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IRISIN AND CHEMERIN LEVELS IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

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Abstract

Context. Changes in the secretion of signaling molecules that originates from adipose tissue and inflammation draw attention in the pathogenesis of type 2 DM. Chemerin, one of the signaling molecules of adipose origin, and irisin, defined as the Renaissance of the metabolism, are among these molecules.

Objectives. This cross-sectional study was planned in order to compare the values of serum irisin and chemerin levels in patients newly diagnosed with T2DM and in healthy subjects.

Subjects and Methods. The study included 41 patients newly diagnosed with T2DM and 49 healthy individuals. The chemistry parameters were analyzed with a biochemistry autoanalyzer, and hormonal parameters were analyzed with an immunoassay analyzer. Plasma irisin and chemerin levels were measured using the enzyme-linked immunosorbent assay method.

Results. There was a significant difference between the groups in terms of glucose, HbA1C, Insulin, HOMA-IR and lipid panel results. Irisin levels in the group of patients newly diagnosed with T2DM were lower than in the control group. Chemerin levels in the group of patients newly diagnosed with T2DM were higher than in the control group.

Conclusion. Consequently, diabetes-dependent changes in chemerin and irisin concentrations suggest that these two hormones have a role in the pathophysiology of DM. Further studies are required to understand the complex structure of the signaling pathways of chemerin and irisin molecules as well as the physiological importance of these molecules as metabolism regulators especially in humans.

Key words: irisin, chemerin, Diabetes Mellitus, adipokines.

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease, with a rapidly increasing global prevalence, characterized by hyperglycemia with disturbances of carbohydrate, protein and fat metabolism. According to the International Diabetes Federation, diabetes affected 425 million people worldwide in 2017 and it is projected to affect 629 million people in 2045 (1, 2). In general, the main problem implicated in the pathogenesis of the disease is insulin deficiency or insufficiency or insulin resistance. Many recent studies have reported that the disease was directly associated with adipokines disturbances (3-6). Among these, it is worth investigating the irisin molecule which consists of 112 amino acids synthesized from the muscle tissue and the chemerin molecule, a chemoattractant protein with a molecular weight of 16.6 kDa mainly released from the adipose tissue (7, 8).

Irisin was discovered by Bostrom *et al*. in 2012 and it is mainly secreted from the muscles (7). Experimental studies conducted on mice and humans have shown that irisin concentrations were significantly increased after exercise and that its concentrations affected the white adipose tissue. It was also shown in some animal models that irisin extended the lifespan, led to decreased diet-induced insulin resistance and reduced body weight by increasing the total energy expenditure. Accordingly, it was asserted that irisin could prevent the development of obesity and DM (7).

The chemerin molecule was first identified by Samson *et al*. on psoriatic skin in 1998 but it was not accepted as an adipokine and called chemerin until 2007 (9). It was shown that chemerin reduces the adipocyte expression of genes that play a role in glucose and lipid homeostasis in adipocytes and regulates adipose tissue differentiation by showing autocrine and/or paracrine effects (10, 11). It was also shown to induce insulin resistance by disrupting glucose uptake and the insulin receptor signal in musculoskeletal cells. The positive correlation between chemerin and parameters such as insulin resistance, body mass index and triglycerides implies that this adipokine has a function in metabolic diseases (12).

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According to the literature, there was no study that evaluated both irisin and chemerin levels in diabetic patients. This study aimed to investigate the relationship of the irisin and chemerin levels with insulin resistance and/or with the pathogenesis of DM in patients newly diagnosed with type 2 DM (T2DM).

MATERIAL AND METHODS

After approval was obtained from the ethics committee of Ankara Numune Training and Research Hospital, a total of 90 subjects, 41 patients newly diagnosed with T2DM who presented to the internal medicine outpatient clinics and 49 control subjects, were included in the study. All participants provided written consent after they were informed about the study. Patients with type 1 DM, those receiving treatment for type 2 DM and patients with any type of systemic disease (coronary artery disease, liver failure, kidney failure, malignancy) were excluded from the study. Detailed medical history was obtained from all subjects and their age, height, weight and waist circumferences were noted in a cross-sectional approach. Body mass index (BMI) was calculated by dividing body weight by the body height squared (kg/m²). Insulin resistance was calculated according to the following formula: HOMA-IR= [fasting insulin (µU/mL) x fasting glucose (mmol/L)/22.5].

Three blood samples were collected from each subject in the patient and control groups after 8-12 hours of fasting and placed in gel tubes, in tubes containing K3-EDTA and in tubes containing 250 KIU/mL aprotinin. Blood samples placed in gel tubes were centrifuged for 10 minutes at 4000 rpm and fasting blood glucose, insulin, cholesterol, HDL-cholesterol, LDL-cholesterol and triglyceride levels in serum were measured. HbA1C assay (with the HPLC method) was carried out on the same day using in blood samples in the tubes containing K3-EDTA. Blood samples placed in tubes containing aprotinin (250 KIU/mL) were centrifuged for 10 minutes at 4000 rpm and the obtained plasma was stored at -20°C until irisin and chemerin assays.

Plasma irisin levels were measured using the Human Irisin ELISA kit (Hangzhou Eastbiopharm Co. Ltd., Hangzhou, China), while plasma chemerin levels were measured using the Human Chemerin ELISA kit (Boster Biological Technology, Pleasanton CA, USA) in an ELx800 device (Biotek, Winooski, VT, USA) with the ELISA method. All analyses were performed on the same day. The detection range and sensitivity of the irisin kit were 0.05µg/mL-15µg/mL and 0.023 µg/mL, respectively. The detection range and sensitivity of the chemerin kit were 0.78 ng/mL-50ng/mL and <20pg/mL, respectively.

Data obtained in the study was expressed with mean ± standard deviation values. The Kolmogorov-Smirnov test was used to check for normality of data distribution before the intergroup comparisons. Chi-square test was used for qualitative parameters. Student's t test was employed in intergroup comparisons and Pearson's correlation coefficient was used to investigate the relationships between the parameters in the groups. $p<0.05$ was considered statistically significant.

RESULTS

Table 1 shows the demographic and biochemical data of the groups. There was no statistically significant difference between the groups in terms of gender distribution ($p>0.05$). There was a statistically significant difference between the control group and the group of patients newly diagnosed with T2DM in terms of BMI, waist circumference and mean age ($p<0.001$). In addition, there was a significant difference between the groups in terms of glucose, HbA1c, Insulin, HOMA-IR and lipid panel results (Table 1).

Irisin levels in the control and patient groups

Table 1. Demographic and biochemical properties of the control and patient groups

	Control n=49	Type 2 DM n=41	*p* value
Sex (F/M)	28/21	24/17	*p*> 0.05
Age (years)	40.18±14.14	47.24±9.8	***p*< 0.01**
BMI (kg/m²)	26.47±3.53	29.80±5.94	***p*< 0.01**
Waist-circumference (cm)	79.0±12.35	102.97±14.04	***p*< 0.001**
Glucose (mg/dL)	86.67±8.41	178.29±79.86	***p*< 0.001**
HbA1c (%)	5.21±0.57	8.51±2.69	***p*< 0.001**
Insulin (µIU/mL)	6.05±1.46	10.08±4.88	***p*< 0.001**
HOMA-IR	1.22±0.29	4.33±2.83	***p*< 0.001**
Cholesterol (mg/dL)	212.24±32.33	223.09±46.69	*p*> 0.05
HDL - Cholesterol (mg/dL)	46.83±11.37	40.73±8.19	***p*< 0.01**
LDL - Cholesterol (mg/dL)	133.61±26.47	141.44±34.74	*p*> 0.05
Triglyceride (mg/dL)	163.12±73.31	203.75±86.66	***p*< 0.05**

were 3.34±0.97 µg/mL and 2.79±0.83 µg/mL, respectively. Irisin levels in the group of patients newly diagnosed with T2DM were lower than in the control group (p<0.01). Chemerin level was 6.44±2.31 ng/mL in the newly diagnosed patient group, which was statistically significantly higher than that in the control group (5.37±2.23 ng/mL) (p<0.05) (Fig. 1).

There was a statistically significant positive correlation between chemerin levels and BMI (r= 0.352, p=0.024), waist circumference (r= 0.331, p=0.035), HOMA-IR (r= 0.359, p=0.021) and insulin (r= 0.377, p=0.015) levels in patients with T2DM. Moreover, there was a negative correlation between irisin levels and BMI (r=-0.275, p=0.082), waist circumference (r=-0.385, p=0.013), insulin (r=-0.303, p=0.054), HOMA-IR (r=-0.261, p=0.099) and triglyceride (r=-0.338, p=0.031) levels. Although there was a negative correlation between chemerin and irisin levels, it was not statistically significant (r=-0.283, p=0.073) (Table 2).

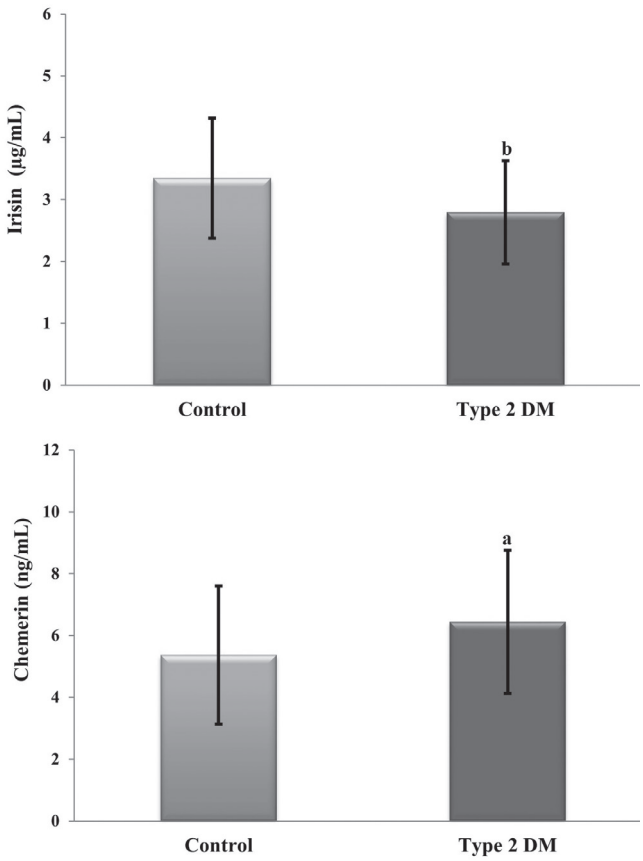

Figure 1. Plasma irisin and chemerin levels of the control and patient groups. **a:** p <0.05; compared with the control group. **b:** p <0.01; compared with the control group.

DISCUSSION

Type 2 DM is a metabolic disease, with a rapidly increasing global prevalence, characterized by impaired insulin secretion, insulin resistance, excessive hepatic glucose production and abnormal lipid metabolism. Considering the burden of T2DM on the economy and the healthcare system, great efforts are made to completely understand its pathophysiology. Changes in the secretion of signaling molecules that originates from adipose tissue and inflammation draw attention in the pathogenesis of T2DM. Chemerin, one of the signaling molecules of adipose origin, and irisin, defined as the Renaissance of the metabolism, are among these molecules (13). Accordingly, this study was planned in order to compare the changes in serum irisin and chemerin levels in patients newly diagnosed with T2DM and in healthy subjects.

Besides functioning as a long-term energy reservoir, white adipose tissue is also known to be an endocrine organ that secretes a number of bioactive molecules defined as adipokines. Adipokines are important regulators of adipose tissue development and function, and they also have important effects on glucose metabolism in various tissues and on the general energy balance at the systemic level. It is known that adiposity changes the circulating levels of many adipokines. It was asserted that this condition coexisted with obesity

Table 2. Correlation of the parameters in the T2DM group

	Irisin	Chemerin	Age	BMI	Glucose	HbA1C	HOMA-IR	Insulin	Cholesterol	HDL	Triglyceride
Irisin	r=1	r=-0.283	r=-0.155	r=-0.275	r=-0.032	r=-0.054	r=-0.261	r=-0.303	r=-0.082	r=0.018	**r=-0.338[a]**
Chemerin	r=-0.283	r=1	r=0.102	**r=0.352[a]**	r=0.121	r=0.143	**r=0.359[a]**	**r=0.377[a]**	r=0.109	r=-0.01	r=0.10
Age	r=-0.155	r=0.102	r=1	r=-0.243	r=-0.204	r=-0.201	r=-0.230	r=-0.134	r=-0.240	r=0.005	r=-0.087
BMI	r=-0.275	**r=0.352[a]**	r=-0.243	r=1	r=-0.154	r=-0.155	r=0.224	**r=0.447[b]**	r=0.152	r=0.139	r=0.163
Glucose	r=-0.032	r=0.121	r=-0.204	r=-0.154	r=1	**r=0.902[c]**	**r=0.556[c]**	r=-0.107	r=0.164	r=-0.292	r=0.236
HbA1c	r=-0.054	r=0.143	r=-0.201	r=-0.155	**r=0.902[c]**	r=1	**r=0.551[c]**	r=-0.110	r=0.204	r=-0.286	r=0.172
HOMA-IR	r=-0.261	**r=0.359[a]**	r=-0.230	r=0.224	**r=0.556[c]**	**r=0.551[c]**	r=1	**r=0.710[c]**	r=0.158	**r=-0.324[a]**	r=0.125
Insulin	r=-0.303	**r=0.377[a]**	r=-0.134	**r=0.447[b]**	r=-0.107	r=-0.110	**r=0.710[c]**	r=1	r=-0.076	r=-0.096	r=-0.052
Cholesterol	r=-0.082	r=0.109	r=-0.240	r=0.152	r=0.164	r=0.204	r=0.158	r=-0.076	r=1	r=0.302	**r=0.444[b]**
HDL	r=0.018	r=-0.01	r=0.005	r=0.139	r=-0.292	r=-0.286	**r=-0.324[a]**	r=-0.324	r=0.302	r=1	r=-0.160
Triglyceride	**r=-0.338[a]**	r=0.10	r=-0.087	r=0.163	r=0.236	r=0.172	r=0.125	r=-0.052	**r=0.444[b]**	r=-0.160	r=1

a: p<0.05; b: p<0.01; c: p<0.001.

and contributed to the metabolic changes that eventually caused T2DM (14-16). Another mechanism in which fluctuating adipokine levels contribute to T2DM involves inflammation-mediated insulin resistance. Insulin resistance leads to elevated glucose concentration by decreasing glucose uptake in peripheral tissues and increasing glucose production in the liver. Insulin resistance causes increased lipolysis and free fatty acid release in adipocytes and increased lipid synthesis in the liver (17, 18). In this study, patients with T2DM had elevated glucose, HbA1c, insulin, total cholesterol, triglyceride and LDL cholesterol levels and decreased HDL cholesterol levels. The mechanisms mentioned above and previous studies are supportive of the results obtained in this study.

It was observed that the level of irisin, a very popular molecule in the recent years, was significantly lower in patients with T2DM than in healthy controls. These results are consistent with the findings of many previous studies (6, 19, 20). According to a study by Shelbaya *et al*. conducted in late 2018, irisin levels were significantly lower in patients with T2DM (21). Exercise considerably increases the level of irisin, which is expressed in the skeletal muscle as type 1 membrane precursor protein FNDC5 and secreted into the circulation after proteolytic cleavage (7). The skeletal muscle, which is the largest organ in the body, is responsible for the majority of glucose uptake as a response to insulin and constitutes the most important area in terms of insulin resistance. Therefore, it is possible to improve insulin sensitivity with interventions including increased physical activity (22). It is known that exercise has an important role in maintaining good health and preventing type 2 diabetes and cardiovascular diseases (23). In experiments conducted by Boström *et al*., it was found that exogenous administration of irisin to mice induced white-to-brown adipose tissue conversion and increased energy expenditure, which resulted in improved glucose tolerance and weight loss. In the light of this information, it is thought that irisin can prevent the development of T2DM, since exercise promotes increased irisin synthesis from the skeletal muscle (7).

Elevated circulating levels of irisin reduce the weight gain due to a diet with a high fat content and increase energy expenditure by improving diet-induced insulin resistance (7, 24). In addition, irisin is secreted from the skeletal muscle as a response to PGC-1α (PPAR-γ co-activator-1α) activation. Studies suggest that PGC-1α is important for mitochondrial homeostasis, regulates mitochondrial biogenesis and oxidative metabolism and that the mitochondrial function plays a role in insulin resistance. PGC-1α expression and activity are lower in patients with T2DM (25). Studies comparing serum irisin levels in controls with normal glucose tolerance and newly diagnosed T2DM patients have shown that serum irisin levels were lower in patients newly diagnosed with T2DM (19, 20). Moreover, elevated irisin levels were linked to a lower risk of developing T2DM. Similar results were also obtained in patients that had T2DM for a long time (21). The fact that circulating irisin levels were lower both in newly diagnosed patients and in patients who had T2DM for a long time suggests that irisin can be a T2DM marker. There are studies showing that the mentioned lower levels of irisin could be associated with low PGC-1 alpha expression and/or activity (25, 26).

In this study, the change in chemerin levels was also investigated in patients newly diagnosed with T2DM because chemerin is thought to have an impact on insulin-mediated glucose regulation. It was observed that chemerin levels were significantly higher in patients newly diagnosed with T2DM than in the control group. There are many studies reporting that chemerin levels were higher in patients with T2DM than in healthy controls, which is consistent with the results of this study (5, 27, 28). Chemerin regulates the key effectors of glucose and lipid metabolism such as diacylglycerol acyltransferase enzyme that plays a role in triglyceride synthesis, adipokines (adiponectin, leptin etc.) and glucose transporter 4 in mature adipocytes (29). The effect of chemerin on glucose metabolism is still debatable due to the contradicting results obtained from *in vivo* and *in vitro* studies. In 3T3-L1 adipocytes, a moderate increase of insulin-induced glucose uptake and IRS-1 phosphorylation was reported after a short stimulation by low concentrations of chemerin, while longer stimulation by higher chemerin concentrations decreased insulin-induced glucose uptake in the same cells (30). In addition, it was found that injecting rats with chemerin led to the inhibition of glucose uptake in the adipose tissue, liver and skeletal muscle and to increased glucose intolerance. While chemerin-induced dysregulation of the glucose uptake in adipocyte and myocyte cultures suggests the insulin-dependent GLUT4 mechanism, decreased serum insulin levels and hepatic glucose uptake in obese/diabetic mice (db/db) implies the insulin-dependent GLUT2 mechanism (30). Therefore, mechanisms of the chemerin-induced change in glucose homeostasis are still unclear and these conflicting results show the necessity of clarifying the role of chemerin in glucose metabolism. According to this study, chemerin levels had a positive correlation with insulin and

HOMA-IR. Considering the information provided here and the results of this study and other recent studies, it is clear that chemerin plays an important role in glucose metabolism and in the pathogenesis of T2DM. Therefore, it is necessary to understand the role of chemerin and the associated receptors in glucose homeostasis. In addition, cell-based studies and studies conducted on animals and humans support the regulatory role of this adipokine in the metabolism.

In conclusion, our knowledge on the mode of action of chemerin and irisin and their effect on the development of diabetes is gradually expanding. The above-mentioned mechanisms and diabetes-dependent changes in chemerin and irisin concentrations suggest that these two hormones have a role in the pathophysiology of DM. Further studies are required to understand the complex structure of the signaling pathways of chemerin and irisin molecules as well as the physiological importance of these molecules as metabolism regulators especially in humans.

Conflict of interest

The authors declare that they have no conflict of interest.

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