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Leptin Resistance as a Risk Marker of Type 2 Diabetes Mellitus in Obese Patients

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The purpose of the study was to investigate the influence of leptin resistance on the formation of the risk of type 2 diabetes mellitus in obese patients.

Materials and methods. We monitored 50 obese patients who consulted an endocrinologist and a gastroenterologist-nutritionist during 2021-2022. The diagnosis of obesity was made on the basis of bio-impedance examination, as well as by calculating the body mass index.

Results and discussion. The article describes and analyzes the level of leptin and leptin resistance as a marker of the risk of type 2 diabetes mellitus in obese patients. To establish the diagnosis of obesity, all patients underwent a bioimpedance examination, and the body mass index was also calculated. Obesity was diagnosed when the body fat content of women was more than 40%, men – more than 28%, and body mass index – more than 30 kg/m^2. To identify the syndrome of insulin resistance, the index of insulin resistance was calculated according to the formula: HOMA-IR = fasting insulin (µIU/ml) x fasting glucose (mmol/l) / 22.5. Values exceeding 2.0 were considered insulin resistance. Leptin resistance was diagnosed by determining the presence of the leptin receptor gene and leptin level in blood serum. Leptin resistance was considered to be values of leptin indicators for men more than 5.6 ng/ml, for women – more than 11.1 ng/ml.

The level of leptin in blood serum in the group of healthy individuals was within the range of 6.36 ± 2.09 ng/ml in women and 2.96 ± 1.84 ng/ml in men. On the other hand, in obese patients, the serum leptin concentration was 51.49 ± 8.33 ng/ml and 29.71 ± ± 6.93 ng/ml, respectively. Also, according to the results of the study, a significantly higher level of insulin resistance was observed in all obese patients compared to the control group. These values were at the level of 6.64 ± 2.81 and 7.11 ± 3.52, respectively. Analyzing the results of the study, a reliable relationship between the level of leptin and the severity of obesity was found in all patients. A clear relationship between leptin level and the degree of insulin resistance was also determined.

A correlation between the level of leptin and HOMA-IR (r=0.70333; p=0.052) was established, as well as a correlation between fat content, body mass index, leptin level and HOMA-IR (r=0.86187, p=0.0086; r=0.93595, p=0.009; r=0.78098, p=0.007). The detected changes indicate a possible role of leptin and leptin resistance in the pathogenesis of type 2 diabetes mellitus and indicate that the level of leptin can be used as a predictor of the risk of developing type 2 diabetes mellitus in obese patients.

Conclusion. An increase in leptin level in blood serum is observed in obese patients. The level of leptin affects the degree of insulin resistance and can be an additional marker of the risk of type 2 diabetes mellitus in obese patients.

Keywords: obesity, type 2 diabetes mellitus, insulin resistance, leptin, leptin resistance.

Introduction. Obesity is a triggering factor for diabetes mellitus associated with insulin resistance. In individuals who are obese, higher amounts of non-esterified fatty acids, glycerol, hormones, and pro-inflammatory cytokines that could participate in the development of insulin resistance are released by adipose tissue [1]. The discovery of leptin changed the view of adipose tissue from that of a passive vessel that stores fat to that of a dynamic endocrine organ that actively regulates behaviour and metabolism. Secreted by adipose tissue, leptin functions as an afferent signal in a negative feedback loop, acting primarily on neurons in the hypothalamus and regulating feeding and many other functions [2].

In obesity, excessive caloric intake promotes a low-grade inflammatory response, which leads to dysregulations in lipid storage and adipokine secretion. In turn, these entail alterations in leptin sensitivity, leptin transport across the blood-brain barrier and defects in post-receptor signaling [3]. Leptin resistance in obese or type 2 diabetes mellitus (T2DM) patients is defined as a decrease in tissue response to leptin. As the prevalence of obesity and diabetes mellitus is continuously increasing, strategies are needed to develop and apply human cell-based models to better understand the precise role of leptin [4].

The purpose of the study was to study the influence of leptin resistance on the formation of the risk of type 2 diabetes mellitus in obese patients.

Materials and methods. We monitored 50 obese patients who consulted an endocrinologist and a gastroenterologist-nutritionist during 2021-2022. The age of the patients was 40-56 years. There were 22 (44.0%) men and 28 (56.0%) women among the examined patients. The control group consisted of 20 practically healthy persons (PHP) aged 40 to 51 years: men – 8 (40.0%), women – 12 (60.0%).

The diagnosis of obesity was made on the basis of bioimpedance examination, as well as by calculating the body mass index (BMI). At the same time, obesity was diagnosed when the fat content in the body of women was more than 40%, men – more than 28%, and BMI – more than 30 kg/m². To detect the syndrome of insulin resistance (IR), the index of insulin resistance (HOMA-IR – Homeostasis Model Assessment of Insulin Resistance) was calculated according to the formula: HOMA-IR = fasting insulin (µIU/ml) x fasting glucose (mmol/l) / 22.5. With IR, the values of indicators exceeded 2.0. The level of leptin in blood serum was also determined. Leptin resistance (LR) was diagnosed by determining the presence of the leptin receptor gene (LEPR) and the level of leptin in blood serum. LR was set at a leptin level of more than 5.6 ng/ml for men, and more than 11.1 ng/ml for women.

The study was carried out in compliance with the basic provisions of the "Rules of ethical principles of scientific medical research with human participation", approved by the Declaration of Helsinki (1964-2013), ICH GCP (1996), EEC Directive No. 609 (dated 24.11.1986), Orders of the Ministry of Health of Ukraine No. 690 (dated 23.09.2009), No. 944 (dated 14.12.2009), No. 616 (dated 03.08.2012). All the participants were informed about the goals, organization, methods of examination and signed an informed consent to participate in the completely anonymous study.

The statistical processing of the patients' results was carried out using program STATISTICA 10.0 (StatSoft Inc., USA).

Research results. For a comprehensive assessment of the degree of obesity, IR and LR, a bioimpedance examination was performed, BMI was determined, HOMA-IR was calculated, and the level of leptin in blood serum was determined (**Table 1**).

As can be seen from the above indicators, IR and LR syndrome were detected in all obese patients, and the indicators were significantly higher compared

Table 1 – Indicators of obesity, IR and LR in the studied patients and the control group

Indicator	Research group (n=50)		PHP (n=20)	
	Women (n=28)	Men (n=22)	Women (n=12)	Men (n=8)
Fat content (%)	45.13±3.68*	37.81±4.72*	31.64±4.19	24.1±2.59
BMI (kg/m²)	37.25±4.42*	34.6±3.77*	23.17±1.09	22.51±1.84
HOMA-IR	6.64±2.81*	7.11±3.52*	1.48±0.4	1.5±0.39
Leptin (ng/ml)	51.49±8.33	29.71±6.93	6.36±2.09	2.96±1.84

Note: * – a statistically significant difference was found between the indicators of the research group and the indicators of the control group (p<0.05)

to the control group. To identify the dependence between the mentioned indicators, we conducted a correlation analysis. At the same time, a strong direct correlation between the level of leptin and HOMA-IR was established (r=0.70333; p=0.052) (**Figure 1**).
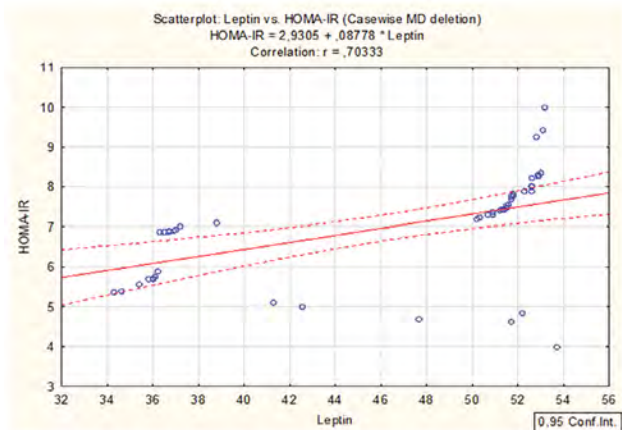

Figure 1 – Correlation between the level of leptin and HOMA-IR

We also established a correlational dependence of the average strength between fat content, BMI, leptin level and HOMA-IR (**Figures 2, 3, 4, 5**).
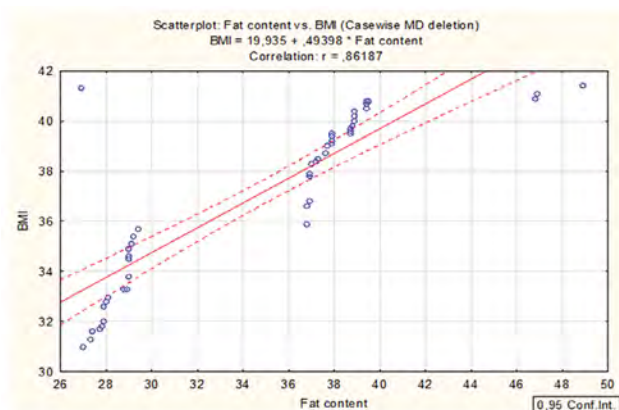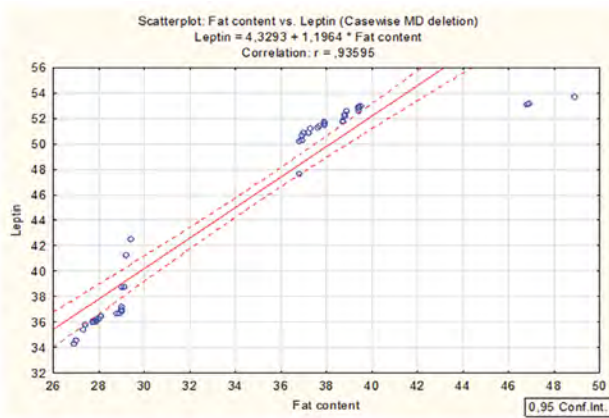

Figure 2 – Correlation between fat content and BMI

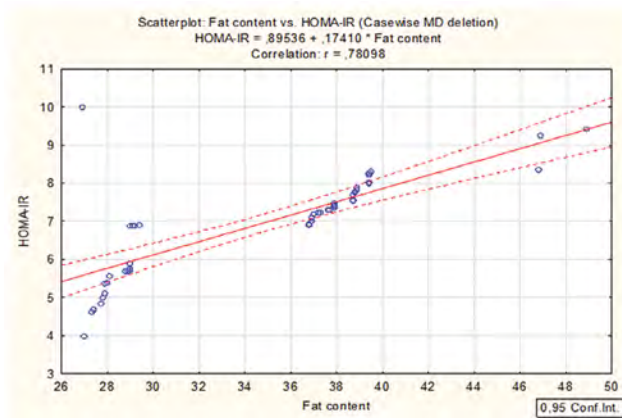**Figure 3 –** Correlation between fat content and leptin level

Figure 4 – Correlation between fat content and HOMA-IR

Discussion. The results of this study confirm the pathogenetic role of leptin resistance as a risk marker for type 2 diabetes mellitus in obese patients. Analyzing the above results, we found a statistically significant relationship between the level of leptin and the severity of obesity in the studied patients. A clear relationship between leptin level and the degree of insulin resistance was also determined. The detected changes may indicate a possible role of leptin and leptin resistance in the pathogenesis of type 2 diabetes mellitus. According to the research results of other authors, abundant evidence has linked obesity and leptin resistance, which may precede or occur simultaneously to IR and T2DM [4].

At the same time, the level of leptin was higher in patients with insulin resistance compared to the control group. These changes also indicate that leptin may be a predictor of risk for type 2 diabetes mellitus. The detected changes confirm the results of other authors, according to which leptin affects the sensitivity of insulin receptors, and high leptin concentrations are directly related to obesity and the subsequent development of metabolic diseases, such as insulin resistance, type 2 diabetes mellitus and cardiovascular diseases [5].

Conclusion. An increase in leptin level in blood serum is observed in obese patients. The level of leptin affects the degree of insulin resistance and can be an additional marker of the risk of type 2 diabetes mellitus in obese patients.

Perspectives of further research. Further research will be dedicated to the study of the role of leptin resistance in the pathogenesis of obesity and type 2 diabetes mellitus.

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ЛЕПТИНОРЕЗИСТЕНТНІСТЬ ЯК МАРКЕР РИЗИКУ ЦУКРОВОГО ДІАБЕТУ 2 ТИПУ У ХВОРИХ З ОЖИРІННЯМ
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Резюме. *Метою* роботи було дослідити вплив лептинорезистентності на формування ризику виникнення цукрового діабету 2 типу у хворих з ожирінням.

Матеріал та методи. В дослідженні прийняли участь 50 пацієнтів віком 40-56 років із ожирінням, які звернулися до ендокринолога та гастроентеролога-дієтолога протягом 2021-2022 років.

Для встановлення діагнозу ожиріння, всім хворим було проведено біоімпедансне обстеження, а також розраховано показник індексу маси тіла. Ожиріння діагностували при вмісті жиру в організмі жінок

більше 40 %, чоловіків – більше 28 %, а також при індексі маси тіла більше 30 кг/м². Для виявлення синдрому інсулінорезистентності було розраховано індекс інсулінорезистентності за формулою: HOMA-IR = інсулін натще (мкМО/мл) х глюкоза натще (ммоль/л)/22,5. Інсулінорезистентністю вважали значення показників, які перевищували 2,0. Лептинорезистентність діагностували визначаючи наявність генулептинового рецептора та рівня лептину у сироватці крові. Лептинорезистентністю вважали значення показників лептину для чоловіків більше 5,6 нг/мл, для жінок – більше 11,1 нг/мл.

Результати та висновки. Рівень лептину у сироватці крові у групі практично здорових осіб знаходився в межах 6,36±2,09 нг/мл у жінок та 2,96±1,84 нг/мл у чоловіків. Натомість, у хворих з ожирінням концентрація сироваткового лептину склала 51,49±8,33 нг/мл та 29,71±6,93 нг/мл відповідно. Також, за результатами проведеного дослідження спостерігалися статистично достовірно вищі показники інсулінорезистентності у всіх хворих з ожирінням порівняно з контрольною групою. Ці значення знаходилися на рівні 6,64±2,81 та 7,11±3,52 відповідно. При цьому було встановлено пряму кореляційну залежність між рівнем лептину та HOMA-IR (r=0,70333; p=0.052), а також кореляційну залежність середньої сили між вмістом жиру, індексом маси тіла, рівнем лептину та HOMA-IR (r=0,86187, p=0,0086; r=0,93595, p=0,009; r=0,78098, p=0,007). Виявлені зміни свідчать про можливу роль лептину та лептинорезистентності у патогенезі цукрового діабету 2 типу та вказують, що лептин може слугувати предиктором ризику виникнення цукрового діабету 2 типу у хворих з ожирінням.

Ключові слова: ожиріння, цукровий діабет 2 типу, інсулінорезистентність, лептин, лептинорезистентність.

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A – Work concept and design, B – Data collection and analysis,
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E – Critical review, F – Final approval of the article

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