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DISCOORDINATION OF ADIPOCYTOKINES AND PRODUCTS OF ADIPOSE TISSUE LIPOLYSIS WITH THE DEVELOPMENT OF INSULIN RESISTANCE IN METABOLIC SYNDROME**Uzbekova N.R.**

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Abstract: The aim of the study was to investigate the possible role of adipocytokines (leptin, adiponectin), triglycerides (TG) and free fatty acids (FFA) in the development of insulin resistance (IR) in patients with metabolic syndrome (MS).

The study included 150 patients with MS (57 men and 93 women). The patients with MS with high HOMA index observed increase in TG, FFA, leptin and decreased adiponectin. In groups of patients with different body mass showed that in individuals with obesity in the development of IR may play a role of increasing concentrations of TG, FFA, and leptin, while in patients without significant obesity - increased levels of TG, FFA and decreased adiponectin. We can assume that leptin, adiponectin, triglycerides and FFA can influence the development of IR, however, their contribution depends on the severity of obesity.

Key words: leptin, adiponectin, triglyceride, free fatty acids, insulin resistance, metabolic syndrome.

A cluster of diseases such as type 2 diabetes mellitus (DM2), atherosclerosis, arterial hypertension (AH), atherogenic dyslipoproteinemia is metabolic syndrome (MS) (4.7). The basis of the syndrome is insulin resistance (IR), which is understood as a decrease in the response of insulin-sensitive tissues to insulin when its concentration is sufficient (2.9).

A special role in the pathogenesis of MS is also played by obesity or the abdominal type of distribution of adipose tissue, which contribute to the development of IR (9,10). Among the mechanisms of development of IR in MS, special attention is paid to changes in the blood levels of adipokines - biologically active proteins produced by adipose tissue (leptin, adiponectin, visfatin, resistin, interleukin-6, tumor necrosis factor- α) (1,3,11). In addition, triglycerides (TG) and free fatty acids (FFA), produced during lipolysis both by adipose tissue and in the bloodstream by TG-rich lipoproteins (10,12), can play an important role in the development of IR (10,12). However, the contribution of each of these substances to the development of IR has not yet been clarified, as well as the extent to which changes in their concentration are associated with the presence of obesity and the pathogenesis of IR in MS (2,10).

The purpose of the study was to study the role of adipose tissue hormones - adipokines (leptin, adiponectin), triglycerides and free fatty acids in the development of insulin resistance in patients with MS.

Material and methods

150 patients with MS (57 men and 93 women) aged 35-70 years (average 51.5 ± 3.93 years) were examined. The control group consisted of 58 people of the same sex and age.

Metabolic syndrome was diagnosed according to the criteria proposed by the US National Cholesterol Education Program Experts (2005). The criteria for MS were considered to be a waist circumference of more than 94 cm in men and more than 80 cm in women; blood pressure 130/85 mm Hg. and higher, fasting plasma glucose level is 5.6 mmol/l or more.

Glucose-insulin homeostasis was determined by the level of fasting blood glucose (FG), the level of insulin (IRI) in the blood using the enzyme immunoassay method in the radioimmune laboratory of the Republican Center of Endocrinology (Tashkent), kits from "Beckman Coulter" (Czech Republic). The HOMA index was calculated (fasting insulin $\mu\text{U/ml}$ x fasting blood glucose

mmol/l: 22.5). When the fasting IRI level was above 12.5 $\mu\text{U/ml}$, hyperinsulinemia was diagnosed. When the HOMA index was above 2.77, patients were considered insulin resistant.

Indicators of blood lipid composition - total cholesterol (TC), HDL cholesterol, TG were determined using the "Reflotron" express analyzer plus" by the company "Roshe" (Germany) with reagent kits "Biocon" (Germany). The content of LDL cholesterol and VLDL cholesterol was calculated using the formula W. Friedwald. The integral indicator - atherogenic coefficient (CA) - was calculated using the formula $KA = (TC - HDL - C / HDL - C)$. The concentration of FFA in blood serum was determined using the N E FAFS test system from Disus (Germany) in the laboratory of the Department of Biochemistry of the Tashkent Medical Academy.

Levels of leptin and adiponectin were determined using a competitive enzyme-linked immunosorbent assay using kits from Bio Vender (Czech Republic), in the "Immunogen-test" laboratory at the Institute of Human Immunology and Genomics of the Academy of Sciences of the Republic of Uzbekistan.

Statistical data processing was carried out using the Statistica-10 software package. To identify connections between the HOMA index and various parameters, correlation and regression analyzes were performed. The significance level was considered significant at $p < 0.05$.

Results and its discussion

The results of the study showed that patients with MS with reduced sensitivity to insulin (groups 2 and 3 according to the HOMA index) have a higher BMI and a more pronounced abdominal distribution of adipose tissue. In addition, in these patients there is an increase in the content of TG, FFA, and total cholesterol and a decrease in HDL cholesterol (Table 1).

Table 1

Clinical and metabolic parameters in patients with MS with different values of the HOMA index

Indicators	NOMA index values		
	1 (n =30)	2 (n =60)	1 (n =60)
NOMA Index	1.22±0.28 (0.81-1.54)	2.32±0.54 (1.55-2.99)	6.85±2.13 (3.00-12.88)
Men/women	13/17	21/39	23/37
Age/years	54.7±10.42	50.8±8.02	52.3±9.18
BMI kg/ m ²	26.2±3.93	33.6±4.71***	38.6±6.04***
OT, cm	94.0±10.21	98.1±11.0*	104.2±12.6**
Leptin, ng/ml	18.6±3.68	23.5±4.16**	30.9±6.42***
Adiponectin, $\mu\text{g/ml}$	7.6±3.52	6.15±3.11*	5.75±2.77**
Fasting glucose, mmol/l	5.9±1.13	6.6±1.32*	8.7±2.78***
Insulin, mU/ml	7.1±2.06	11.3±4.41**	18.13±9.41***
THC, mmol/l	6.21±1.64	6.90±1.93*	7.51±2.56**
TG, mmol/l	1.94±1.03	2.18±1.97*	2.43±1.34**
HDL cholesterol, mmol/l	1.02±0.16	0.94±0.13*	0.84±0.10**
LDL cholesterol, mmol/l	4.32±1.85	4.85±2.03*	5.33±2.71**
IA	4.91±1.78	5.41±2.21*	6.8±2.96**
FFA, mmol/l	0.60±0.35	0.75±0.42*	0.86±0.69**

Note: * - significance values for differences among groups: differences are significant according to compared with group 1 with: * - $p < 0.05$; ** - $p < 0.01$; *** - $p < 0.001$.

Correlation relationships indicate a connection of the HOMA index with AO and atherogenic changes in the lipid spectrum, independent of BMI. These changes are consistent with the known ideas about the close relationship between AO and IR, as well as the important role of IR in the

development of atherogenic dyslipoproteinemia in obesity with MS (7,9). However, the mechanisms of development of IR in MS remain poorly understood (3). One approach to studying this problem is to study the role of substances produced by adipose tissue, such as adipokines, TG and FFA (1,10). The results showed that a decrease in tissue sensitivity to insulin is accompanied by an increase in the blood levels of TG and FFA, leptin and a decrease in adiponectin (8).

Each of the presented factors, according to correlation analysis, has connections with IR independent of BMI (Table 2).

The literature also provides information on a BMI-independent association of IR with concentrations of FFA, leptin and adiponectin (5,6). We can say that changes in the levels of TG, FFA and adipokines are a reflection of not only obesity, but also IR, and therefore, we can assume the participation of these substances in the development of IR. The question remains little studied: whether these substances can participate in the pathogenesis of IR in individuals with normal and overweight, or whether changes in their concentration in the development of IR are more important in obesity with MS.

Table 2

Relationship between the HOMA index and clinical and metabolic parameters in patients with MS

Parameter	Correlation
Age, years	-0.22 *
BMI, kg/ m ²	0.45 *
OT, cm	0.43 *
Leptin, ng/ml	0.33 *
Adiponectin, µg/ml	-0.37 *
TG, mmol/l	0.39 *
FFA, mmol/l	0.44 *
THC, mmol/l	0.23 *
HDL cholesterol, mmol/l	-0.36 *
CA	0.30 *

Note: * - reliability of correlation at $p < 0.05$

We present data on the content of TG, FFA, leptin, adiponectin in patients with different body weights and HOMA index. As shown, in IR, the levels of TG, FFA and leptin change only in obese individuals ($BMI \geq 28 \text{ kg/m}^2$), while the concentration of adiponectin changes in the examined individuals without severe obesity ($BMI < 28 \text{ kg/m}^2$) (Table. 3).

Table 3

Blood levels of TG, FFA, leptin and adiponectin in patients with MS with different BMI and HOMA index values

Indicators	Patients with MS with normal and overweight ($BMI < 28 \text{ kg/m}^2$)		Obese patients ($BMI \geq 28 \text{ kg/m}^2$)	
	NOMA < 1.5	NOMA > 2.77	NOMA < 1.5	NOMA > 2.77
Number of patients	33	27	thirty	60
Husband/wives	15/18	12/15	13/17	23/37
Age, years	53.7±9.2	51.9±8.51*	50.7±8.04	52.9±9.36
BMI, kg/ m ²	24.4±2.67	26.9±3.96*	33.1±4.80 ###	37.7 ± 5.73 *###
NOMA index	1.14±0.31	4.85±1.49***	1.31±0.49	5.76± 2.08 *** #
TG, mmol/l	1.93±1.03	2.11±1.83**	2.04 ± 1.62	2.42± 1.61#
FFA, mmol/l	0.60±0.35	0.72±0.39**	0.71±0.43	0.85±0.17* #

Leptin, ng/ml	12.6±3.09	16.7±5.03**	21.5±4.04 ###	28.5± 5.87 ** ###
Adiponectin μg/ml	7.5±3.58	6.11±3.42**	6.03±3.41	5.75±2.93* #

Note: 1. The differences are significant compared to non-obese individuals in the HOMA category when: * - $p<0.05$; ** - $p<0.01$; *** - $p<0.001$. 2. The differences are significant compared to insulin-sensitive individuals in the BMI category at: # - $p<0.05$; ## - $p<0.01$; ### - $p<0.001$.

Levels of TG and FFA are still associated with IR in patients with BMI<28 kg/m², although this correlation is less pronounced compared to the group of patients suffering from obese MS (Table 4). It can be assumed that in patients with MS without severe obesity, TG, FFA and adiponectin are involved in the development of IR, but adiponectin, unlike FFA and leptin, is not associated with the development of IR in patients with obesity (3,4).

Table 4

Relationship between the HOMA index and the content of TG, FFA, leptin and adiponectin in patients with MS with different BMI

Parameter	Overweight patients (BMI<28 kg/m ²)	Obese patients (BMI≥28 kg/m ²)
TG, mmol/l	0.30 *	0.41 *
FFA, mmol/l	0.29 *	0.40 *
Leptin, ng/ml	0.27	0.33 *
Adiponectin, μg/ml	-0.29 *	-0.16 *

Note: * – correlation is significant at $p<0.05$

The reasons for the identified differences in the relationships between the content of TG, FFA and adipokines with IR at different degrees of excess body weight remain unknown (1,2). However, it is conceivable that differences in the production of other substances by adipose tissue (e.g., other adipokines, which also, by affecting insulin sensitivity, may reduce the effects of leptin and adiponectin on IR) may underlie these differences (6).

However, according to another study, the level of adiponectin decreased with IR in both normal and overweight individuals, as well as in obese patients (9). This was probably explained by the fact that the concentration of adiponectin in obese patients without IR was as high as in normal and overweight patients without IR (9,10). Adiponectin levels were significantly reduced in those with normal insulin sensitivity and obesity. Apparently, an important reason for the lack of influence of adiponectin on IR in patients with MS and obesity is the low range of its concentrations in this group and, accordingly, the low degree of its effect.

Regression analysis showed that the HOMA index was influenced by the levels of adiponectin ($\beta = -0.30$, $p < 0.01$), leptin ($\beta = 0.22$, $p < 0.01$), TG ($\beta = 0.25$, $p < 0.01$), FFA ($\beta = 0.24$, $p < 0.01$).

An analysis of the literature revealed that we have not encountered studies that simultaneously study the influence of TG, FFA and adipokines on the development of IR in MS. However, there are works that also show that adiponectin and leptin are independent predictors of IR (3,6). However, much remains unclear regarding the effect of adiponectin and TG on insulin sensitivity. It is assumed that adiponectin exerts this effect by stimulating TG and FFA oxidation by reducing glucose production by hepatocytes. These effects are not due to the adipokine's effects on insulin signal transduction (11). The signaling pathways of adiponectin remain unknown (3,11). However, the association of adiponectin with IR in patients with MS found in our study suggests that a decrease in adiponectin levels plays an important role in the development of IR in patients with MS.

Conclusion

1. In patients with MS, the content of leptin, adiponectin, TG, and FFA changes not only with obesity, but also with the development of IR.
2. An independent role of leptin, adiponectin, TG, and FFA in the development of IR in patients with MS was discovered.
3. In individuals with MS and obese, increased concentrations of leptin, TG, and FFA play a role in the development of IR, while in MS individuals without severe obesity, a decrease in adiponectin and an increase in TG, FFA levels play a role.

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