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FEATURES OF LIPID METABOLISM IN PATIENTS WITH TYPE 2 DIABETES MELLITUS AND GOUT

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The aim: *To study the relationship between lipid metabolism parameters, chemerin, and adenosine monophosphate-activated protein kinase (AMPK) activity in patients with type 2 diabetes mellitus (T2DM), as well as in patients with a combined course of T2DM and gout.*

Materials and methods. *To assess lipid metabolism disorders, 100 patients were examined and divided into 2 groups: 1st group – patients with T2DM and gout (n=70), 2nd group – patients with gout (n=30), control group (CG) – practically healthy individuals (n=20). The levels of total cholesterol (TC), triglycerides, high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), and very low-density lipoprotein cholesterol (VLDL) were analyzed. As markers of insulin resistance (IR), the content of AMPK and chemerin was investigated. Statistical data processing was carried out using the statistical data processing program package version 8.0 STATISTICA (StatSoft Inc).*

The results. *A significant difference was found between the levels of lipid parameters (except HDL) when comparing patients with the combined pathology of T2DM and gout, with a monocourse of gout and representatives of CG ($p<0.001$). It was also found that among lipidogram indicators, in all groups, an inverse correlation of AMPK value with LDL level was found (strong for patients of the 1st group and medium strength for representatives of the 2nd group and CG). Another indicator with which AMPK levels in all groups were statistically reliably correlated was TC. The presence of a direct correlation between the levels of LDL and chemerin in the 2nd group and CG, as well as the levels of TC and chemerin in patients with a combination of T2DM with gout and an inverse correlation in the other groups (all $p<0.05$) was established.*

Conclusions: *Statistically significant relationships were found between lipid metabolism indicators, chemerin and AMPK activity in patients with T2DM, as well as in patients with combined course of T2DM and gout*

Keywords*: type 2 diabetes mellitus, gout, AMPK, chemerin, lipid metabolism*

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1. Introduction

Type 2 diabetes mellitus (T2DM) is the most important medical and social problem today with a tendency to spread rapidly. According to data from the International Diabetes Federation (IDF), the number of patients with type 2 diabetes mellitus will reach 67 million by 2023 [1]. The increase in morbidity is connected, first of all, with the growth of obese patients, leading to a less active lifestyle and abuse of tobacco and alcohol. Thus, the presence of obesity of the 2nd degree increases the risk of type 2 diabetes by 93 % [2, 3]. T2DM and gout are widespread metabolic disorders characterized by a complex interplay of genetic, endocrine, immune, and environmental factors. T2DM, in particular, is a leading cause of morbidity and mortality worldwide due to its complications, such as cardiovascular disease, nephropathy, retinopathy, and neuropathy [4]. The presence of obesity contributes to the formation of insulin resistance (IR) and an increase in the production of adipokines, including chemerin, resistin, leptin, visfatin and others [5].

In recent years, the attention of researchers has focused on studying the role of adipokines, in particular chemerin, in the regulation of glucose and lipid metabolism, as well as in the mechanisms of IR development and inflammatory processes accompanying metabolic diseases [6, 7]. Chemerin is an adipocytokine with pleiotropic properties that plays a significant role in the pathogenesis of inflammatory and metabolic disorders in various organs, such as adipose tissue, the cardiovascular system, the reproductive system, and the musculoskeletal system [8, 9]. Chemerin levels were found to be positively correlated with body mass index (BMI) and obesity-related biomarkers. Analyzing the data over the last decade, it was established that chemerin plays an important role in the regulation of energy balance, which makes it a promising marker for the development of strategies for the pharmacological treatment of obesity and IR.

Adenosine monophosphate-activated protein kinase (AMPK) is another key regulator of energy balance and metabolic pathways in cells, playing a central role in maintaining glucose homeostasis, as well as in regulating lipid metabolism [10, 11]. The ability of AMPK to control a variety of metabolic processes makes it an attractive target for therapeutic interventions in the treatment of T2DM and other metabolic diseases, particularly gout [12, 13].

Considering the above, **the aim of our study** was to study the relationship between lipid metabolism indicators, chemerin and AMPK activity in patients with T2DM, as well as in patients with a combined course of T2DM and gout. The results of this study may provide new insights into the mechanisms underlying these diseases and contribute to the development of new treatment strategies.

2. Materials and methods of the research

The main group of studied patients consisted of women and men who were treated in the rheumatology and endocrinology departments of the CNE KRC "Regional Clinical Hospital" in 2020–2022, which is the clinical base of the Department of Internal Medicine No. 3 and Endocrinology of the Kharkiv National Medical University.

100 patients aged 45 to 65 years were selected for the study and divided into 2 groups: 1a – women and men with comorbid T2DM and gout (n=70, average age – 55.9±5.89 years), 2a – women and men with monocourse of gout (n=30, average age – 55.3±6.29 years). The control group (CG) consisted of 20 relatively healthy men and women of the appropriate age.

The diagnosis of T2DM in all examined patients was established on the basis of clinical and laboratory data, namely the determination of indicators of carbohydrate metabolism - fasting venous blood glucose (using the Hagedorn-Jenson glucose oxidase method using the "Felisit" reagent kit), glycemic profile (glucose oxidase method using the "Felisit" reagent kit), glycosylated haemoglobin (by the kinetic method using the DAC-Spectro Med kit), insulin determination (by the immunoenzymatic solid-phase method using the ELISA reagent kit, manufactured by DRG); HOMA (homeostasis model assessment) IR index by mathematical calculation. Verification of the diagnosis was carried out in accordance with the generally accepted criteria in clinical practice and the order of the Ministry of Health of Ukraine No. 1118 dated 12.21.2012.

The diagnosis of gout was established in accordance with the approved order of the Ministry of Health of Ukraine, "Clinical protocol for providing medical care to patients with gout" No. 676 dated 12.10.2006. According to the standard methodology, the following studies were conducted: X-ray of the small joints of the feet; general blood test; biochemical blood test – uric acid level (by colourimetric method using the SpineLab, UricasePOD, Ukraine reagent kit). C-reactive protein in blood serum.

Lipid profile indicators were investigated according to standard biochemical methods with the determination of total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL), (enzymatic-photometric method with cholesterol oxidase/peroxidase using the DAC-Spectro Med kit), low-density lipoprotein cholesterol (LDL) (mathematical calculation according to the Friedwald formula), very low-density lipoprotein cholesterol (VLDL).

Along with the analysis of the standard clinical symptoms of the course of gout in T2DM patients, at the current stage, for scientific purposes, the content of AMPK, chemerin, which were determined by the immunoenzymatic method, was investigated. To determine the levels of AMPK and blood chemerin, a variant of the indirect non-competitive heterogeneous enzyme immunoassay was used on the "Labline-90" analyzer (Austria) using a commercial test system manufactured by the company "Elabscience" (China).

The statistical processing of the obtained data was carried out using the statistical data processing program package version 8.0 STATISTICA (StatSoft Inc). The relationship between the obtained characteristics was determined using Spearman's rank correlation coefficient r. If r was in the range from 0 to –1.0, the correlation was considered inverse; if it was from 0 to 1.0 – it was a straight line. r coefficients from 0 to 0.3 (from 0 to –0.3) stated the presence of a weak connection between the studied features; from 0.4 to 0.7 (from –0.4 to –0.7) – moderate strength and from 0.7 to 1.0 (from –0.7 to –1.0) – high strength. The result was presented in the form of the value r of the coefficient and the corresponding level of reliability r. To evaluate the differences between the average values of indicators in independent groups, ANOVA variance analysis was used.

The criteria for inclusion in the study were the presence of voluntary consent to participate in the study, the presence of gout, T2DM, and the patient's age from 45 to 65 years.

Exclusion criteria from the study were: patients aged 18 to 44 years, patients with type 1 diabetes, patients with secondary hyperuricemia (against blood diseases, hereditary disorders of purine metabolism), patients with stage 4–5 chronic kidney disease, patients with hypertension III stage disease, patients with decompensated heart failure, cancer patients, patients with a history of alcohol abuse.

All patients signed an informed consent to participate in the study in accordance with the Code of Ethics of the World Medical Association (Declaration of Helsinki). The research protocol was approved by the decision of the Committee on Ethics and Bioethics of the Kharkiv National Medical University (October 7, 2020).

3. Results

When examining the state of lipid metabolism in the subject patients, signs of dyslipidemia, hypercholesterolemia, and increased levels of LDL and VLDL were noted.

Table 1

Indicators of lipid metabolism in patients with T2DM and gout, isolated gout (M±m)

Indicator	Patients with T2DM and gout, n=70	Patients with isolated gout, n=30	p-criterion
TC, mmol/l	5.92±0.89	5.51±0.83	p<0.001
TG, mmol/l	2.21±0.86	1.8±0.86	p<0.001
HDL, mmol/l	1.4±0.2	1.43±0.16	p>0.05
LDL, mmol/l	3.34±0.89	3.23±0.64	p>0.05
VLDL, mmol/l	1.11±0.44	0.96±0.42	p<0.001

The obtained results illustrate those patients with a combination of T2DM and gout are characterized by higher levels of TC and TG (5.92±0.89 and 2.21±0.86, respectively) compared to similar indicators among patients with a single course of gout – 5.51 ±0.83 and 1.8±0.86, respectively (p<0.001). It should also be noted that statistically reliable patterns were not found for all indicators of different groups of lipoproteins. Thus, HDL and LDL levels were comparable in the studied groups, respectively. However, VLDL levels among patients with comorbid pathology compared to patients with monocourse of gout turned out to be higher – 1.11±0.04 and 0.96±0.04, respectively (p<0.01).

Based on the obtained results of lipid metabolism indicators in patients with T2DM and gout, the levels of interdependencies of lipid metabolism indicators: TC, TG, HDL, LDL, and VLDL were investigated with a monocourse of gout.

Based on the obtained data in the study, it was concluded that TC levels had a probable inverse relationship of medium strength with AMPK values (r=–0.46, p=0.008), and a strong correlation was established between LDL and AMPK indicators. relationship (r=–0.73, p<0.001). It also revealed the presence of a direct probable correlation between the average strength of these indicators and chemerin – r=0.35 and r=0.44, respectively (p<0.05). It should be emphasized that reliable correlations between AMPK and chemerin with other indicators of lipid metabolism: TG, HDL, and VLDL were not established.

For patients with a monocourse of gout, the presence of an inverse average strength of correlation between AMPK and LDL levels was determined: r=–0.58, p=0.006. Probable direct relationships of the average strength of AMRK levels with TC, TG, and VLDL values were also noted (all p<0.05). As in the case of the representatives of the 1st group, in the 2nd group, there was proved the existence of a strong direct correlation between the levels of chemerin and LDL (r=0.76, p<0.001), as well as an inverse correlation of medium strength between by the values of chemerin and TC (r=–0.44, p=0.008).

4. Discussion of research results

The direct correlation between LDL and chemerin, which was found in our study, may indicate the complex role of this adipokine in metabolic and inflammatory processes associated with dyslipidemia, which was confirmed in studies [14, 15].

When analyzing the studies of Yue G et al. [16] found that high LDL levels can promote oxidative stress and chronic inflammation, which in turn induces chemerin expression through NF-κB and other inflammatory signalling pathways, which was also noted in our study.

In our study, it was emphasized that the inverse correlation between AMPK activity and LDL level confirms the role of AMPK as a key regulator of energy metabolism, lipid homeostasis, and insulin sensitivity [17]. In the course of research He L. et al. [18] it was confirmed that AMPK activation leads to increased fatty acid oxidation, inhibition of lipid synthesis and improvement of glucose homeostasis.

The interaction between LDL, chemerin and AMPK may be particularly important in the context of gout, where chronic inflammation plays a central role. Elevated levels of LDL can promote the formation and deposition of urate crystals, triggering an inflammatory response.

Thus, the results of our study indicate the complexity of the interactions between the lipid profile, adipokines, and kinases that regulate energy metabolism and emphasize the need for further research to better understand these relationships and their role in the pathogenesis of T2DM and gout.

Practical value. The obtained results of the study may provide an opportunity to optimize the treatment of patients with T2DM and gout, affecting various pathogenetic links leading to IR.

Study limitations. There were no restrictions during the research.

The influence of martial law conditions. The state of war in Ukraine did not affect the conduct of scientific research.

Prospects for further research. Based on the obtained information, it is planned to create a prognostic model of the risks of development and progression of IR in patients with T2DM and a combined pathology, such as gout.

5. Conclusions

1. Statistically significantly higher levels of TC, TG and VLDL were noted among patients with a comorbid combination of T2DM and gout compared to the indicators of patients with a monocourse of gout.

2. The presence of statistically reliable direct correlations between chemerin and LDL levels, as well as inverse probable relationships between AMPK and LDL indicators in patients with gout, regardless of the presence of comorbid T2DM pathology, was established.

3. An increase in the levels of chemerin and a decrease in the level of AMPK is evidence of the intensity of the inflammatory process and dysregulation of lipid metabolism, which occurs in patients with obesity, T2DM and gout.

4. Determining the relationship between lipid metabolism and indicators of AMRK and chemerin, as regulators of cellular metabolism, is appropriate for improving the treatment tactics of comorbid patients.

Conflict of interest

The authors declare that they have no conflict of interest in relation to this study, including financial, personal, authorship, or any other, that could affect the study and its results presented in this article.

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Data availability

Data will be provided upon reasonable request.

Use of artificial intelligence technologies

The authors confirm that they did not use artificial intelligence technologies when creating the presented work.

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