration, and metalloproteinase-9 activity in surrounding myocardial zones. Elevated levels of CRP have been associated with unstable angina pectoris, acting as a risk factor for serious adverse cardiac events [6].

Oxidized low-density lipoprotein (LDL) and CRP are positively correlated in patients with ACS, confirming their direct role in the progression of the inflammatory component in the pathogenesis of atherosclerosis. An increase in the concentration of CRP in the early period of ACS, before tissue necrosis, can be a surrogate marker of concomitant CVD. STEMI patients had significantly higher CRP levels compared to NSTEMI patients. Assessment of CRP content can help in risk stratification after MI [2].

The level of CRP is an independent predictor of rapid angiographic progression of coronary artery (CA) stenosis and is significantly correlated with the angiographic degree of CA stenosis. CRP can also serve as a useful biomarker for improving risk assessment and secondary prevention of CAD in patients without hypercholesterolemia

[8].

Elevated plasma levels of both leptin and CRP have been reported in a number of conditions, including obesity, and have been associated with cardiovascular pathophysiology and increased cardiovascular risk. Interestingly, these two biomarkers are able to mutually regulate their bioavailability through complex mechanisms that are not yet fully understood. There is clinical evidence to suggest not only an independent correlation between circulating levels of CRP and leptin, but also that their assessment in tandem may lead to an increased ability to predict CVD. Clinical data highlight the importance of both markers for cardiovascular risk assessment and strongly suggest that additional value will be gained by assessing them together, especially in clinical conditions such as obesity where chronically elevated CRP levels and leptin resistance coexist. Molecular studies show that leptin is able to modulate CRP expression levels, both indirectly through its action on other pro-inflammatory molecules such as IL-6, and directly by promoting its production in the liver and blood vessels. In turn, CRP can regulate the bioavailability of leptin in the blood circulation, since it has been demonstrated that in extracellular conditions the two molecules co-precipitate, this interaction impairs the ability of leptin to bind its receptor and activate intracellular signaling [4].

The exact relationship between hyperleptinemia and CVD remains incompletely defined. It is still unknown whether hyperleptinemia itself or the presence of leptin resistance in obese individuals contributes to CVD. The conflicting findings in these cases suggest that additional factors such as age, sex, BMI, and dietary habits should be taken into account when evaluating the effects of leptin on cardiovascular health [12].

Research material and methods

In order to evaluate the dependence of leptin levels and the state of coronary and functional reserves in patients with stable angina pectoris (AP), 42 patients with a diagnosis of AP II and III functional classes (FC) were examined. All patients were divided into three clinical groups - 1st - patients with an increase in the initial level of leptin (50.0% of cases), 2nd - patients with no changes in leptin level (11.90% of cases)

and 3rd – patients with a decrease in the initial level of leptin (38.10% of cases). At the beginning of inpatient treatment and after 3 months. all patients underwent clinical, laboratory and instrumental examination.

The research used general clinical objective methods of examination with measurement of blood pressure, resting heart rate (HR) and determination of anthropometric indicators, laboratory (study of lipid profile, determination of blood leptin and CRP) and non-invasive instrumental (electrocardiography (ECG), echocardiography (echocardiography), cycle ergometry (CEM)) examination. Transthoracic echocardiography was performed according to the usual protocol in M- and B-modes on a Toshiba "SAL-38AS" device (Japan) to assess the structural and functional state of the heart chambers, LV systolic function. End-systolic (HR) (cm) and end-diastolic (KDR) LV (cm), thickness of the interventricular membrane in diastole (TMShPd) (cm) and thickness posterior wall (TSS) LVd (cm) was determined from the left parasternal approach along the long axis in the B-mode according to the Penn convention method. Blood leptin and CRP levels were measured by ELISA using the DRG reagent kit (Germany) for leptin and for HS- CRP. According to this method, the reference levels of leptin were considered to be 2.05-5.63 ng/ml for women. 3.63-11.09 ng/ml. The reference levels of CRP are 0.068-8.2 mg/l. Statistical processing of the obtained electronic databases was carried out using the programs "Microsoft Excel 97" and "Statistica for Windows v 5.0" (StatSoft Inc., USA) with calculation of average values and their standard errors and determination of probable quantitative difference indicators using the Student's t-test with a significance level at p for the t-test <0.05.

Research results

In an intergroup comparison, it was noted that more severe angina pectoris and heart rhythm disturbances are associated with a subsequent increase in the level of blood leptin, likely when comparing patients with growth and an unchanged level of this marker ($p<0.05$ and $p<0.001$, respectively) and unlikely when comparing the group with increase and decrease of blood leptin (in both cases $p>0.1$). Heart failure (HF) of the II A century. predicts further growth of the analyzed indicator is improbable when comparing all groups (in both cases $p>0.1$). According to the literature, an increase in

the level of leptin is closely related to an increase in the risk of developing HF in men, regardless of body mass index [12]. The dynamics of the level of the studied indicator does not depend on the age and gender of the patients, as well as the presence of hypertension (in all cases p>0.5) (Table 1).

Table 1 - Clinical characteristics of patients of groups with different blood leptin dynamics

Indicator	The level of leptin increased	Leptin levels did not change	Leptin level decreased
Age, years	49.62±1.26	46.60±3.14	49.24±1.45
Women, %	52.38±10.90	20.00±12.89	50.00±12.50
Men, %	47.62±10.90	80.00±12.89	50.00±12.50
AP III FC, % of cases	71.43±9.86	20.00±12.89*	50.00±12.50
AP II FC, % of cases	28.57±9.86	80.00±12.89*	50.00±12.50
AG, % of cases	85.71±7.64	60.00±21.91	81.25±9.76
HF IIA, % of cases	52.38±10.90	20.00±12.89	31.25±11.59
Rhythm disturbances, % of cases	38.10±10.60	0*	18.75±9.76

*Note. *- probable differences between groups with growth and unchanged leptin level (p<0.05).*

The following is noted when analyzing the parameters of laboratory research. Along with a probable decrease in the level of leptin (p<0.001), an improbable decrease in the content of triglycerides (TG) (p>0.1), LDL cholesterol (cs) (p>0.1) with a tendency to decrease in total cholesterol was determined. The levels of CRP and HDL cholesterol in this group did not change (in both cases p>0.5). With a probable increase in leptin (p<0.001), a tendency towards an increase in CRP (p>0.2) and total cholesterol (p>0.2) was noted with an unchanged concentration of LDL cholesterol (p>0.5), HDL cholesterol (p>0 .5) and TG (p>0.5). At the same time, positive dynamics are associated with a likely more frequent decrease in CRP (respectively, 62.5±12.1 and 28.57±9.86% of cases, p<0.05), total cholesterol (respectively, 50.00±12.5 and 9 ,52±3.4% of cases,

p<0.05), improbably more frequent decrease in TG (respectively 50.00±14.43 and 22.22±9.80% of cases, p>0.1) and with the absence of a single case of LDL-C growth.

In patients with an unchanged level of leptin (p>0.5), there were no significant changes in CRP (p>0.5) and total cholesterol (p>0.5), however, a tendency to decrease LDL cholesterol (p>0 ,2), TG (p>0.2) and HDL cholesterol growth (p>0.2). When comparing the 1st and 2nd groups, only with unfavorable changes in the level of leptin, there was an increase in total cholesterol and LDL cholesterol, a decrease in TG was determined incredibly less often (respectively, 22.22±9.80 and 50.00±25.00, p>0 ,1), the growth of HDL cholesterol is probably less frequent (respectively 33.33±15.71 and 100% of cases, p<0.001) (Table 2).

Table 2 - Laboratory characteristics of patients of groups with different blood leptin dynamics

Indicator	Leptin level increased		Leptin levels did not change		Leptin level decreased	
	Start of observation	End of observation	Start of observation	End of observation	Start of observation	End of observation
Leptin, ng/ml	9.65±1.38	23.2±4.06	11.74±4.29	11.04±3.98	26.18±4.17	9.53±2.41
CRP, mg/l	4.50±1.05	6.44±1.70	2.00±1.12	4.14±2.58	3.82±0.97	4.87±2.04
Total cholesterol, mmol/l	5.11±0.27	5.52±0.32	5.45±0.60	5.02±0.53	4.77±0.23	4.55±0.28
HDL cholesterol, mmol/l	1.72±0.16	1.6±0.22	1.62±0.26	1.9±0.22	2.22±0.17	2.14±0.24
LDL cholesterol, mmol/l	4.41±0.33	4.60±0.46	4.99±1.43	3.00±1.46	4.84±0.36	4.18±0.4
TG, mmol/l	2.27±0.19	2.39±0.13	2.45±0.46	2.08±0.25	1.98±0.14	1.72±0.17

*Note. *- probable differences within the group (p<0.05).*

Examination of the echocardiogram parameters (Table 3) showed the absence of a relationship between any dynamics of the leptin level and changes in LV volumes

and ejection fraction (EF) of the LV, since these indicators did not change significantly in all groups (in all cases p>0.5). This is consistent with some literature data that the level of this marker does not significantly correlate with indicators of LV diastolic and systolic function in men and women [10].

When analyzing the data of the bicycle test, it was established that a decrease in the blood leptin level is correlated with a probable increase in the parameters of the threshold load (PN) (p<0.01) and the work performed (p<0.05), while with an increase in leptin, the increase in these indicators is improbable (respectively p>0.1 and p>0.2). No significant differences in the frequency of detection of the specified changes were found in any of the groups - in relation to PN, respectively, 53.85 ± 13.83 and 50.00 ± 11.79% of cases (p>0.5) and in relation to the performed work, respectively, 46.15 ± 13.83 and 50.00±11.79% of cases (p>0.5).

Table 3 - Characterization of the results of instrumental studies of patients of groups with different blood leptin dynamics

Indicator	The level of leptin increased		Leptin levels did not change		Leptin level decreased	
	Start of observation	End of observation	Start of observation	End of observation	Start of observation	End of observation
EDV LSH, Jr	113.92±6.12	108.81±3.81	103.84±11.94	103.84±11.94	116.14±8.09	116.14±8.09
ESV LSH, Jr	46.38±3.82	43.19±2.26	37.68±6.04	37.68±6.04	45.78±3.39	45.78±3.39
LVEF, %	59.62±0.97	60.14±0.80	63.40±2.69	63.40±2.69	59.88±0.78	60.06±0.76
Mon, Tues	68.84±8.31	84.75±9.83	125.40±17.73	153.40±19.79	84.54±7.81	124.39±13.10*
Work, kJ	20.36±3.86	25.54±4.20	49.98±10.02	59.68±12.08	24.30±3.47	42.54±6.31*

*Note. *- probable differences within the group (p<0.05).*

Patients with an unchanged level of leptin have an improbable increase in PN (p>0.1), however, the performance indicator did not change (p>0.5). When comparing the 1st and 2nd groups, the frequency of detection of an increase in the specified

parameters does not differ - in both cases, respectively, 50.00 ± 11.79% and 60.00 ± 21.91 cases (p>0.5).

Correlation analysis revealed a weak probable inverse correlation between blood leptin level and PN (r=–0.3, p<0.05) (Figure 1).

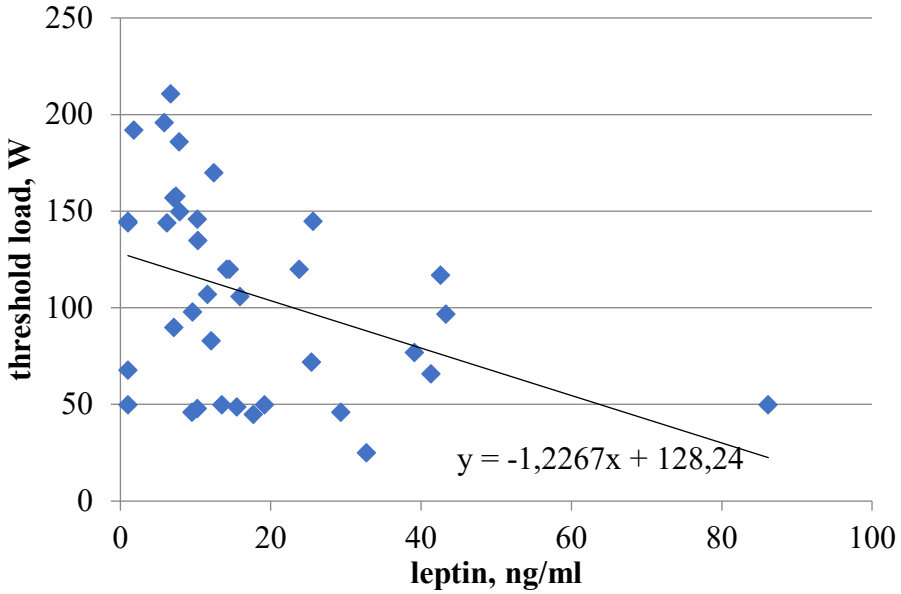

Figure 1 - Correlation between blood leptin level and threshold load.

Thus, leptin is a predictor of higher FC of angina pectoris and heart rhythm disorders, and a decrease in its level is accompanied by an increase in PN indicators and work performed during a stress test with a weak probable inverse correlation between the level of blood leptin and PN. Hyperleptinemia predicts negative changes in the lipid composition of the blood, as it is accompanied by an increase in total cholesterol, LDL cholesterol, as well as a less frequent increase in HDL cholesterol. Leptin can be used as an indirect marker of systemic inflammation, since a decrease in its level predicts a more frequent decrease in CRP. Further study of the role of leptin in the progression of atherosclerosis is expedient in order to determine risk stratification in AP.

Conclusions

1. The female gender predicts a higher blood leptin level ($p<0.01$) with the preservation of this tendency in the distribution according to the severity of angina pectoris. A decrease in the initial level of leptin is accompanied by an increase in threshold load indicators ($p<0.01$) and work performed during a stress test ($p<0.05$) with a weak probable inverse correlation between blood leptin level and threshold load ($r=– 0.3$, $p<0.05$).

2. Leptin can be used as an indirect marker of systemic inflammation, since a decrease in its level predicts a more frequent decrease in C-reactive protein ($p<0.05$).