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PATHOGENESIS AND CLINICAL COURSE OF TYPE 2 DIABETES MELLITUS CONCOMITANT WITH OBESITY

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The paper considers the role of obesity in the development of type 2 diabetes mellitus. Features of the conjoint pathogenesis are specified. Purpose: to study the features of the clinical course of type 2 diabetes mellitus concomitant with obesity on the basis of the comprehensive study of the indicators of systemic nonspecific inflammation, insulin resistance, carbohydrate and lipid metabolism. 268 patients with type 2 diabetes mellitus have been treated. The patients were randomized into 2 groups: type 2 diabetes mellitus without obesity and type 2 diabetes mellitus and obesity. The analysis of carbohydrate and lipid metabolism, biomarkers of inflammation and indicators that characterize insulin resistance in all patients with type 2 diabetes mellitus and obesity has found the significantly higher indicators in contrast to patients with diabetes without obesity. It is recommended to consider obesity as the basis for the adverse course of the type 2 diabetes mellitus concomitant with obesity and the onset and progression of complications.

Key words: diabetes mellitus, visceral obesity, insulin resistance, chronic low-intensity inflammation.

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ПАТОГЕНЕЗ ТА ПЕРЕБІГ ЦУКРОВОГО ДІАБЕТУ 2 ТИПУ НА ТЛІ ОЖИРІННЯ

У статті наведені дані про роль ожиріння в розвитку цукрового діабету 2 типу. Вказані особливості спільного патогенезу. Мета: дослідити особливості клінічного перебігу цукрового діабету 2 типу у поєднанні з ожирінням на підставі комплексного вивчення показників системного неспецифічного запалення, інсулінорезистентності, вуглеводного та ліпідного обмінів. Проліковано 268 хворих з цукровим діабетом 2 у поєднанні з ожирінням. Пацієнти рандомізовані на 2 групи: цукровий діабет 2 типу без ожиріння та цукровий діабет 2 типу у поєднанні з ожирінням. При проведені аналізу вуглеводного та ліпідного обмінів, біомаркерів запалення та показники, які характеризують інсулінорезистентністьу у всіх хворих на цукровий діабет 2 типу в поєднанні з ожирінням були виявлені значно вищі показники, ніж у хворих з цукровим діабетом без ожиріння. Рекомендовано при виборі тактики у хворих на цукровий діабет 2 тип у поєднанні з ожирінням, наявність ожиріння виносити на перший план, як основу несприятливого перебігу захворювання та виникнення і прогресування ускладнень.

Ключові слова: цукровий діабет, вісцеральне ожиріння, інсулінорезистентність, хронічне низькоінтенсивне запалення.

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Obesity is a chronic recurrent disease that develops as a result of metabolic disorders and eating behavior and is characterized by the accumulation of adipose tissue in the body. Obesity increases mortality, worsens the quality of life and is a significant socio-economic burden. Among the working population of Ukraine, obesity is diagnosed in almost 30 % of cases, and every fourth individual is overweight [6, 7, 15].

Diabetes mellitus (DM) is a condition of chronic hyperglycemia that occurs due to absolute or relative insulin deficiency, insulin resistance and is caused by a variety of exogenous, immune, endocrine and genetic factors or their combination. The increase in the incidence of DM 2 is closely correlated with the incidence of obesity. Almost 90 % of patients with diabetes are overweight or obese [1, 2].

Currently, type 2 diabetes mellitus and obesity have become pandemic, affecting all segments of the population, regardless of age, gender, social status, race and ethnicity [2].

At the beginning of the 21st century, the number of obese and diabetic patients exceeded 300 million and 245 million people, respectively [7, 15].

The nature of the distribution of adipose tissue is the risk factor for development of type 2 diabetes mellitus, and in abdominal obesity it increases by 3.5 times. Recent numerous studies have shown that visceral obesity, which is determined by the waist circumference (WC), is a more pronounced indicator of the development of diabetes and cardiovascular disease compared to body mass index (BMI) [3, 8]. Currently, adipose tissue is positioned as an endocrine organ because, in addition to secreting free fatty acids, it produces numerous proteins with autocrine, paracrine, and endocrine functions, marked as adipokines/adipocytokines. These substances have such biological effects as regulation, absorption and expenditure of energy, regulation of glucose and lipid metabolism, anti- and pro-inflammatory properties [8].

Adipose tissue of people with obesity and patients with type 2 diabetes mellitus is infiltrated by mononuclear cells and is in the state of chronic systemic low-grade inflammation (CSLI) [10, 13]. Adipocytes and infiltrating monocytes/macrophages secrete tumor necrosis factor alpha (TNF-α), resistin, interleukin 6 (IL-6), plasminogen activator-1 inhibitor, angiotensinogen, which induce insulin resistance and atherogenesis [3, 10]. CSLI is the basis for the development of multiple chronic diseases, especially atherosclerosis and its ischemic complications, obesity, type 2 diabetes mellitus, hypertension and many others [12].

It is known that numerous pathological processes in the human body are developed as a result of imbalance of the prooxidant and antioxidant systems. Patients with insulin resistance (IR), which interrelates with type 2 diabetes mellitus, obesity and hypertension, are characterized by hyperglycemia and increased production of proinflammatory cytokines, which significantly enhances oxidative stress [3, 8, 9].

The purpose of the study was to establish the features of the clinical course of type 2 diabetes mellitus concomitant with obesity on the basis of the comprehensive study of the indicators of systemic nonspecific inflammation, insulin resistance, carbohydrate and lipid metabolism.

Material and methods. The study involved 268 patients of both genders, aged 40 to 76 years with type 2 diabetes mellitus and obesity and type 2 diabetes mellitus without obesity. The study was performed in the Endocrinology Department of M.V. Sklifosovsky Poltava Regional Clinical Hospital, Research Institute of Genetic and Immunological Foundations of Pathology and Pharmacogenetics of PSMU. The subjects have been randomized into 2 groups: comparison group (n=119; type 2 diabetes mellitus without obesity) and study group (n=149; type 2 diabetes mellitus and obesity).

To diagnose obesity and its degree, the WHO classification criteria (1997) have been used. BMI of 19–24.99 kg/m^2 is normal body weight; BMI of 25–29.99 kg/m^2 is overweight; BMI from 30 to 34.99 kg/m^2 is Class I obesity; BMI from 35 to 39.99 kg/m^2 is Class II obesity; BMI over 40 kg/m^2 is Class III obesity [14, 15].

The diagnosis of type 2 diabetes mellitus was made in compliance with the "Unified clinical protocol of primary and secondary (specialized) medical care type 2 diabetes mellitus" (Order of the Ministry of Health of Ukraine No. 1118 as of 21.12.2012) [4].

The state of the inflammatory response was monitored and the level of TNF-α and IL-6 in both groups was determined (a set of test systems of CJSC Vector-Best, Russia). Additionally, C-peptide was determined by enzyme-linked immunosorbent assay (ELISA) using the test systems DRG (USA) and the HOMA index was calculated.

Changes in carbohydrate metabolism have been studied by determining the fasting blood glucose concentration, as well as levels of postprandial glycemia and serum glycosylated hemoglobin (HbA1c) (BIO-LA-TEST test system set, Erba – Lachema, Czech Republic).

The dynamics of the state of lipid metabolism was evaluated by measuring the level of total cholesterol (TC), triglycerides-, low- and high-density lipoproteins cholesterol (LDL cholesterol; HDL cholesterol) (a set of test systems "Bio – Lacbema – Tect", Czech Republic).

The following anthropometric parameters have been estimated: body weight, body mass index (BMI), waist circumference (WC), thigh circumference (TC), WC/TC ratio. Abdominal obesity in men was indicated by: WC≥102 cm, WC/TC index>1.0. Indicators in women: WC≥88 cm and WC/TC ratio>0.85 [1, 6].

Statistical analysis of the findings was performed using the BioStat software (Analyst Soft Inc., ver. 2009 for Windows), using the Mann – Whitney U test (for independent samples), Wilcoxon test (for dependent samples) and χ^2.

Results of the study and their discussion. The comparison of the findings of the study has shown that BMI was statistically significantly higher in the group of patients with type 2 diabetes mellitus and obesity (36.61±0.39 kg/m^2), compared to the group of type 2 diabetes mellitus without obesity (26.44±0.24 kg/m^2) ($p<0.001$). The WC/TC ratio in the study group was significantly higher (0.95±0.02) compared to the comparison group (0.79±0.01). Consequently, the findings of the study have established the presence of obesity, namely, abdominal.

Unsatisfactory glycemic control was revealed according to the data of average daily glycemia and glycosylated hemoglobin. The study of the indices of carbohydrate metabolism revealed statistically significantly higher rates of glycosylated hemoglobin in the group of patients with type 2 diabetes mellitus and obesity; the average daily blood glucose statistically did not differ between the comparison and study groups (table 1).

Table 1

Estimated glycemia

Index	Study group (n=149)	Comparison group (n=119)
Average daily blood glucose, mmol/L	9.55±0.21	9.27±0.2
p	p=0.516	
HbA1c, %	9.20±0.15	8.72±0.18
p	p<0.05	

Disrupted lipid metabolism is characteristic of both type 2 diabetes mellitus and type 2 diabetes mellitus with obesity. The comparison of the TC level in the group of patients with type 2 diabetes mellitus and obesity and type 2 diabetes mellitus without obesity has revealed higher TC level in the group with obesity; however, no statistical difference was found (p=0.554) (table 2). Moreover, the increase in LDL-C level, triglycerides and the decrease in HDL-C level was established in the study group (table 2). Significant disorders of lipid metabolism are probably caused by inadequate control for DM and the presence of obesity.

Table 2

Estimated lipid metabolism

Index	Study group (n=149)	Comparison group (n=119)	p*
TC, mmol/L	6.26±0.21	6.72±0.24	p=0.554
LDL-C, mmol/L	4.47±0.22	4.03±0.18	p<0.05
HDL-C, mmol/L	0.99±0.04	1.20±0.05	p<0.001
Triglycerides, mmol/L	2.82±0.21	2.27±0.18	p<0.05

The description of the carbohydrate and lipid metabolism state, namely hyperglycemia, high levels of glycosylated hemoglobin, elevated total cholesterol, LDL-C, triglycerides and lower HDL-C level shows the inadequate control of the disease and predict the further development of atherosclerosis. Apparently, the state of chronic hyperglycemia leads to disorders of lipid metabolism, and the prominence of the disorders may correlate with the severity of dyslipidemia [11].

Recent data have broadened understanding of the role of proinflammatory cytokines in many pathological conditions. Therefore, we have analyzed the content of nonspecific inflammatory mediators.

The analysis of the level of IL-6 and TNF-α cytokines has found that patients of the study group had significantly higher levels of these cytokines: IL-6 – 7.65±0.10 vs. – 5.61±1.12 pg/ml in comparison group, TNF-α – 4.13±0.10 vs. 1.6±0.4 pg/ml, respectively (p<0.001), which confirms the presence of chronic systemic inflammation in this category of patients.

The study of insulin resistance, based on the calculation of the HOMA index, has shown statistically higher results in the group of patients with type 2 diabetes mellitus concomitant with obesity (4.27±0.61). In the study group there was a significant increase in the level of C-peptide (3.44±0.77 ng/ml) compared to patients of the comparison group (2.40±0.85 ng/ml) (p<0.05). The increase in the index of HOMA and C-peptide give evidence of the apparent insulin resistance in patients of the study group. However, currently, hyperinsulinemia and IR are considered not only as the leading links in the development of type 2 diabetes mellitus and its complications, but also as a component actively involved in the pathogenesis of atherosclerosis, hypertension and other diseases. Numerous studies have shown that insulin can accelerate the development of atherosclerotic complications [8, 9, 11].

Therefore, the findings of our study provided data on the higher intensity of chronic inflammation and insulin resistance in subjects with diabetes mellitus type II and obesity.

The combination of type 2 diabetes mellitus and obesity is widespread in clinical practice, and this condition significantly aggravates the clinical course and complicates approaches to the therapy [5, 10, 12]. The studies have shown that it is abdominal obesity that is an independent risk factor for not only carbohydrate metabolism disorders, but also for dyslipidemia, cardiovascular diseases and mortality [5, 11, 12].

The Gothenburg study confirmed that one of the markers of visceral obesity, namely, the waist-to-hip ratio (WHR), is an independent risk factor for myocardial infarction and stroke and increases the risk of mortality from them. Notably, the WHR correlates with these diseases more precisely than the obesity degree, estimated by the body mass index (BMI) [6].

Judging by the statistics on the incidence of the disease, the problem of diabetes mellitus and obesity is relevant for any country worldwide and put the health at risk, leading to disability, early invalidization, reduced life expectancy and quality of life. The Diabetes Prevention Program and the Finnish Diabetes Prevention Study has found that even moderate weight loss (5–7 % of baseline) due to diet and lifestyle changes was accompanied by 58 % – reduction of the risk for developing of type 2 diabetes mellitus [14]. Reducing body weight per kilogram increases the life expectancy of a patient with diabetes concomitant with obesity by an average of 3–4 months [2].

Lifestyle changes lead to low expression of pro-inflammatory and increased anti-inflammatory genes. After weight loss, even the short-term dietary restrictions or the coming back to normal home activity and workload result in lowering of the level of inflammatory markers such as CRP, IL-6, IL-18, TNF-alpha and its receptors [10].

Therefore, it is the IR level, but not the BMI values, that is relevant to determining the GCR degree.

IR occurs long before the type 2 diabetes mellitus manifestation, possibly already in the child age [3, 8, 9] and is the leading factor of GCR. Numerous prospective studies show that cardiovascular diseases start developing well before the manifestations of DM 2 [11]. Consequently, the prevention of cardiovascular diseases should be based on the determination of the IR degree.

Numerous multicenter studies aimed at determining the impact of the various modes of hyperglycemia treatment and their meta-analyses have shown that "hard" control of the glycated hemoglobin level has only a moderate effect on the risk of the development of cardiovascular complications (CVC), indicating about the importance of other factors, not only hyperglycemia, in their development [13].

The IR correction is one of the important strategic lines for the prevention of cardiovascular diseases, which should be applied long before the onset of type 2 diabetes mellitus. being the end point of the IR development. Consideration should be given to the possibility of preventive prescription of medications that reduce the IR to individuals who, for various reasons, cannot adjust the IR through a diet and physical exercise [10].

Carbohydrate metabolism disorders in obese patients can be hidden for long period of time and almost undiagnosed. However, such disorders, as hyperglycemia, impaired glucose tolerance, hyperinsulinemia, shift of the lipid profile towards atherogenesis, blood coagulation system disturbances, hypercortisolemia, are markedly manifested in the clinical picture of type 2 diabetes mellitus [12].

Obesity is a leading modifying pathogenetic factor of type 2 diabetes mellitus. The rise in the incidence of type 2 diabetes mellitus is closely correlated with the obesity rate.

Conclusions

1. It is recommended to consider obesity as the basis for the adverse course of the type 2 diabetes mellitus concomitant with obesity and the onset and progression of complications.

2. Patients with type 2 diabetes mellitus concomitant with obesity are characterized by poor control of carbohydrate and lipid metabolism, regardless of disease duration, age and gender.

3. Patients with type 2 diabetes mellitus and obesity have revealed elevated concentrations of biomarkers of inflammation (IL-6 – 7.65±0.10 pg/ml, TNF-α – 4.13±0.10 pg/ml) and indicators of insulin resistance (C-peptide – 3.44±0.77 ng/ml, HOMA index – 4.27±0.61), which confirms the presence of insulin resistance and chronic systemic inflammation in this category of patients.

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