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IMPACT OF DIABETES MELLITUS ON SERUM IRISIN LEVEL AND OTHER BIOCHEMICAL PARAMETERS

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УТИЦАЈ ДИЈАБЕТЕС МЕЛИТУСА НА СЕРУМСКЕ КОНЦЕНТРАЦИЈЕ ИРИСИНА И ДРУГЕ БИОХЕМИЈСКЕ ПАРАМЕТРЕ

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ABSTRACT

Objective. Type 2 diabetes mellitus (T2DM) is a metabolic condition characterized by elevated blood sugar levels (hyperglycemia). Although T2DM can occur at any age, it is the most common form of diabetes and often develops in adulthood. People who have T2DM exhibit resistance to the effects of the hormone insulin, which the pancreas normally secretes to regulate blood sugar levels. The objective of this study was to measure the irisin hormone level as well as some biochemical parameters associated with T2DM.

Methods. A total of 65 T2DM patients and 60 healthy subjects as a control group were recruited in this cross-sectional study. The demographic information of the participants was obtained. Also, blood samples were collected from T2DM patients and the control group. The serum was separated from the blood samples and used for biochemical analysis. Irisin, fasting serum glucose (FBS), insulin, C-peptide, total cholesterol (TC), triglycerides (TG), high-density lipoprotein (HDL-C), low-density lipoprotein (LDL-C), and very low-density lipoprotein (VLDL-C) were the parameters measured in the patients and control groups. A fraction of blood samples was also processed for the measurement of glycated haemoglobin (HbA1c).

Results. There was a significant ($p \leq 0.01$) decrease in the irisin concentration in patients with T2DM compared to the control group. The results revealed a non-significant difference in the irisin levels between T2DM patients and the control group, based on sex, age, and BMI.

Conclusion. Irisin may be used as a measured parameter in T2DM patients, in addition to lipid profile and glucose level, to indicate the prognosis or clinical follow-up of patients.

Key words: *diabetes mellitus; fibronectins; C-peptide.*

САЖЕТАК

Увод. Дијабетес мелитус (T2DM) метаболичко је обољење које карактерише повишен ниво глукозе у крви (хипергликемија). Иако се T2DM може јавити у било ком узрасту, најчешће се развија у одраслом добу. Пацијенти са T2DM показују отпорност на ефекте инсулина, хормона панкреаса који регулише ниво глукозе у крви. Мерење нивоа хормона ирисина и неких биохемијских параметара повезаних са дијабетесом мелитусом тип 2.

Методе. Овим истраживањем било је обухваћено укупно 125 испитаника, 65 пацијената са дијагнозом T2DM у испитиваној групи и 60 здравих испитаника у контролној групи. Социодемографксе карактеристике узете су у обзир с вредностима концентрације аналита од значаја у серуму, и то: ирисин, концентрација глукозе (FBS), инсулин, C-пептид, тотални холестерол (TC), триглицериди (TG), липопротеин високе густине (HDL-C), липопротеин ниске густине (LDL-C) и липопротеин велике густине (VLDL-C). У испитиваној и контролној групи анализиран је гликолизирани хемоглобин (HbA1c).

Резултати. Дошло је до значајног ($p < 0,01$) смањења концентрације ирисина код пацијената са T2DM у односу на контролну групу. Резултати су открили значајну разлику у нивоу ирисина између T2DM пацијената и контролне групе, засноване на полу, годинама и вредности БМИ.

Закључак. Ирисин се може користити као дијагностички параметар код T2DM пацијената поред липидног профила и нивоа глукозе, да би се указало на прогнозу или клиничко праћење пацијената.

Кључне речи: *шећерна болест; фибронектини; Ц-пептид.*

INTRODUCTION

Type 2 Diabetes Mellitus (T2DM) is a metabolic condition characterized by elevated blood sugar levels (hyperglycemia). Although T2DM can occur at any age, it is the most common form of diabetes and often develops in adulthood. People who have T2DM exhibit resistance to the effects of the hormone insulin, which the pancreas normally secretes to regulate blood sugar levels (1). Due to this resistance, the cells of the body do not respond to insulin as well as they should, preventing glucose from entering the cells where it may be used as energy (2). As a result, there is an accumulation of glucose in the bloodstream, which raises blood sugar levels (1). Since T2DM is a metabolic condition that affects more than 400 million individuals globally, it is regarded as a complicated and multifaceted disease (3). Type 2 diabetes can occur due to several causes, including genetics,

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obesity, a sedentary lifestyle, a poor diet, and certain medical conditions such as the metabolic syndrome. Although genetics plays a role, lifestyle factors are generally significant contributors to the development of the condition (4).

A novel myokine resulting from the effects of exercise on activating the transcription factor peroxisome proliferator-activated receptor gamma co-activator-1 (PGC1-α) was discovered in 2012 (5). It was found to regulate thermogenesis and encourage the browning of adipose tissue. It enables white adipose tissue to be converted to brown, resulting in the conversion of white adipose tissue into brown adipose tissue. Irisin, a form of brown fat that is physiologically more active, can burn more calories to generate heat (6). Additionally, irisin has been shown to improve glucose homeostasis and insulin sensitivity, which can help treat and prevent T2DM (7). Some studies have also suggested that irisin may have anti-inflammatory properties and could potentially play a role in protection against chronic diseases, such as cardiovascular disease (8). Irisin is abundantly expressed in the heart, brain, liver, skeletal muscles, and salivary glands (7).

In the membrane extracellular fibronectin type III domain-containing protein 5 (FNDC5), the N-terminal region is cleaved by proteases to produce irisin, a 112-amino acid hormone (12 KDa) (9). The protein is made up of a single peptide, the fibronectin type III domain, and the C-terminal domain. The protein FNDC5 has 209 amino acid residues (5). This protein has a transmembrane domain with 19 amino acids, a signal sequence at the N-terminus with 29 amino acids, a fibronectin type III domain with 94 amino acids, an unidentified area with 28 amino acids, and a C-terminal section with 39 amino acids (10). While the C-terminal component of FNDC5 is located in the cytoplasm, the extracellular N-terminal section of FNDC5 is proteolytically cleaved to produce irisin, which is then released into the circulation. Under the control of peroxisome PGC1-α, FNDC5 is degraded by protease at amino acid sites 30 and 142 to generate irisin (12, 13).

The present study was conducted to evaluate irisin hormone levels and a few other biochemical indicators related to T2DM.

MATERIAL AND METHODS

Subjects, blood sample collection and analysis

A total of 65 diabetic patients and 60 healthy volunteers were recruited after obtaining informed consent from them. Demographic data were also recorded. The study excluded smokers, alcohol abusers, and patients with chronic diseases. The Diabetic Laboratory Unit of Azadi Teaching Hospital, Duhok City collected 65 samples of serum from patients with T2DM for pathological analysis, noting that the patients had been confirmed by specialist doctors. Information on the patients was recorded by a questionnaire. Also, 60 blood samples from healthy participants as a control group were collected.

Biochemical analysis. Blood samples were obtained from all participants. Biochemical parameters like glucose and insulin, insulin resistance (HOMA-IR), C-peptide, total cholesterol (TC), triglyceride (TG), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), HbA1c%, and plasma irisin levels were measured.

Estimation of body mass index (BMI). The equation below was used to estimate the BMI (14): BMI (Kg/m^2) = Weight (Kg) / Height (m^2)

Estimation of irisin hormone level. Irisin was estimated based on the sandwich with two biotin-binding antibodies assigned to the hormone using the analysis kit from the Chinese company (Fine Test) by employing the enzyme-linked immunosorbent assay (ELISA) technique (15).

Estimation of glucose level. Using a kit from the French company, Biolab and an enzymatic technique, serum glucose concentration was determined (16).

Estimation of insulin level. The insulin level was measured using the COBAS E 411, which functions as electrochemiluminescence with Roche's analytics kit based on the Sandwich principle (17).

Estimation of the level of C-peptide concentration. The serum concentration of C-peptide was estimated using a kit based on chemiluminescent immunoassay technology (CLIA) using the Roche/HITACHI COBAS E 411 device (Germany) (18).

Measurement of insulin resistance (HOMA IR). Insulin resistance was calculated based on both C-peptide and glucose concentrations, according to the following equation (19):

Estimation of the level of total cholesterol. The total cholesterol concentration in the blood serum was measured using a Biolab kit (France), which is an enzymatic method (20).

Estimation of the level of triglycerides. The serum concentration of triglycerides was measured using a kit from Biolab, a French company, by an enzymatic method (20).

Estimation of high-density lipoprotein-cholesterol (HDL-C). The level of HDL-C was estimated using an analytics kit from Biolab (France), where the lipoproteins present in the blood serum were deposited with the addition of phosphophenoxytic acid in the presence of magnesium ions. After centrifugation, the HDL remained in the filtrate, and the rest of the lipoproteins were deposited (21).

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Measurement of low-density lipoprotein-cholesterol (LDL-C). The concentration of LDL-C was calculated using the Friedewald equation, which is as follows (22): LDL concentration (mg/dl) = Conc. of T.C – HDL – TG/5

Determination of very low-density lipoprotein-cholesterol (VLDL-C). The VLDL-cholesterol concentration was calculated using the following equation (23): VLDL-C Concentration (mg/dl) = Triglycerides/5

Estimation of the percentage of HbA1C: The rate of glycated haemoglobin in the blood was estimated using a ready-made analytics kit with a special device from the Chinese company, Biohemes, which is a chromatographic method for quantitative measurement of haemoglobin in the blood (24).

Statistical analysis

The data were statistically analyzed using the GraphPad Prism program. The results are presented as the mean±standard deviation of three experiments. A statistically significant difference was set at $p \leq 0.001$.

RESULTS

Irisin was significantly ($p \leq 0.001$) reduced in patients with T2DM (1.53±0.079ng/ml) compared to the control group (10.96±1.35ng/ml), as shown in Figure 1A. The results (Figure 1B) revealed that there were no significant differences in the level of irisin between the sexes in both the control group and the T2D patients. There was no significant difference in the level of irisin among the age groups of T2DM patients or the controls (Figure 1C). Concerning the body mass index, as observed in Figure 1D, there was a non-significant difference in the levels of irisin between the T2DM patients and the healthy group.

The T2DM patients have significantly ($p \leq 0.001$) higher levels of glucose, HOMA-IR, TG, and LDL-C than the control subjects. Also, there was a significant ($p \leq 0.01$) increase in insulin, HbA1c, TC, and VLDL-C concentrations in patients with T2DM compared with the control group. In contrast to the control group, there was a significant ($p \leq 0.001$) decrease in the amount of HDL-C in T2DM patients. The serum irisin levels were significantly lower in the T2DM group than in the control group with values of 1.53±0.079 and 10.96±1.35 ng/ml, respectively. Only C-peptide was significantly ($p \leq 0.05$) increased in the T2DM patient group compared with the control group, as highlighted in Table 1. Concerning the relationship between baseline metabolic parameters and serum irisin levels, it was observed that the levels of serum irisin were adversely linked with those of glucose, insulin, HOMA-IR, HbA1c, and VLDL-C. Furthermore, C-peptide, TC, TG, HDL-C, and LDL-C levels were significantly positively linked with serum irisin levels (Table 2).

DISCUSSION

Irisin, a myokine-like circulating hormone, has been shown to regulate energy balance and mediate the positive effects of aerobic activity on health (25). Irisin has the potential to be used as a new therapeutic strategy for obesity and T2DM because of its function in browning white adipose tissue and, as a result, boosting energy expenditure through better thermogenesis (26). When compared to non-diabetic controls, it was observed that circulating irisin was significantly decreased in T2DM participants in the current investigation. This observation is consistent with the findings of Elizondo-Montemayor and coworkers in 2019 (25). Although the exact cause of decreased irisin levels in T2DM patients is unknown, it is thought that decreased PGC-1 activity in patient muscle

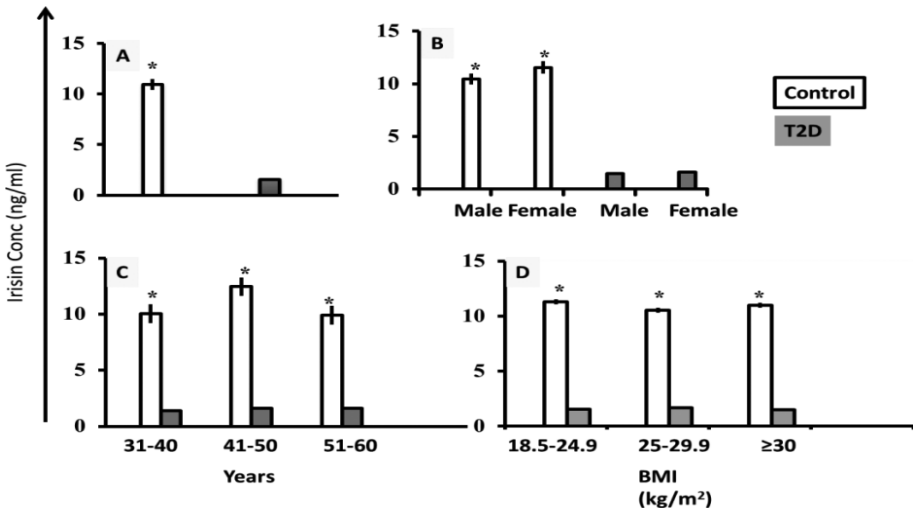

*Figure 1. Irisin concentrations in diabetic patients and the control group. A: Diabetic patients versus control; B: Gender-based variation of irisin concentration; C: Age-based variation of irisin concentration; D: Body mass index (BMI)-based variation of irisin concentration; Data expressed as Mean±SE; *: p<0.05.*

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Table 1. Biochemical parameters of the studied groups.

Parameter	Control (n=60)	Type 2 Diabetes (n=65)
Glucose (mg/dl)	91.34±2.73	207.34±13.32***
Insulin (µU/ml)	11.08±0.01	14.74±0.08**
HOMA-IR	2.6±0.05	9.14±0.02***
HbA1c%	5.39±0.034	8.45±0.27**
C-peptide (ng/ml)	1.69±0.07	2.18±0.01*
TC (mg/dl)	135.56±2.91	199.03±8.63**
TG (mg/dl)	123±8.69	198.27±17.56***
HDL-C (mg/dl)	56.19±1.76	37.63±1.68**
LDL-C (mg/dl)	71.94±4.08	113.61±5.63***
VLDL-C (mg/dl)	23.29±1.51	37.79±3**
Irisin (ng/dl)	10.96±1.35	1.53±0.079***
Data expressed as Mean±SD; *: p≤0.05; **: p≤0.01; ***: p≤0.001		

Table 2. Correlations between serum irisin levels and the baseline parameters.

	Irisin	
Parameter	R-value	P- value
Glucose(mg/dl)	-0.876	0.001***
Insulin(µU/ml)	-0.641	0.01**
HOMA-IR	-0.552	0.01**
HbA1c (%)	-0.571	0.001***
C-peptide (ng/ml)	0.865	0.001***
TC (mg/dl)	0.747	0.01**
TG (mg/dl)	0.684	0.001***
HDL-C (mg/dl)	0.664	0.01**
LDL-C (mg/dl)	0.722	0.001***
VLDL-C (mg/dl)	-0.494	0.01**

tissue may explain it. Reduced PGC-1α activity in the muscle tissues of T2DM patients consequently reduced FNDC5 synthesis and decreased irisin production. Furthermore, the combination of increased free fatty acid distribution brought on by insulin resistance and hyperglycemia resulted in decreased PGC-1α activity (27).

The two primary processes of glucose metabolism are the secretion and action of the insulin hormone, so the molecular processes underlying its synthesis and secretion are tightly regulated. Whether the high glucose is caused by a defect in the secretion of insulin by the cells of the pancreas or by the ability of the insulin-sensitive tissue to respond appropriately to insulin was not significant. It could lead to the development of the disease, a metabolic imbalance that raises blood sugar levels, a failure in one or more of the systems that underlie these processes, or both (28). The high level of insulin in patients is due to high glucose levels in the blood, which stimulate the pancreas to produce more insulin to lower the high levels of glucose. Given that insulin is necessary for the entry of glucose into cells, any disruption in the transmission of insulin signals is linked to hyperglycemia because cells are unable to utilize glucose (29). Poor glycemic control and the severity of T2DM are both indicated by elevated HbA1c values (30). Also, a high level of C-peptide suggests that the pancreas is still able to produce insulin, which suggests that beta-cell activity is still mostly intact. This is in contrast to type 1 diabetes, where C-peptide levels are usually low. The immune system of the body, by accident, can attack and destroy it. The pancreas contains beta cells, which reduce the amount of insulin produced. In people with T2DM, the main problem is usually insulin resistance, which implies that the cells of their bodies have difficulty responding to insulin. However, the pancreas still frequently produces more insulin than necessary to counteract insulin resistance, and this compensatory reaction raises C-peptide levels (31).

In T2DM, several factors can affect cholesterol levels, including insulin resistance, obesity, unhealthy food choices, and a sedentary lifestyle. An increase in the level of glucose in the blood will promote the formation of acetyl-CoA by activating the Krebs cycle pathway, which ends with the synthesis of cholesterol (32). Triglycerides are broken down into free fatty acids by lipoprotein lipase (LPL). Insulin typically increases LPL activity (33). Meanwhile, in T2DM, a drop in insulin activity results in a decrease in the activity of LPL and hepatic lipase, which causes a rise in the triglyceride level of the serum sample (34). Due to the abundance of cytokines released from cells in response to local stimuli, the localized milieu and circulatory system also include a high number of trophic factors in addition to irisin (35, 36).

Recent studies reveal that the levels of irisin, a hormone produced by skeletal muscle, are significantly reduced in diabetic patients regardless of their sex, age, and BMI. Irisin is known for its role in regulating glucose metabolism and energy expenditure, making it a vital component in the development and progression of diabetes. The findings of this study suggest that the decrease in irisin levels may contribute to the impaired

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glucose control observed in diabetic individuals, and it could potentially serve as a biomarker for the disease. It is interesting to note that this reduction in irisin levels is not influenced by factors such as sex, age, or BMI, suggesting that it may be a common feature observed in diabetic patients across different demographics. Further research is needed to unravel the underlying mechanisms causing this decrease in irisin and its implications for the management of diabetes. Understanding the role of irisin in diabetes may pave the way for novel therapeutic approaches and diagnostic tools to effectively manage this common metabolic disorder.

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