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Clinical and prognostic value of leptin resistance in the hospital period of myocardial infarction

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ABSTRACT

Aim. To evaluate the prevalence of leptin resistance (LR) and its clinical and prognostic value in association with metabolic disorders and features of the proinflammatory state in the hospital period of myocardial infarction.

Materials and methods. The study included 114 men diagnosed with ST segment elevation myocardial infarction (MI). On day 1 and 12 of MI, the levels of leptin and leptin receptor were measured in patients, and the free leptin index (FLI) was calculated. Leptin resistance (LR) was recorded at leptin > 6.45 ng / ml and FLI > 25. A comparative analysis of clinical and anamnestic characteristics, biochemical parameters, and cardiovascular prognosis was carried out between patients with and without LR. Statistical data processing was carried out using the Statistica 10.0 software package and SPSS 17.0 for Windows**.**

Results. The prevalence of LR in the hospital period of MI was 64%. LR was associated with cardiovascular pathology in the family history, arterial hypertension, dyslipidemia, and obesity. The presence of LR was accompanied by a significant increase in the level of glucose, free fatty acids (FFA), and interleukin (IL)-6 on day 1 of MI and by a significant rise in insulin, C-peptide, tumor necrosis factor (TNF)-alpha, and plasminogen activator inhibitor-1 (PAI-1) throughout the hospital stay. Patients with LR were characterized by multi-vessel and more severe lesions of the coronary bed and were more often subject to early post-infarction angina, recurrent MI, rhythm and conduction disturbances during hospital stay for MI.

Conclusion. Patients with MI are characterized by high prevalence of LR during the hospital stay. LR is associated with cardiovascular risk factors, metabolic disorders, formation of insulin resistance, and increased proinflammatory and prothrombogenic factors. The identified features in the presence of LR probably contribute to the development of adverse cardiovascular events in the hospital period of MI.

Keywords: leptin, leptin resistance, hospital period, myocardial infarction

Conflict of interests. The authors declare the absence of obvious or potential conflict of interest related to the publication of this article.

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Conformity with the principles of ethics. All patients signed an informed consent to participate in the study. The study was approved by the local Ethics Committee at the Research Institute for Complex Issues of Cardiovascular Diseases.

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Клинико-прогностическая значимость лептинорезистентности в госпитальном периоде инфаркта миокарда

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РЕЗЮМЕ

Цель: оценить распространенность лептинорезистентности (ЛР) и ее клинико-прогностическую значимость во взаимосвязи с метаболическими нарушениями и особенностями провоспалительного статуса в госпитальном периоде инфаркта миокарда (ИМ).

Материалы и методы. В исследование включены 114 мужчин с установленным диагнозом ИМ с подъемом сегмента ST. Пациентам на 1-е и 12-е сут ИМ измеряли концентрацию лептина, рецептора лептина, рассчитывали индекс свободного лептина (ИСЛ). Лептинорезистентность фиксировали при уровне лептина более 6,45 нг/мл и ИСЛ более 25. Проведен сравнительный анализ клинико-анамнестических характеристик, биохимических показателей и кардиоваскулярного прогноза между пациентами с наличием ЛР и без ЛР. Статистическую обработку данных проводили с использованием программного пакета Statistica 10.0 и SPSS 17.0 for Windows.

Результаты. Распространенность ЛР в госпитальном периоде ИМ составила 64%. Лептинорезистентность ассоциирована с факторами риска сердечно-сосудистых заболевания (ССЗ) – наследственная отягощенность по сердечно-сосудистой патологии, артериальная гипертензия, дислипидемия, ожирение. У пациентов с ЛР наблюдались равные доли поражения передней и задней стенки левого желудочка. Наличие ЛР сопровождалось статистически значимым увеличением содержанием глюкозы, свободных жирных кислот и интерлейкина-6 в 1-е сут ИМ, инсулина, С-пептида, фактора некроза опухоли альфа и ингибитора активатора плазминогена 1-го типа на протяжении всего госпитального периода. Пациенты с ЛР характеризовались многососудистым и более тяжелым поражением коронарного русла, были чаще подвержены ранней постинфарктной стенокардии, рецидиву ИМ, нарушениям ритма и проводимости в госпитальном периоде ИМ.

Заключение. Для пациентов с ИМ характерна высокая распространенность ЛР в госпитальном периоде. Лептинорезистентность ассоциирована с факторами риска ССЗ, нарушениями метаболизма, формированием инсулинорезистентности, усилением провоспалительных и протромбогенных факторов. Выявленные особенности при наличии ЛР, вероятно, могут способствовать развитию неблагоприятных кардиоваскулярных событий в госпитальном периоде ИМ.

Ключевые слова: лептин, рецептор лептина, лептинорезистентность, госпитальный период, инфаркт миокарда

Конфликт интересов. Авторы декларируют отсутствие явных и потенциальных конфликтов интересов, связанных с публикацией настоящей статьи.

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Соответствие принципам этики. Все пациенты подписали информированное согласие на участие в исследовании. Исследование одобрено локальным этическим комитетом НИИ КПССЗ.

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INTRODUCTION

Leptin has historically been one of the most important adipokines, playing a key role in the regulation of energy metabolism. In addition to the main effect, leptin exerts many pleiotropic effects, including those on the cardiovascular system (CVS). The role of leptin in cardiovascular disease (CVD) has been widely discussed over the years. Elevated leptin levels have potentially atherogenic, thrombotic, and angiogenic effects on the CVS. High concentrations of leptin stimulate proliferation and hypertrophy of smooth muscle cells in the vessel wall and accumulation of cholesterol esters in foam cells. They also enhance the proinflammatory activity of interleukin (IL)-6 and activate platelet aggregation [1]. Leptin-induced aldosterone secretion contributes to hypertension and endothelial dysfunction [2]. However, most of the evidence is obtained from cellular and animal models, so the role of leptin in human CVS and the fact whether leptin directly affects cardiac function or acts through a leptin-regulated neurohumoral pathway remain unclear.

Relatively recently, the phenomenon of leptin resistance (LR) has been discussed in modern literature. LR is a condition that develops as a result of a defect in intracellular signaling at the level of the leptin receptor or in the context of a decrease in leptin transport across the blood – brain barrier. As a result, leptin is not able to exert physiological effects, despite its elevated level [3]. In CVS, LR has an adverse effect on the cardiovascular response to stress and promotes cardiac remodeling [4]. To date, a lack of precise criteria for assessing the presence of LR makes studying this phenomenon difficult. Therefore, data on the contribution of LR to the development and prognosis of CVD, and, in particular, myocardial infarction (MI), are scarce; moreover, they are extremely contradictory.

The aim of the study was to evaluate the prevalence of LR and its clinical and prognostic value in association with metabolic disorders and features of the proinflammatory state at the in-hospital phase of MI.

MATERIALS AND METHODS

The study was conducted in accordance with the principles set forth in the Declaration of Helsinki and approved by the local Ethics Committee at the Research Institute for Complex Problems of Cardiovascular Diseases. The study included 114 men diagnosed with ST segment elevation myocardial infarction (STEMI). The average age of the patients was 60.0 [56.0; 70.0] years. The exclusion criteria were age over 75 years, as well as the presence of concomitant clinical conditions such as anemia, type 1 and type 2 diabetes, cancers, autoimmune diseases, and kidney and liver failure. All patients signed an informed consent to participate in the study.

In the examined individuals, the prevailing anamnestic risk factors for MI were arterial hypertension (AH), smoking, angina pectoris in the medical history, as well as cardiovascular pathology in the family history. More than 60% of patients were overweight and with varying degrees of obesity. The features of the developed MI included the predominance of Q wave MI and equal damage to the anterior and posterior walls of the left ventricle (LV). Preserved left ventricular ejection fraction (EF) was registered in about 65% of patients with MI (Table 1).

Table 1

Clinical and anamnestic characteristics of the examined patients, *n* = 114

Parameter	Absolute value	Relative value, %
Age, years, *Me* [Q_1; Q_3]	60.0 [56.0; 70.0]	–
Medical history		
Cardiovascular pathology in the family history	52	45.6
Smoking	58	50.8
Arterial hypertension	102	89.9
Dyslipidemia	20	17,5
Clinical manifestations of angina pectoris before MI	54	47.4
Previous myocardial infarction	31	27.2
Chronic heart failure	9	7.9
Body mass index (BMI)		
– under 25 kg / m^2; – 25.0–29.9 kg / m^2; – 30.0–39.9 kg / m^2	38 54 22	33.3 47.4 19.3
Coronary artery disease		
One-vessel coronary artery disease	64	56.1
Double-vessel coronary artery disease	35	30.7
Multivessel coronary artery disease	15	13.2

Table 1 (continued)

Parameter	Absolute value	Relative value, %
Myocardial infarction (MI)		
Q wave MI	96	84.2
Non-Q wave MI	18	15.8
Localization:		
– Anterior wall of the LV	50	43.9
– Posterior wall of the LV	55	48.2
– Posterior wall of the LV and right ventricle (RV)	9	7.9
Left ventricular ejection fraction (LVEF)		
≤ 50%	74	64.9%
40–49%	34	29.8%
> 40%	6	5.3%

On days 1 and 12 of MI, the levels of leptin and leptin receptor were determined in all patients by the enzyme immunoassay using standard commercial test systems (BioVendor, Czech Republic; eBioscience, Austria). The free leptin index (FLI) was calculated as the ratio of total leptin concentration (ng / ml) to the soluble leptin receptor concentration (ng / ml) multiplied by 100. LR was recorded at leptin levels > 6.45 ng / ml and FLI > 25 [5].

A comparative analysis of metabolic, proinflammatory, and adipokine profile parameters between patients with and without LR was carried out. The assessment of the glucose level, lipid profile (total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDLC), low-density lipoprotein cholesterol (LDLC)), and C-reactive protein (CRP) in the blood serum was carried out using standard commercial test systems from Thermo Fisher Scientific on an automated biochemistry analyzer Konelab 30i (Finland). The content of C-peptide, insulin, IL-6, plasminogen activator inhibitor-1 (PAI-1), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) in the blood serum was determined using the enzyme-linked immunosorbent assay using standard commercial tests systems (BioVendor, Czech Republic; eBioscience, Austria; Cloud-Clone Corp. USA) according to the manufacturer's protocol. To assess insulin resistance (IR), the QUICKI index (Quantitative Insulin Sensitivity Check Index) was calculated: QUICKI = 1/[log(I0) + log(G0)], where I0 is basal plasma glucose (mmol / l), and G0 is basal insulin (μIU / ml). The severity of IR was assessed according to A. Katz et al. [6]. The mean QUICKI value of 0.382 ± 0.007 indicated normal tissue sensitivity to insulin; QUICKI values equal to 0.331 ± 0.010 and 0.304 ± 0.007 indicated moderate and severe tissue IR, respectively.

Coronary angiography was performed by the Judkins technique on the Innova angiographic system (USA). Xenetix-350 was used as a radiopaque agent. The SYNTAX Score was used to assess the severity of coronary lesions. An unfavorable outcome during an early in-hospital phase was registered with the development of early post-infarction angina, recurrent acute myocardial infarction (AMI), and life-threatening cardiac arrhythmias and conduction disorders.

As reperfusion therapy, all patients underwent primary percutaneous coronary intervention with stenting of the infarct-related artery. Continuous 24-hour infusion of nitroglycerin and heparin at standard doses with control of hemodynamic parameters and activated partial thromboplastin clotting time (aPTT) was performed. During the in-hospital phase of MI, we used β-blockers (in 100% of patients), angiotensin-converting enzyme inhibitors (89.4%), calcium channel blockers (88.5%), diuretics (31.7%), nitrates (17.3%), aspirin (98%), heparin (100%), clopidogrel (100%), and statins (100%).

Statistical data processing was carried out using Statistica 10.0 and SPSS 17.0 for Windows. The Kolmogorov – Smirnov test was used to check normality of data distribution. The data were presented as the median and the interquartile range *Me* [Q_1; Q_3]. The Mann – Whitney test was used to compare two independent samples. The differences were considered statistically significant at $p < 0.05$. The frequency analysis was carried out using 2x2 contingency tables. The logistic regression analysis with the calculation of odds ratio (OR) and 95% confidence interval (CI) was performed. In all statistical procedures, the differences were considered statistically significant at $p < 0.05$.

RESULTS

In patients with MI, during the entire observation period, an increased level of leptin was registered relative to the reference interval of 2.0–5.6 ng / ml. Thus, on days 1 and 12 of MI, the leptin concentration in patients with MI was 11.6 [6.6; 20.5] ng / ml and 11.5 [5.4; 13.9] ng / ml, respectively. The content of the leptin receptor did not go beyond the established reference interval and amounted to 40.8 [28.8; 46.1] ng / ml on day 1 of MI and 34.8 [27.1; 46.6] ng / ml on day 12. FLI was 32.7 [14.3; 70.5] on day 1 and 31.9 [16.2; 64.5] on day 12. At the time of patient division into groups with and without MI, the prevalence of LR was 64%.

LR in patients with myocardial infarction was associated with the presence of CVD risk factors: cardiovascular pathology in the family history, AH, and dyslipidemia. Patients in both groups were overweight, however, patients with LR were characterized by different degrees of obesity, in contrast to patients without LR. In patients with LR, equal damage to the anterior and posterior wall of the LV was observed, in patients without LR, equal damage to the posterior wall of the LV was noted. Q wave MI was significantly more common in the group of patients with LR. Patients with LR were characterized by an intermediate and critical decrease in LVEF (Table 2).

A comparative analysis of the metabolic profile revealed a significant increase in the level of glucose (p = 0.02), insulin (p = 0.02), and C-peptide (p = 0.03) on day 1 of MI, a rise in insulin (p = 0.01) and C-peptide (p = 0.03) on day 12 of the disease, and a decrease in the QUICKI index (p = 0.03) throughout the entire hospital stay in patients with LR compared to patients without LR (Table 3).

Table 2

Clinical and anamnestic characteristics of patients with and without leptin resistance, abs. (%)

Parameter	Patients with LR, n = 73	Patients without LR, n = 41	p
Medical history			
Cardiovascular pathology in the family history	39 (53.4%)	13 (31.7%)	0.02
Smoking	32 (43.8%)	18 (39%)	0.52
Arterial hypertension	72 (98.6%)	30 (73.2%)	0.01
Dyslipidemia	16 (21.9%)	4 (9.8%)	0.001
Clinical manifestations of angina pectoris before MI	35 (47.9%)	19 (46.3%)	0.61
Previous myocardial infarction	20 (27.4%)	11 (26.8)	0.82
Chronic heart failure	6 (8.2%)	3 (7.3%)	0.63
Body mass index (BMI)			
– under 25 kg / m^2; – 25.0–29.9 kg / m^2; – 30.0–39.9 kg / m^2	15 (20.6%) 29 (39.7%) 29 (39.7%)	21 (51.2%) 20 (49.8%) 0 (0%)	0.01 0.08 0.001
Myocardial infarction (MI)			
Q wave MI Non-Q wave MI	64 (87.7%) 9 (12.3%)	32 (78.1%) 9 (21.9%)	0.04 0.02
Localization of MI: – Anterior wall of the LV; – Posterior wall of the LV; – Posterior wall of the LV and RV	 34 (46.6%) 30 (41.1%) 9 (12.3%)	 16 (39%) 25 (61%) 0 (0%)	 0.03 0.01 0.001
Left ventricular ejection fraction (LVEF)			
≥ 50% 40–49% < 40%	40 (54.8%) 28 (38.4%) 5 (6.8%)	34 (83.0%) 6 (14.6%) 1 (2.4%)	0.001 0.02 0.01

Table 3

Comparative characteristics of carbohydrate and lipid metabolism parameters and proinflammatory and prothrombotic state in patients with and without leptin resistance, *Me* [Q_1; Q_3]

Parameter	Patients with LR		Patients without LR	
	Day 1	Day 12	Day 1	Day 12
Glucose, mmol / l	6.7 [5.6; 8.6]	6.1 [5.4; 7.2]	5.9 [5.4; 6.9]	5.9 [5.2; 7.2]
Insulin, μIU / ml	10.9* [5.8; 18.7]	12.2* [4.7; 19.5]	7.5 [2.8; 12.8]	5.3 [3.2; 10.2]
C-peptide, ng / ml	1.23* [0.62; 2.1]	1.2 * [0.58; 1.89]	0.99 [0.56; 1.47]	0.99 [0.56; 1.47]
QUICKI index	0.34* [0.31; 0.39]	0.31 * [0.29; 0.39]	0.38 [0.33; 0.45]	0.39 [0.35; 0.50]
FFA, mmol / l	1.64* [1.21; 1.94]	0.64 [0.5; 1.1]	1.1 [0.8; 1.26]	0.5 [0.43; 0.79]
CRP, mg / ml	25.0 [8.3; 52.4]	8.3 [5.0; 15.0]	20.0 [9.6; 29.0]	7.0 [3.0; 25.0]
IL-6, pg / ml	17.5* [13.3; 25.8]	9.6 [3.3; 11.0]	12.7 [10.9; 20.0]	10.4 [4.8; 16.3]
TNF-α, pg / ml	20.6* [1.4; 23.3]	19.8* [1.9; 24.9]	1.92 [0.7; 11.5]	2.36 [0.84; 12.4]
PAI-1, ng/ml	127.8* [39.9; 153.6]	88.65* [32.4; 148.0]	89.1 [72.0; 140.8]	60.14 [30.43;72.62]

* statistically significant differences between groups of patients with and without LR, $p < 0.05$.

In the group of patients with LR, 45 people (61.8%) had moderate and severe IR, in the group of patients without LR, this phenomenon was observed in 12 patients (29.2%). The correlation analysis revealed a significant direct correlation between the level of insulin on day 12 of MI and FLI (r = 0.509, p = 0.02), as well as an inverse correlation between the QUICKI index on day 12 and FLI (r = –0.367, p = 0.01).

Among the lipid metabolism parameters in the in-hospital phase of MI, only the level of free fatty acids (FFA) on day 1 of the disease was higher in the group of patients with LR than in the group without LR (p = 0.03).

In patients with MI, the level of CRP was higher than normal values throughout the observation period, however, there were no significant differences between the study groups. In patients with LR on day 1 of the disease, an increase in the concentration of IL-6 (by 1.4 times) and TNFα (by 10.7 times) was observed; on day 12, a rise in the level of TNFα (by 8.3 times) was noted compared to patients without LR. The values of PAI-1 in the group of patients with LR were significantly higher throughout the entire in-hospital phase of MI compared to the group without LR (Table 3).

Patients with LR were characterized by both moderate and severe lesions of the coronary bed. In patients without LR, only a minor lesion of the coronary artery was found (Table 4).

LR in patients with MI was more often associated with multivessel coronary artery disease (Figure).

Table 4

Comparative characteristics of patients with and without LR, depending on the severity of coronary lesions according to the SYNTAX score, abs. (%)

Severity of coronary lesion	Patients with LR	Patients without LR
Minor lesion (≤ 22 points)	55 (75.4%)	41 (100%)
Moderate lesion (23–32 points)	9 (12.3%)	0 (0%)
Severe lesion (> 32 points)	9 (12.3%)	0 (0%)

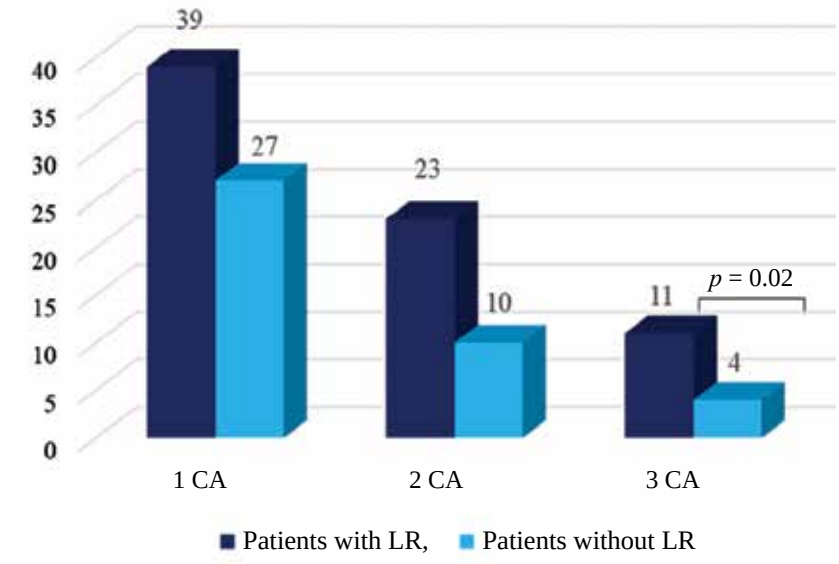

Figure. Characteristics of coronary bed lesions

The logistic regression analysis revealed the most significant parameters for verification of LR in patients with MI during the in-hospital phase of the disease. The closest relationship with LR was revealed for BMI, the number of affected arteries, and LVEF.

Among the carbohydrate and lipid metabolism parameters, a rise in the content of glucose in the blood serum on day 1 of the disease by 1 mmol / l increased the chances of detecting LR by 2.2 times, FFA – by 6.3 times. Among the markers of

proinflammatory and prothrombotic state, the closest relationship with LR was determined for IL-6 on day 1 of MI (Table 5).

Table 5

Markers of the proinflammatory and prothrombotic state in MI patients with LR

Parameter	OR	95% CI	*p*
BMI, kg / m²	2.34	1.07–5.20	0.03
Number of affected arteries	6.21	1.24–31.24	0.03
LVEF, %	0.53	0.23–0.84	0.01
Glucose on day 1, mmol / l	2.21	1.07–4.57	0.03
FFA on day 1, mmol / l	6.35	1.332–30.22	0.02
IL-6 on day 1, pg / ml	1.19	1.09–1.20	0.03

When analyzing adverse outcomes in the in-hospital phase of MI, it was found that patients with LR are more susceptible to cardiovascular events. Early post-infarction angina and recurrent AMI developed in 10.9% (8 / 73) and 6.8% (5 / 73) of patients, in patients with LR; in patients without LR, these complications were not registered. Conduction disorders were significantly (p = 0.03) more often recorded in patients with LR. This complication occurred in 34.2% (25 / 73) of patients with LR and in 12.2% (5 / 41) of patients without LR. On the whole, the incidence of adverse events in the in-hospital phase of MI in patients with LR was greater than in patients without LR. Thus, in the group of patients with LR, it was 44.4%, while in patients without LR, it was 12.2% (p = 0.01).

According to the logistic regression analysis, the prognostic value in relation to the risk of adverse cardiovascular events in the in-hospital phase of MI was determined for FLI both on days 1 and 12 of the disease, for BMI and the levels of FFA and IL-6 – on day 1 of MI, and for TNFα – on day 12 of MI (Table 6).

Table 6

The risk of developing adverse cardiovascular events in patients in the in-hospital phase of MI

Parameter	OR	95% CI	*p*
BMI, kg / m²	1.66	1.03–2.69	0.03
FLI on day 1	1.17	1.03–1.26	0.03
FLI on day 12	1.18	1.01–1.37	0.04
FFA on day 1, mmol / l	2.91	1.18–4.74	0.02
IL-6 on day 1, pg / ml	1.15	1.01–1.32	0.04
TNF-α on day 12, pg / ml	1.42	1.0–2.02	0.04

DISCUSSION

Currently, data on studying the incidence of LR in MI are extremely scarce in the scientific literature. However, the relevance of this issue is undeniable, since the assessment of LR in CVD will reduce the risk of developing cardiovascular complications in the future. In addition, the issue of choosing criteria for the LR assessment remains unresolved. To date, there is no generally accepted method to establish the presence of LR, as there is no single rule for its selection. One of the approaches to the diagnosis of LR is the presence of elevated leptin levels.

Many authors believe that hyperleptinemia is evidence of insensitivity to leptin and serves as an indirect sign of LR [7]. It is assumed that a high level of leptin is due to impaired interaction between leptin and its receptors, as a result of which LR develops. However, elevated levels of leptin can only characterize the concentration of the hormone which production increases without reflecting changes that led to hyperleptinemia [4]. The second approach is to evaluate the FLI. This method makes it possible to assess the relationship between leptin and the receptor and reflects the functional activity of leptin [8]. Both approaches were used in the present study. Thus, according to our data, the incidence of LR in the in-hospital phase of MI was 64%.

High prevalence of LR may be due to the inclusion of more than 60% of overweight and obese patients in the study. LR is characterized by impaired sensitivity of leptin receptors in the hypothalamus and peripheral tissues, which leads to a decrease in the feeling of satiety, excessive intake of nutrients, and an increase in body fat, expressed in higher BMI [9].

In the present study, we analyzed the relationship between LR and metabolic, proinflammatory, and adipokine profiles in patients with MI. When studying the carbohydrate metabolism parameters, hyperglycemia was detected on day 1 of the disease in patients of both groups. The pathogenetic mechanisms underlying hyperglycemia in the acute phase of MI have not been fully elucidated. Blood glucose levels can be transiently elevated either as a stress response to an acute process or as a result of inflammatory and adrenergic adaptation to ischemic injury leading to release of catecholamines, steroids, and induction of glycogenolysis [10]. However, patients with LR had a significantly higher glucose level on day 1 after MI compared to patients without LR. One explanation to this phenomenon in LR may be the inability of leptin to exert a physiological hypoglycemic effect. Leptin lowers blood glucose levels both through the central nervous system (by binding to its receptor on GABAergic neurons,

in particular pro-opiomelanocortin (POMC) neurons and agouti-related proteins (AgRP) in the hypothalamus) and through a direct effect on peripheral tissues – the pancreas, muscles, and the liver [11]. As a result, glucagon synthesis is suppressed, glucose uptake is increased, and glucose production by the liver is inhibited. However, in LR, the transmission of intracellular signals is impaired either at the level of the leptin receptor or against the background of a decrease in leptin transport through the blood – brain barrier [12]. Consequently, sensitivity of tissues to leptin is reduced despite its abundant amount, leading to an increased content of glucose in the blood plasma.

According to the scientific literature, leptin is involved in the regulation of sensitivity to insulin, whereas the presence of LR can serve as one of the triggers for the development of IR. More than 60% of patients with LR and about 30% of patients without LR had moderate and severe IR according to the QUICKI index. Apparently, high prevalence of IR in the LR group is associated with a significantly higher insulin level in these patients. Under physiological conditions, leptin inhibits biosynthesis and secretion of insulin by pancreatic β-cells. When sensitivity to leptin is impaired, its physiological effect disappears, leading to increased insulin synthesis despite hyperleptinemia. In addition, it has been experimentally shown that insulin stimulates the production and secretion of leptin by fat cells, thereby maintaining a high level of leptin [13] and forming a "vicious circle". The above assumption is confirmed by the results of the correlation analysis – the FLI had a direct relationship with insulin concentrations and an inverse relationship with the values of the QUICKI index on day 12 after the MI onset.

Decreased sensitivity to insulin observed in MI also affected FFA metabolism [14]. According to our data, an increased level of FFA was observed on day 1 after MI in both groups, while LR was associated with a more pronounced increase in the content of FFA in the blood. At early stages of IR formation, the amount of FFA increases due to a loss of the inhibitory effect of insulin on lipolysis in adipocytes. The incidence of IR in the group of patients with LR was 2.1 times higher than in the group of patients without LR, which apparently explains the significant increase in the concentration of FFA in this group of patients. The association of IR and FFA is confirmed by the data of the correlation analysis. An inverse relationship was found between the QUICKI index and the content of FFA on day 1 after MI (r = –0.424, p = 0.02). On day 12 after MI, the content of FFA decreased in both studied groups, which is probably due to increased utilization of FFA by the myocardium, which are necessary for synthesis of ATP, the main substrate for energy production for cardiomyocytes.

Patients of both groups were characterized by an increase in markers of proinflammatory and prothrombotic state throughout the entire observation period. Acute myocardial ischemia causes cellular damage and death of various components of the myocardium – cardiomyocytes, endothelial cells, fibroblasts, and interstitium. This, in turn, initiates an acute inflammatory response and leads to release of various proinflammatory mediators that induce recruitment of inflammatory cells to the area of MI and enhance the inflammatory response after MI [15]. High content of PAI-1 in the in-hospital phase of MI can be maintained by TNFα, which is one of the most powerful activators of PAI-1 synthesis [16]. However, patients with LR were characterized by a significant increase in the concentration of IL-6, TNFα, and PAI-1 in the blood serum compared to patients without LR.

One possible explanation to this phenomenon may be a high concentration of leptin observed in LR. Hyperleptinemia functionally activates circulating monocytes and dendritic cells and stimulates their proliferation. As a result, increased production of IL-6 and TNF-α is induced [17]. High concentrations of leptin also activate B lymphocytes via the JAK2 / STAT3 signaling pathways, causing the secretion of IL-6 and TNFα. Binding of leptin to the leptin receptor on B lymphocytes results in the formation of a receptor complex that allows JAK2 to be activated by phosphorylation. Activated JAK2 phosphorylates several tyrosine residues and provides a docking site for STAT3. STAT3 translocates to the nucleus and modulates the transcription of genes, including proinflammatory cytokine genes [18]. In addition, a high level of leptin probably enhances the expression of PAI-1 in vascular endothelial cells through the activation of ERK1/2, resulting in its increased secretion [19].

The identified changes in body reactivity in LR, being potentially atherogenic and thrombotic, probably contribute to the development and progression of atherosclerotic lesions of the coronary arteries [20]. The results obtained confirm this assumption. Thus, patients with LR had a higher degree of coronary damage according to the SYNTAX Score. Multivessel

coronary artery disease was also more common in the group of patients with LR compared to patients without LR.

Extensive and profound myocardial injury, characterized by predominant damage to the anterior wall of the LV and Q-wave MI, was most common in the group of patients with LR. Hyperleptinemia disrupts NO-dependent vasorelaxation induced by acetylcholine, reducing blood flow to tissues and contributing to the aggravation of ischemic heart damage. Elevated leptin levels may act synergistically with other factors such as inflammation. In particular, the response of the hypothalamic – pituitary – adrenal axis to inflammation causes activation of the sympathetic nervous system, leading to coronary vasoconstriction, affecting both macro- and microcirculation and contributing to more profound myocardial damage. In addition, it was found that IR increases sensitivity of the myocardium to ischemia, thereby leading to a decrease in left ventricular contractility. Thus, according to our data, patients with LR were significantly more likely to have reduced LVEF compared to patients without LR.

When carrying out the logistic regression analysis, we found a possibility of verifying LR in patients during the in-hospital phase of MI using BMI, the number of affected arteries, LVEF, as well as the concentration of glucose, FFA, and IL-6 on day 1 after MI. Patients with LR were more likely to experience adverse cardiovascular events compared to patients without LR. Patients with LR in the early in-hospital phase of MI were characterized by the development of early post-infarction angina and recurrent AMI. These complications did not occur in the group of patients without LR.

One of the reasons for the development of early post-infarction angina and recurrent AMI is a stenosing lesion of other branches of the coronary arteries. The development of early post-infarction angina and recurrent AMI in patients with LR may be explained both by elevated leptin levels throughout the in-hospital phase of MI and by the revealed changes in metabolism that accompany LR. Leptin has a direct effect on platelet aggregation, since the leptin receptor is also present on platelets. Thus, in LR characterized by elevated leptin levels, ADP-induced platelet aggregation increases [21]. According to our study, LR increases the content of prothrombotic and antifibrinolytic protein – PAI-1.

PAI-1 has antiprotease activity and is the main physiological inhibitor of tissue and urokinase-type plasminogen activators. Elevated levels of PAI-1 lead to inhibition of intravascular fibrinolysis, which may potentiate atherothrombosis. LR is also accompanied by a pronounced increase in proinflammatory cytokines with proatherogenic effects. The proatherogenic effect of TNFα on the endothelium is due to its role in the production of reactive oxygen species, a decrease in the bioavailability of NO, and an increase in the permeability of the endothelium for components and cells of the circulating blood. As a result, the above effects observed in LR can provoke the development of arterial thrombosis and, as a result, early post-infection angina and recurrent AMI.

Rhythm and conduction disorders were typical of patients with LR. For patients with STEMI, the most common complication of arrhythmia is atrial fibrillation (AF). Currently, there are studies proving the role of LR in the development of A.F. Anaszewicz et al. conducted a comparative study of 80 patients with AF and 169 patients without AF and confirmed that patients with AF have higher levels of leptin. In addition, a 1 pg / ml rise in the blood leptin concentration increased the risk of AF by an average of 2%. [22]. The observed changes in the body reactivity in LR might lead to more pronounced ischemia and myocardial necrosis, thereby contributing to the morphological and electrophysiological changes necessary for the development of AF.

According to the results of our study, an increase in the FLI, one of the criteria for LR, may increase the odds for developing cardiovascular complications in the in-hospital phase of MI. In addition, according to the data of the logistic regression analysis, the prognosis can be affected by BMI, FFA, and IL-6 on day 1 of MI and by TNF-α on day 12 of MI, an increase in which is observed in patients with LR.

CONCLUSION

Patients with MI are characterized by high prevalence of LR in the in-hospital phase of MI. LR is associated with CVD risk factors, metabolic disorders, IR formation, and increased markers of the proinflammatory and prothrombotic state. The identified features in the presence of LR may contribute to the development of adverse cardiovascular events in the in-hospital phase of MI.

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