RESEARCH ARTICLE

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A New Predictor for Prediabetes: Chemerin

ABSTRACT

Objective: It was aimed to investigate irisin and chemerin levels in prediabetic individuals and their value in predicting prediabetes.

Method: Thirty-eight prediabetic patients aged 18-65 years (22 impaired fasting glucose (IFG), 10 impaired glucose tolerance (IGT), 6 patients with coexisting IFG and IGT) and thirty-five healthy volunteers were included in which was designed as a cross-sectional study. The basic demographic characteristics of all participants in the case and control groups were compared with the serum chemerin, irisin, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), high-density lipoprotein (HDL-cholesterol), low-density lipoprotein (LDL-cholesterol), triglyceride (TG), free thyroxine (sT4), and thyroid-stimulating hormone (TSH) levels.

Results: Serum chemerin level was found to be higher in the prediabetic group (p=0.03), while no significant difference was found for the irisin level between the two groups. In the multivariate logistic regression analysis, we showed that chemerin was an independent risk factor in predicting prediabetes. There was a positive correlation (p=0.01, r=0.279) between all participants' body mass index (BMI) and chemerin level and a negative correlation between irisin level and high-density lipoprotein cholesterol (HDL-C) level, and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) (p=0.04 r=-0.295, p=0.01 r=-0.407, respectively).

Conclusion: Chemerin is a new generation chemokine that predicts prediabetes. Studies aimed at irisin and chemerin may provide important role to prevent the prediabetes to Type 2 diabetes progression.

Keywords: Chemerin, Diabetes Mellitus, Irisin, Prediabetic State, Predictive Value of Tests.

Prediyabet İçin Yeni Bir Prediktör: Kimerin

ÖZET

Amaç: Prediyabetik bireylerde irisin ve kimerin düzeylerini ve bunların prediyabeti öngörmedeki değerini araştırmak amaçlandı.

Gereç ve Yöntem: Kesitsel bir çalışma olan dizayn edilen çalışmamıza; 18-65 yaş arası 38 prediyabetik hasta (22 bozulmuş açlık glukozu (IFG), 10 bozulmuş. glukoz toleransı (IGT), 6 IFG ve IGT birlikte bulunan hasta) ve 35 gönüllü sağlıklı kişi dahil edildi. Vaka ve kontrol grubundaki tüm katılımcıların temel demografik özellikleri ile serum kimerin, irisin, kreatinin, Alanin Aminotransferaz (ALT), Aspartat Aminotransferaz (AST), düşük dansiteli lipoprotein (LDL-kolesterol), yüksek dansiteli lipoprotein (HDL-kolesterol), trigliserit (TG), serbest tiroksin (sT4) ve tiroid stimülan hormon (TSH) düzeylerinin sonuçları karşılaştırıldı.

Bulgular: Her iki grup arasında irisin düzeyi için fark saptanmazken, kimerin düzeyi prediyabetik grupta daha yüksek saptandı (p=0.03). Yaptığımız çok değişkenli lojistik regresyon analizinde kimerinin prediyabeti ön gördürücü bağımsız bir risk faktörü olduğunu gösterdik. Ayrıca tüm katılımcıların beden kitle indeksi (BKİ) ile kimerin düzeyi arasında pozitif korelasyon (p=0.01, r=0.279); irisin düzeyi ile high density lipoprotein kolesterol (HDL-C) düzeyi ve Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) arasında negatif korelasyon (sırasıyla; p=0.04 r=-0.295, p=0.01 r=-0.407) saptadık.

Sonuç: Kimerin prediyabeti predikte eden yeni nesil bir kemokindir. İrisin ve kimerin hedefli yeni çalışmalar prediyabetin diyabete dönüşmesinin önlenmesinde önemli aşamalar sağlayabilir.

Anahtar Kelimeler: Kimerin, Diabetes Mellitus, İrisin, Prediyabetik Durum, Testlerin Prediktif Değeri.

INTRODUCTION

Type 2 Diabetes Mellitus (T2D) has a daily increasing incidence. Four hundred twenty-five million people in the adult age group around the world and approximately 7 million people in our country have T2D. It is estimated that it will increase to 700 million around the world in 2045 and that the population with T2D in Turkey will reach 12 million (1). It is important to determine patients in the prediabetic stage and to prevent progression to T2D (2).

The views on the hormonal regulation of the metabolism have changed significantly over the past two decades. It was demonstrated that some substances released from adipose tissue and muscle tissue take part in metabolic regulation and can predict T2D (3, 4).

Irisin is a cytokine secreted from many tissues such as adipose tissue, kidneys, ovaries, and stomach, especially myocytes (5). Irisin, which plays a significant role in energy consumption, insulin resistance, and thermogenesis, is a molecule with a messenger role between muscle and adipose tissue. It also plays a role on transformation of white adipose tissue to brown adipose tissue, which has a positive effect on weight control and energy balance. Known effects of irisin on the regulation of blood glucose and body weight has caused it to become a promising molecule for diabetes and obesity treatment (2, 6).

Chemerin is one of the newest members of the adipokine family that has been discovered in recent years. Mainly the liver and especially the white adipose tissue secretes it . In many studies, the role of chemerin on insulin resistance, metabolic syndrome, polycystic ovary syndrome, obesity, and T2D pathogenesis has been shown (3, 7). Chemerin, which is also an inflammatory chemokine, contributes to the proper regulation of glucose tolerance by providing insulin secretion induced glucose uptake in peripheral tissues, but its exact mechanism is not clear (8, 9). In addition, no relationship was found between prediabetes and chemerin levels in the literature.

Based on this information, it was aimed to investigate irisin and chemerin levels in prediabetic individuals and their value in predicting prediabetes in this study.

MATERIAL AND METHODS

It was designed as a cross-sectional study. Eighty individuals (n=80) aged 18-65 years who were admitted to Keçiören Training and Research Hospital (Health Sciences University), Endocrinology and Metabolic Diseases and Internal Medicine polyclinics between 01/12/2018 and 28/02/2019 and whom underwent oral 75 g glucose tolerance test (OGTT) were included in the study. Patients who have fasting blood glucose level between 100 mg/dL and 125 mg/dL were taken to the IFG group and between 140 mg/dL and 199 mg/dL were taken to the IGT group of the 2nd-hour measurement after the oral intake of 75 g of glucose. The patients with the 2nd-hour plasma glucose of ≥ 200 mg/dl in the 75 g OGTT were diagnosed with T2D (10). Seven patients were excluded from the study since they were diagnosed with T2D. The study was completed with 38 patients (n=38) diagnosed with prediabetes and 35 healthy volunteers (n=35) who were diagnosed with NGT and had no systemic disease. The exclusion criteria were being diagnosed with Type 1 or Type 2 Diabetes Mellitus (DM), pregnancy, breastfeeding, to have hematological or solid organ malignancies, chronic systemic diseases, infectious diseases, and the use of all kinds of drugs. Patients' body mass indexex (BMI), and serum creatinine, triglyceride (TG), low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), free thyroxine (fT4), and thyroid-stimulating hormone (TSH), alanine aminotransferase (ALT), aspartate aminotransferase (AST) measurements, which were examined after 12-hour fasting, were recorded. Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) values were calculated by the [Fasting serum glucose (mg/dl) × fasting insulin level (μU/ml)] / 405 formula. Blood analysis was done to the patient and the control groups' samples for the measurement of irisin and chemerin levels. These blood samples were centrifuged at 4000 rpm for 10 minutes, and their serums were taken to Eppendorf tubes to include 2 cc and stored at -80 ºC in a deep freezer. After patient admission was completed, serum irisin and chemerin levels were asessed using ELISA kit (USCN Life Science, Wuhan, China, with a coefficient of variation (CV) of < 10% intra-assay and < 10% inter-assay for irisin and Boster's Human/ chemerin Kit, B Valley Ave, Pleasanton, CA, USA with a CV ≤ 8% inter-assay and ≤ 5.6% intra-assay for chemerin).

Statistical Analysis: The Statistical Package for the Social Sciences version 15.0 (SPSS) was used for the analysis. The one-sample Kolmogorov-Smirnov test was used for the data distribution. Continuous variables were expressed as the median or mean SD [median (minimum-maximum)for skew-distributed, mean SD for normally distributed] whereas categorical variables as the number and percentage. For analyzing categorical variables The Fisher's exact test or a chi-square test was used and for analyzing numeric variables Student's t-test or Mann-Whitney U-test used, where appropriate. Correlation analysis was made with Spearman's rank-order or Pearson's correlation coefficient. Logistic regression analysis was made for detached predictors of prediabetes. Hosmer-Lemeshow was used for assessing model fit. P value <0.05 was accepted for statistically significance.

RESULT

In this study, 38 patients diagnosed with prediabetes (22 patients had IFG, 10 patients had IGT, and 6 patients had both) and 35 healthy individuals were included. Gender, age and BMI did not differ between groups (Table 1).

Fasting plasma glucose level, and 2nd hour plasma glucose level were higher in the prediabetes group. There was no difference between the groups in terms of ALT, AST, creatinine, total cholesterol, HDL-C, LDL-C, TG, insulin levels, and HOMA-IR measurements (p>0.05) (Table 1).

Table 1. The comparison of Demographic and laboratory findings between prediabetes and control groups

	Prediabetes (n=38)	**Control (n=35)**	**p value**
Age (year)	47 (19-60)	41 (20-65)	p>0.05
Gender (female)	28 (73.7 %)	28 (80 %)	p>0.05
BMI (kg/m²)	32 (19.5-43.5)	30.12 (19.7-44.1)	p>0.05
Creatinine (mg/dl)	0.8 (0.6-1)	0.8 (0.5-1.2)	p>0.05
ALT (IU/l)	16.5 (7-73)	19 (7-55)	p>0.05
AST (IU/dl)	19 (13-39)	18 (12-43)	p>0.05
Total Cholesterol (mg/dl)	199 (126-259)	182 (125-324)	p>0.05
HDL-C (mg/dl)	41 (33-79)	42.5 (28-58)	p>0.05
LDL-C (mg/dl)	118 (59-189)	116 (55-238)	p>0.05
Triglyceride (mg/dl)	132 (54-493)	113 (37-533)	p>0.05
Fasting plasma glucose (mg/dl)	103.5 (76-125)	91 (70-99)	**p<0.001**
Second hour glucose (mg/dl)	132.5 (65-181)	101 (77-131)	**p=0.008**
Insulin (mIU/ml)	14.4 (5.8-21)	13.9 (2.5-37.6)	p>0.05
Chemerin (ng/ml)	0.758 (0.062-14.435)	0.398 (0.039-2.284)	**p=0.03**
Irisin (ng/ml)	1.512 (0.088-2.174)	1.633 (0.093-2.451)	p>0.05
HOMA-IR	3.4 (1.69-5.07)	2.87 (0.52-10.11)	p>0.05

Chemerin levels were significantly higher in the prediabetes group [prediabetes group: 0,758 ng/ml (0,062-14,435), control group: 0,398ng/ml (0,039-2,284), p: 0.03] (Figure 1) however, irisin did not differ between groups. Also, irisin and chemerin levels did not significantly differ among IGT, IFG and IFG+IGT subgroups. Irisin and chemerin levels did not differ between obese patients (BMI≥30 kg/m²) and lean subjects (BMI<30 kg/m²). Including both patient and control groups, chemerin and BMI were significantly correlated (p=0.01, r=0.279) (Figure 2). Irisin levels were negatively correlated with the measurement of HDL-C (p=0.04, r=-0.295), and with HOMA-IR (p=0.01 r=-0.407). There was no correlation between Chemerin level and HOMA-IR level in both prediabetes and control groups. Logistic regression analysis revealed that chemerin measurements can significantly predict prediabetes (Table 2).

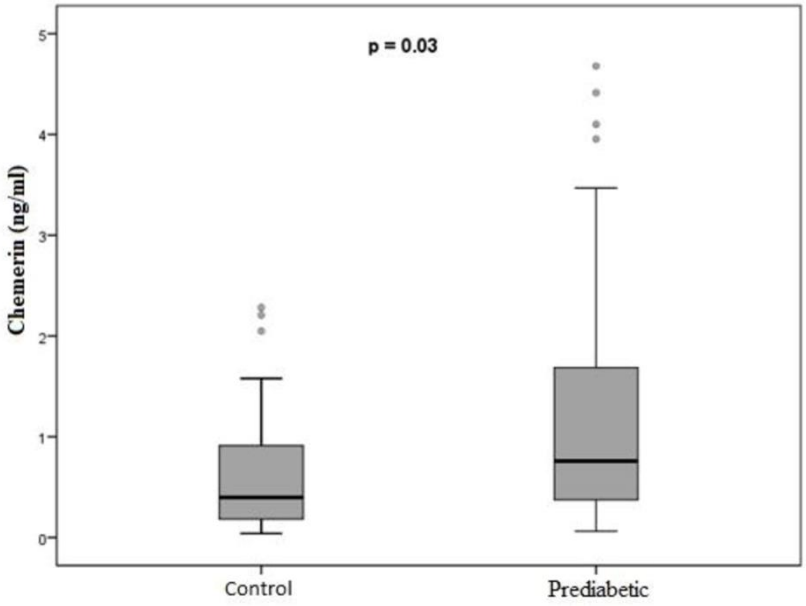

Figure 1. Comparison of the prediabetes and the control groups in terms of chemerin

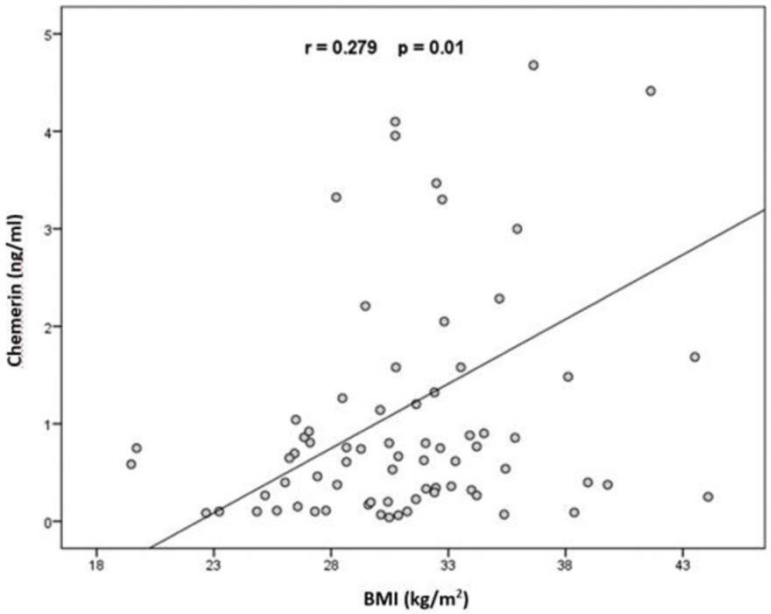

Figure 2. Correlation of the body mass index with chemerin level for all participants

Table 2. Logistic regression analysis of factor correlates with the existence of prediabetes

	OR	P	95% CI
Chemerin measurement	1.8	0.03	1.06-3.09

OR: Odds ratio; CI: Confidence Interval

-DISCUSSION

In this study, we found a correlation between prediabetes and chemerin. However, irisin levels did not differ between prediabetic patients and healthy controls. We also found that chemerin may predict prediabetes.

Since T2D has a high prevalence and can lead to severe mortality and morbidity, recent studies have focused on the early diagnosis of T2D (4, 11). Patients with T2D are usually obese or overweight. Obesity is a disease with chronic systemic inflammation. In obesity, there is an increased oxidative stress in adipocytes due to excess adipose tissue mass decreases blood circulation in adipocytes and stimulating the release of reactive oxygen species (ROS). As a result, macrophages are collected, and adipokines are released. Many inflammatory cytokines including C-reactive protein (CRP), tumor necrosis factor-alpha (TNF-alpha), and interleukin 6 (IL-6) are released from adipose tissue. These immune phenomena are associated with obesity, with insulin resistance, and also with T2D risk (12). Chemerin is a molecule that is involved in metabolic dysregulation and is mainly secreted from adipose tissue (3). It was demonstrated that chemerin was also positively correlated with inflammatory markers in overweight individuals with T2D Chemerin level is also considered to be a good predictor for the insulin resistance level (13, 14).

In many studies on chemerin, it is remarkable that metabolic syndrome parameters are positively correlated with the chemerin level. In a study conducted by Thomas et al., it was observed that serum chemerin level was strongly correlated with metabolic syndrome parameters (15). In a study conducted on Mexican Americans, patients with T2D had higher serum chemerin levels compared to normoglycemic controls, also obese and overweight individuals had higher concentrations compared to thin controls. There was also shown a positive correlation between chemerin levels and BMI, fasting glucose, fasting serum insulin, plasma TG, and total serum cholesterol levels, and a negative correlation with HDL-C level (16). In another study conducted in a mixed ethnic group, serum chemerin levels were significantly higher in overweight and/or obese individuals, and there was a positive correlation with HOMA-IR and TG level, and a negative correlation with HDL-C level (17). In a study on the white race, a positive correlation was found between chemerin and glucose level, TG level, blood pressure (systolic and diastolic) in patients with metabolic syndrome (7). In a study involving 1431 individuals, plasma chemerin levels were higher in participants with T2D compared to non-diabetic participants. Furthermore, significantly higher chemerin levels were detected in individuals with a BMI > 30 kg/m^2 in the non-diabetic group compared to those with a BMI < 25 kg/m^2 (16). These correlations indicate that chemerin may be a new marker of metabolic syndrome and obesity and

may be a metabolic risk factor leading to insulin resistance in T2D (18). Similarly to these studies, we found a positive correlation between serum chemerin level and BMI. However, unlike this study, no correlation between chemerin level and fasting serum glucose and TG levels was found. In a recently published article, it was indicated that chemerin predicted T2D (3). In our study, it was determined that the chemerin level was correlated with BMI and was higher in the prediabetic patient group having one of the metabolic syndrome components compared to healthy individuals. As a result of the analysis in this study, it was confirmed that chemerin predicted prediabetes. In another study with patient and control groups similar to our study, no difference had been found between the groups in terms of chemerin level (19). However, we think that the limited number of participants both in our study and in that study affected the results.

It is reported that high chemerin levels are correlated with BMI (13). Although, no significant difference was found between the obese and non-obese groups' chemerin levels in our study. Actually, we observed that the chemerin level was positively correlated with BMIs of all participants. We considered that it was due to the fact that the mean BMI level was above 30 kg/m² in both groups and the number of participants with a BMI below 25 kg/m^2 was low. Although there is a consensus that chemerin is an adipocytokine that takes part in glucose homeostasis, the role of chemerin in glucose tolerance regulation still remains uncertain due to conflicting results obtained from various studies. Exogenous chemerin administration decreases serum insulin level and thus exacerbates glucose intolerance (20). It was determined that the chemerin receptor was protective against obesity but impaired insulin secretion and decreased glucose uptake in the skeleton, muscle, and adipose tissue (21). It was demonstrated that the administration of recombinant chemerin decreased insulin-stimulated glucose uptake in adipocytes under *in vitro* conditions (22).

Different results were also found in the studies on the correlation of irisin with glucose metabolism, as well as in the studies on chemerin. Serum irisin levels were demonstrated to be lower in patients with T2D compared to non-diabetic patients (23, 24). In another study, irisin was not found to be correlated with fasting c-peptide and insulin levels (25). On the other hand, irisin was found to be positively correlated with circulating insulin levels in individuals with NGT. These findings suggest that irisin take part in regulation of the beta-cell function (26). In our study, contrary to the literature, there was no significant difference in the analyses performed with the prediabetic group, control group and all participants in irisin levels. When the comparison of irisin levels with demographic data and biochemical parameters was examined, there was no significant correlation which may be due to the fact that most of the participants were obese, the number of male participants was lower, and the kit we used was different from those used in other studies. We found a positive correlation between irisin level and HOMA-IR similar to the literature (27,28). On the other hand, it has been stated in the literature that irisin level is positively correlated with insulin resistance. We think that these contradictory results are due to exercise-related and/or muscle mass-related changes in irisin level. Although the exercise-related short-term increase in irisin level varies according to age groups, the effect of exercise on the initial irisin level remains unclear (29,30). In obese individuals, lipid tissue is responsible for the basic irisin level in the blood (30). It is seen that the relationship between HDL-C and irisin levels also differs in the literature due to factors such as the difference in the ratio of white-brown lipid tissue, changes in body fat composition, etc. Elizondo-Montemayor et al. found a positive correlation between serum irisin and HDL-C levels; on the other hand, Hirsch et al. observed a negative correlation (31, 32).

Current studies have shown that irisin can accelerate the mouse beta-cells' generation especially and also increase the number of the beta-cells (33, 34). The idea of the regeneration of human pancreatic beta-cells will open a new page for the T2D management. It has been demonstrated that irisin stimulates insulin secretion due to beta-cell proliferation. The circulating levels of irisin may have positive effects on glucose tolerance and reduce insulin resistance, which can be used as an effective strategy for the treatment of T2D (35).

In a study conducted in a population consisting of healthy Korean participants, the possible relationship between serum irisin levels and T2D development in a follow-up period of approximately 2.5 years was investigated. Irisin levels were positively correlated with HbA1c and postprandial (2nd hour) glucose levels (36). When all participants were analyzed, only negative correlation of the irisin level was with the HDL-C level and HOMA-IR.

Our study has some limitations. The main limitation of our study was that it was a cross-sectional study. Furthermore, the generalizability of our results was poor due to the low number of participants. Our results represented males at a low level due to a lower number of male participants. Another limitation was that the mean BMI of our participants was high, most of our participants were overweight and obese. Furthermore, we consider that the results have been affected by the high insulin resistance in the control group. The strong aspects of our study were that the prediabetes and control groups were similar in terms of age, gender, and BMI, and participants with comorbidities were excluded from the study.

CONCLUSION

Future researches aiming chemerin could prevent the progress of prediabetes to T2D. There is a need for further studies that will reveal the effects of these cytokines more clearly and show whether they can be a part of treatment strategies in our century during which technology is developing rapidly.

Conflict of Interest: There is no conflict of interest for this project.

Ethical Approval: All procedures in this study involving human participants were in accordance with the Helsinki Declaration (1964) and its later amendments or comparable ethical standards. The ethics committee approval from Health Sciences University Keçiören Training and Research Hospital, Clinical Research Ethics Committee was obtained (Project No: 2012-KAEK-15/1780). Written and verbal informed consent was obtained from all participants.

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