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THE ROLE OF CHEMERIN IN THE DEVELOPMENT OF METABOLIC DISORDERS AND INFLAMMATORY REACTION IN PATIENTS WITH TYPE 2 DIABETES AND OBESITY

Abstract. *This article presents an assessment of the effect of chemerin on the development of metabolic disorders and inflammatory response in patients with type 2 diabetes and obesity. The findings show that type 2 diabetes on the background of altered BMI is accompanied by an increase in the content of adipocytokine chemerin, which may be the result of both chronic inflammatory process in blood vessels and metabolic disorders. Increased chemerin content in patients with type 2 diabetes and obesity can be used as one of the indicators of systemic vasoconstriction in the mechanisms of vascular reactions and maintenance of the ischemic component of pathogenesis.*
Key words*: diabetes, metabolic syndrome, obesity, chemerin, adipocytokine.*

Introduction. Obesity as a background disorder in many diseases of the internal organs of non-infectious origin is an unfavorable factor in their progression and the formation of complications. This is due to the development of metabolic shifts due to active synthesis by white adipose tissue adipocytes of hormone-like substances (biologically active adipose tissue molecules) and proinflammatory cytokines (low molecular weight protein cellular regulators) involved in intercellular interactions [1].

Cytokine cascade plays a key role in the development of the T-lymphocyte-initiated chain of immunoinflammatory reactions, and the synthesized hormones give these reactions a specific color due to the extended direction of their reactions [2].

The biological, pathophysiological and metabolic effects of adipokines contribute to the development of metabolic disorders, and thus provoke the formation of complications of the underlying disease. The production of most inflammatory mediators increases in obesity and results in the progression of the disease itself and obesity-related metabolic disorders. That is, derivatives of adipokines should be considered as biological markers of pathological processes, and their study will create the conditions for preventive measures and contribute to a positive response to the treatment process [3]. Thus, the presence of obesity can be considered as a constant stimulus of adipocytes, which contributes to the chronic flow of active substances into the blood.

In recent years, researchers have focused on a relatively new adipocytokine, chemerin. Chemerin was identified in 1997 by differential display as a product of the retinoid response gene present in human skin psoriatic cells.

Experimental studies have shown that a high-fat diet in mice leads to increased expression of both chemerin and CMKLR1 – chemokine-like receptor 1 (CMKLR1) [4].

The potential role of chemerin in the regulation of carbohydrate metabolism and in the formation of insulin resistance is quite controversial and insufficiently studied. Thus, a number of researchers have found that the content of chemerin depends on the state of carbohydrate metabolism: it increases in type 2 diabetes

compared with patients with normal glucose tolerance [5]. Moreover, chemerin levels significantly correlated with body mass index, plasma triglyceride levels, and blood pressure [6].

In a clinical study by Adriana F. et al., patients with high obesity had high serum chemerin levels that positively correlated with insulin resistance (IR) and oxidative stress (r = 0.6) [7].

In contrast, a study by Erifili H. et al. showed no significant relationship between serum chemerin and IR in patients with obesity and non-alcoholic fatty liver disease (r> 0.18), although scientists suggest a possible association of chemerin with increased pancreatic beta cell function [8]. That is, according to the authors, the predominant cause of glucose intolerance in chemerin-deficient mice was a decrease in insulin synthesis, rather than existing IR [9].

These data were the basis for determining the content of chemerin and its role in patients with type 2 diabetes with various stages of obesity, as well as the impact on serum lipid profile.

The purpose of the study: to investigate the content of chemerin in the serum of patients with type 2 diabetes, which occurs on the background of obesity, and to determine its prognostic value in a combination of nosologies.

Materials and methods of the study. The study involved 103 patients with type 2 diabetes, which in 83 cases occurred in combination with overweight or obesity (main group). In 20 patients with type 2 diabetes, the disease was not accompanied by an increase in body mass index (comparison group). The age of patients ranged from 31 to 55 and the average for the groups was 43 ± 4.6 years and 44.1 ± 2.1 years, respectively. Both groups of patients predominantly comprised men, 44 (53%) and 11 (55%). The duration of the disease was registered in the range from 1 to 13 years.

Prior to the study, all patients signed an agreement to conduct a study that meets the ethical and moral requirements of the Regulations of the Ukrainian Association of Bioethics and GCP (1992), GLP (2002), in accordance with ICH requirements and standards, standard provisions on ethics of the Ministry of Health of Ukraine No. 66 of 13.02.2006

The diagnosis of type 2 diabetes was established according to the criteria of the unified protocol of medical care “Diabetes” (Order of the Ministry of Health of Ukraine of 21.12.2012 No. 1118). Obesity (OB) and its degree were diagnosed according to the WHO classification criteria (1997) with determination of the body mass index (BMI) by the Kettle formula: BMI = body weight (kg) / height (m2).

Determination of adipose tissue distribution in the body was carried out using scales to characterize body composition – OMRON BF511 (Japan). The content of visceral adipose tissue (VAT) and subcutaneous adipose tissue (SAT) was determined.

The level of chemerin in the serum of the examined patients was evaluated by enzyme-linked immunosorbent assay using commercial test systems Human Chemerin ELISA Kit (Kono Biotech Co., Ltd., China) according to the instructions included in the kit on the enzyme-linked immunosorbent assay “Labline-90” (Austria).

Statistical analysis was performed using the software package “Statistica 10.0” and Excel 2010.

Results and discussion. In the study, patients with diabetes were divided into groups depending on the presence and degree of concomitant obesity. Thus, the first group (comparison) included 20 patients with type 2 diabetes and normal body weight (BMI <25 kg / m2), including 11 men and 9 women. The second group of patients (14 subjects, including 8 men and 6 women) had type 2 diabetes and overweight (BMI <30 kg / m2); the third group comprised 23 patients, including 8 men and 15 women, with type 2 diabetes and first degree obesity (BMI <35 kg / m2); the fourth group (31 subjects, including 19 men and 12 women) had type 2 diabetes and second degree obesity (BMI <40 kg / m2); the fifth one had 15 subjects with diabetes and third degree obesity (BMI> 40 kg / m2, including 9 men and 6 women).

Taking into account the severity of the disease, the patients of the main group and the comparison group were distributed as follows: 29 (35%) and 6 (30%) subjects, respectively, had moderate severity and 17 (20.5%) and 3 (15%) patients, respectively had severe course.

In most cases (44.5% and 55% of patients, respectively) there was a subcompensation of carbohydrate metabolism.

The distribution of adipose tissue in patients with type 2 diabetes with normal body weight (20 patients) corresponded to: 22.6 ± 1.9% SAT and 14.0 ± 1.4% VAT.

Evaluation of the percentage distribution of visceral and subcutaneous adipose tissue in patients of the main group showed that increased BMI enhanced the percentage of adipose tissue, but its redistribution between SAT and VAT was different (Table 1).

That is, although at all stages of obesity there was an increase in adipose tissue content, but as BMI increased, the percentage of VAT rose compared to the pool of VAT. For example, in patients with NBW, the ratio of adipose tissue components (VAT and SAT) corresponded to an increase of 1.8 and 1.4 times, while in 3rd degree OB it was 2.8 and 1.8 times, respectively. The presence of a significant percentage of VAT was the basis for determining the content of adipokine chemerin in patients with type 2 diabetes with different stages and components of the autonomic fat pool (Table 2).

Thus, changes in chemerin parameters were

Table 1.

Distribution of adipose tissue in patients with type 2 diabetes, taking into account the localization of adipose components

Indicator of body composition	BMI index				
	Control (n=20)	NBW (n=14)	1st degree OB (n=23)	2nd degree OB (n=31)	3rd degree OB (n=15)
SAT, %	21.8±1.7	30.6±1.4*	32.7± 1.4*	41.7±1.8*^	38.3±1.9*^’
VAT, %	10.2 ± 1.3	19.0 ± 1.2*	18.1 ± 1.3*	22.1±1.4*^ #	28.4±1.5*^’

*Note: p <0.05 * as compared with the control group; p <0.05 ^ as compared with the NBW group; p <0.05 ‘as compared with the group of 1st degree OB; p <0.05 # as compared with the group of 3rd degree OB.*

Table 2.

The content of chemerin (ng / ml) in the serum of patients with type 2 diabetes depending on BMI

BMI	The content of visceral adipose tissue, %	The content of chemerin, ng / ml
Control group	10.2 ± 1.3	3.89 (3.7; 4.2)
Overweight	19.0 ± 1.2	5.61 (4.8; 6.9) *
1st degree obesity	18.1 ± 1.3	6.53 (5.1; 7.2) *
2nd degree obesity	22.1 ± 1.4	5.85 (4.9; 7.1) *
3rd degree obesity	28.4 ± 1.5	5.31 (4.3; 6.2)*
Comparison group (normal weight)	12.1±1.3	4.84 (4.5; 5.3) *

*Note: p <0.05 * as compared with the control group;*

found to correlate with the content of VAT and, consequently, the stage of obesity.

At the same time, comparison of the obtained indicators of chemerin between the provided groups showed no significant changes.

In our opinion, the increase in chemerin levels in patients with type 2 diabetes and obesity can be considered from two sides. On the one hand, chemerin is an adipocytokine, the action of which is associated with pro-inflammatory reactions. It is involved in the inflammatory response: it takes part in stimulating the adhesion of macrophages to fibronectin, adhesion molecules ISAM-1 (intercellular adhesion molecule-1) and VCAM-1 (vascular cell adhesion molecule-1) [10]. At the same time, a number of researchers have proven that chemerin has no effect on basal inflammatory status, but promotes the production of nitric oxide and activation of the PI3K-Akt-eNOS signaling pathway. That is, changes in this indicator may be the result of endothelial dysfunction, which occurs in many diseases, including diabetes. Thus, the ability of chemerin to increase arterial tone determines the vasoconstrictor effect of this adipocytokine in the regulation of vascular reactions [11].

Another mechanism of chemerin increase may be related to its involvement in the regulation of

carbohydrate metabolism and the formation of insulin resistance. Thus, Adriana F. et al. found high levels of serum chemerin in obese patients, which positively correlated with IR and oxidative stress [12]. That is, the accumulation of products of free radical oxidation of lipids, which occurs against the background of antioxidant defense, can be a "stimulator" of chemerin synthesis and an indirect "organizer" of metabolic disorders.

Conclusions. Patients with type 2 diabetes with changes in body mass index were shown to have an increase and redistribution of the component adipose tissue composition with an emphasis on the predominant accumulation of visceral adipose tissue.

The course of type 2 diabetes on the background of altered BMI is accompanied by an increase in the content of adipocytokine chemerin, which may be the result of both chronic inflammatory process in blood vessels and metabolic disorders.

Increased chemerin content in patients with type 2 diabetes and obesity can be used as one of the indicators of systemic vasoconstriction in the mechanisms of vascular reactions and maintenance of the ischemic component of pathogenesis.

Prospects for further research. In the future it is planned to study the peculiarities of metabolic shifts in germinal factors (fibroblast growth factor 23, Klotho protein, sclerostin) in patients with diabetes and obesity.

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