THE ROLE OF ADIPONECTIN IN THE DEVELOPMENT AND PROGRESSION OF METABOLIC SYNDROME

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Annotation. *Metabolic syndrome (MS) is a complex interrelated pathogenetic symptoms and metabolic disorders that increase the risk of developing atherosclerosis and coronary heart disease (CHD) among which highlight violations such as obesity and/or abdominal fat distribution, insulin resistance (IR), atherogenic dyslipidemia, arterial hypertension (AH), hyperuricemia, and several other manifestations [2,3,5].*

Keywords: biologically active, increase in cholesterol, smooth muscle.

Currently, more and more attention is paid to the role of adipokines, biologically active proteins expressed and secreted into the blood by adipose tissue, in the genesis of this complex of disorders [1,3]. For example, there is evidence of a positive relationship between MS manifestations and the expression and plasma levels of such substances as tumor necrosis factor-a (TNF-a), interleukin-6 (IL-6), resistin, and leptin, and a negative relationship with adiponectin [1,6,7,13]. The latter is interesting because, according to the results of studies on transgenic mice, it has an antiatherogenic and antidiabetogenic effect. The antidiabetogenic effect of adiponectin is associated with an increase in the sensitivity of tissues to insulin under the action of this substance, while the antiatherogenic effect is explained by a number of adiponectin effects [6]. These include a decrease in triglycerides (TG), increase in cholesterol, high density lipoprotein (HDL cholesterol), improving endothelial function, inhibition of transformation of macrophages and smooth muscle cells of the vascular wall in foam cells, migration and proliferation of smooth myocytes media, production of cytokines in the vascular wall, adhesion of monocytes to the endothelium of blood vessels, reduction of free fatty acids (FFA) [11,12,13].

Despite the active interest in the study of this adipokine in the world, its role in the development of MS remains unclear.

The aim of the study was to study the parameters and role of adiponectin in the development of clinical and metabolic disorders in metabolic syndrome.

Material and methods

40 MS patients (18 men and 22 women) aged 35-67 years (mean 48.7±5.6 years) were examined. The control group (volunteers) consisted of 20 people of the same sex and age.

Metabolic syndrome was diagnosed according to the criteria proposed by experts of the US National Cholesterol Education Program. The criteria for MS were waist circumference greater than 94 cm in men and more than 80 cm in women; blood pressure 130/85 mm Hg and above, fasting

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plasma glucose level 5.6 mmol / l or more. Body mass index (BMI, Quetelet index) was calculated using the formula BMI= body weight (kg) / height (^{m2}).

Glucose-insulin homeostasis was determined by the level of fasting blood glucose (GN), the level of insulin in the blood by the enzyme-linked immunosorbent assay in the radioimmune laboratory of the Republican Center of Endocrinology (Tashkent), and by theBeckman Coulter kits» (Czech Republic). The HOMA index was calculated (fasting insulin mcEd / ml x fasting blood glucose mmol / l: 22.5). Hyperinsulinemia was diagnosed when fasting insulin levels were higher than 12.5 UED/ml. If the HOMA index was higher than 2.27, patients were considered insulin resistant.

Indicators of blood lipid composition-total cholesterol(TC), HDL cholesterol, TG were determined using a rapid analyzer "Reflotron plus"manufactured by"Roshe" (Germany) with reagent kits "Biocon" (Germany). The content of LDL-C, VLDL-C was calculated by the formula W. Friedwald. The integral indicator-the coefficient of atherogenicity (CA) - was calculated by the formula CA= (TC-HDL/HDL).

The FFA concentration in blood serum was determined using theNe FAFS test systemfrom company «Disus(Germany).

The level of adiponectin was determined using a competitive version of the enzyme-linked immunosorbent assay on kits made byBio Vender-Laboratorni medicina E..S.(Czech Republic), in the laboratory "Immunogen-test" at the Institute of Immunology of the Academy of Sciences of Uzbekistan.

Statistical data processing was carried out using the variational system method using tStudent's t - criteria. The results were processed using the Statistica software packageStatistica. Pearson correlation analysis and regression analysis were performed to identify the relationship between adiponectin levels and various parameters.

Results

The main clinical and metabolic parameters are shown in Table 1. When comparing the adiponectin (ADN) content in MS patients and controls, it was found that the ADN level was significantly reduced in MS patients. In addition, changes in a number of biochemical, anthropometric, hormonal, and hemodynamic parameters were observed in patients with MS. So, among the biochemical parameters in patients with MS, there was an increase in the levels of insulin, glucose, HOMA index, TG, FFA, CA, as well as a decrease in HDL cholesterol. In addition, MS patients were characterized by an increase in BMI and OT, as well as a greater increase in DBP and SBP compared to the control group.

Table 1.

Adiponectin content and clinical and biochemical parameters in patients with metabolic syndrome

Indicator	**Control** (M±m)	**MS** (M±m)
Absolute number	20	40
Age, years	47.5±6.6	48.7±5.6
Floor (m / w)	10/10	18/22
BMI, kg /^{m2}	23.5±4.7	31.2±4.6

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FROM, cm	80.0±5.5	99.1±13.6
SBP, mmHg	122.5±10.2	191.6±16.4
DBP, mmHg	80.3±7.6	103.4±13.2
Glucose, mmol / l	5.0±0.5	6.5±1.9
Insulin, mcEd / ml	8.5±3.1	16.3±5.2
HOMA index	1.81±0.92	3.43±1.05
FFA, mmol / l	0.42±0.15	0.87±
0.49 TC, mmol / ml	4.2±0.9	6.5±1.7
TG, mmol / L	0.94±0.1	2.76±0.7
HDL cholesterol, mmol/L	1.12±0.18	0.85±0.11
LDL CHOLESTEROL, mmol/L	2.2±0.8	5.11±1.45
KA	4.5±0.9	6.1±1.9
Adiponectin, mcg / ml	10.2±4.1	5.79±2.2

In a detailed study, the group of patients with low ADN was mostly dominated by men. There was a direct relationship between the level of ADN and the age of patients. With an increase in the level of ADN, there is a decrease in the values of such indicators as BMI and OT. There is an inverse relationship between ADN levels and glucose and insulin levels, the HOMA index. As the ADN content increases, FFA and TG levels decrease. The relationship between the level of ADN and the concentrations of LDL and HDL cholesterol is significantly less pronounced.

For a more detailed study of the relationship between the level of ADN and clinical and metabolic parameters, a correlation analysis was performed (Table 2).

Its results confirm the data on the positive relationship of ADN level with age and negative- with BMI, OT, glucose, insulin, HOMA index, FFA and TG concentrations. The strongest correlation was found with the level of TG in ADN (r= -0.46). In addition, significant correlations of ADN level with HDL-C and DBP concentrations were revealed.

Comparison of MS patients by gender and age led to a slight decrease in the correlations of ADN content with BMI, OT, FFA, and TG levels, and correlations of ADN concentration with glucose - insulin homeostasis and HDL cholesterol levels were no longer detected (Table 2). Comparison by gender and age did not affect the relationship of ADN plasma levels with DBP, while the correlation with SBP became slightly higher and became reliable.

Table 2.

Correlation of adiponectin levels with clinical and metabolic parameters in patients with metabolic syndrome

Indicator	**Adiponectin** (without equalization of indicators)	**Adiponectin** (after gender and age adjustment)
Age	0.28*	-
BMI	-0,37*	-0,28*
FROM	-0,33*	-0,25*
SD2	-0.03	-
Glucose	-0.26*	-0.18
Insulin	-0.27*	-0.17

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NOME Index	-0,34*	-0,23*
SZHK	-0,27*	-0,24
OHS	*OHS-0.00	-0.12
TG	-0,46*	-0,4*
HDL-	C 0.27*	0.21
LDL	-C 0.19	0.13
KA	-0,12	-0,25*
GARDEN	-0,23	-0,26*
DBP	-0,33*	-0,35*

Note: * - correlation is significant ($p<0.05$)

During regression analysis, it was shown that only the TG content (r= -0.33, p=0.04) and gender (r= -0.28, p=0.04) are independent factors associated with the level of ADN (r=0.36, p=0.04). The levels of ADN (r= -0.31, p=0.02), FFA (r=0.44, p=0.04) and HDL-C (r=0.26, p=0.04) from all the above indicators were independent factors associated with the concentration of TG in the blood. There was an independent relationship between gender, age, and BMI, as well as an association between ADN and TG levels.

Discussion

In recent years, the role of ADN in the genesis of many disorders in MS has been actively discussed in the literature [2, 10]. The associations of reduced ADN with abdominal fat distribution and IR, hypertriglyceridemia, hypocholesterolemia, and hypertension revealed by various authors support the increasing role of this substance in the genesis of MS [2,3].

Our analysis revealed a number of relationships between the level of ADN and some gender, age, clinical and biochemical parameters in patients with MS.

We were able to show that the level of ADN is lower in men than in women, and also that it increases with the age of patients. These data are consistent with the results of studies conducted by foreign authors [12]. A decrease in ADN levels in men may be one of the factors predisposing them to an increased incidence of MS [1-2]. Also, the data on the negative relationship of ADN level with obesity, OT, glucose, insulin, HOMA index, TG, FFA, blood pressure levels and a positive relationship with HDL cholesterol were once again confirmed.

The mechanisms responsible for reducing ADN in MS patients remain poorly understood. It is suggested that TNF-a and IL-6, whose expression and secretion in adipose tissue increases with obesity, may play a major role [14]. Thus, these cytokines are known to reduce ADN expression [7]. In addition, a decrease in ADN levels may be mediated by hyperinsulinemia, since insulin also reduces ADN production [10]. In addition to the effect of insulin on the level of ADN, the literature describes the opposite effect - a decrease in the level of insulin under the influence of ADN. Thus, in mice transgenic for ADN, as well as in mice that were administered ADN, a decrease in insulin levels was observed, and this effect was explained by an increase in tissue sensitivity to insulin. However, despite the association of ADN level with insulin content and the HOMA index, it decreased and became unreliable after comparing patients by gender and age.

In general, our data do not confirm the conclusions of foreign researchers about the direct effect of ADN on glucose-insulin homeostasis in animals [11]. Of all the indicators, the level of ADN was associated with the level of TG. According to the results of regression analysis, this relationship did not depend on gender and age parameters, lipid and carbohydrate metabolism. At the same time, the level of ADN was also an independent determinant only for TG. The mechanisms by which ADN

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is associated with TG independently of these factors are still unknown. However, literature data suggest that this relationship can be realized through the direct effect of ADN on the formation of TG in hepatocytes, resulting in reduced liver production of VLDL [6]. Thus, ADN transgenosis of leptin-deficient mice (ob/ob line) resulted in a decrease in TG accumulation in the hepatocytes of these animals.

This effect is realized through activation of the intracellular target ADN-AMP-dependent protein kinase, an enzyme that reduces the formation of intracellular TG in hepatocytes. These data are also confirmed by foreign colleagues [6].

Conclusion

Thus, data on the association of ADN levels with a number of clinical and metabolic manifestations of MS were confirmed. Negative correlations were found between the level of ADN and abdominal obesity, insulin resistance, FFA level, hyperlipidemia, A/D level, and a positive relationship with the content of HDL cholesterol. However, regardless of gender, age, and BMI, only TG and DBP levels are associated with ADN. It is once again confirmed that ADN, in turn, is an independent determinant only for TG.

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