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Evaluation of Irisin Level in Iraqi Patients with Type 2 Diabetes and Pre-Diabetes Status as a Predictive Factor

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Abstract

The prevalence of diabetes is increasing rapidly and is now recognized as a significant global health problem. Diabetes occurs when a person does not produce enough insulin due to an imbalance in insulin production. This can lead to the failure of organs and tissues such as the kidneys, heart, blood vessels, eyes, nerves, and kidneys. As a result, early diagnosis and classification of type 2 diabetes mellitus (T2DM) are critical to aiding physician assessments. Subsequently, the current study aims to determine irisin levels in patients with T2DM and pre-DM as early predictors for disease cases. The current study included 138 subjects divided into three groups based on fasting blood glucose (FBG) and glycosylated hemoglobin criteria, including T2DM, 46 patients, pre-diabetes, 46 participants, and healthy subject groups, 46 persons) when they enrolled in the National Diabetes Center/ Al-Mustansiriya University. Enzyme-linked immunosorbent assays were used to detect the levels of irisin and insulin, and spectrophotometric techniques were used to determine the levels of FBG and lipid profile. The results of irisin revealed significant differences among the studied groups. Also, the insulin results showed substantial differences between the diabetic and control groups. Moreover, the results of HOM-IR and HOMA-IS and lipid profiles showed significant differences between the studied groups. The results showed that irisin can serve as an early indicator of pre- diabetes. These results were reinforced by the results of the ROC analysis, which indicated that irisin is an excellent indicator for diagnosing the studied condition.

Keywords: HOMA-IR, HOMA-IS, insulin, irisin, pre-diabetes, type 2 diabetes mellitus.

1. Introduction

The prevalence of diabetes is rapidly increasing and is now recognized as a significant worldwide health problem (1). Diabetes mellitus (DM) is a type of metabolic disorder in which patients experience high blood sugar levels as a result of their bodies' inability to react to or

produce enough insulin; this hormone helps to stabilize the blood glucose level by instructing cells to take up glucose and prevent the production of hepatic glucose (2,3). The primary sign of diabetes is hyperglycemia. Long-term exposure to hyperglycemia will have physiological effects on the organs, including chronic progressive lesions and organ and tissue failure in the kidneys, heart, blood vessels, eyes, nerves, and kidneys (4,5). Diabetic complications were investigated in numerous previous studies that include diabetic nephropathy (6), diabetic with osteoporosis (7), and diabetic with periodontitis (8). Obesity represents an unhealthy excess in body fat mass characterized by developing a chronic, widespread, low-grade inflammatory state. Obesity-related inflammation can affect insulin signaling in tissues sensitive to insulin (including skeletal muscle and Adipose tissue), leading to insulin resistance (IR) (9). As a result, the global obesity pandemic is causing an essential rise in the incidence of cardiometabolic diseases, such as type 2 DM (T2DM), at the same time. Obesity, pre-diabetes (pre-DM), and IR are all intimately related, as is widely known (10). Pre-DM is quite common, particularly in elderly person groups and obese people. It represents a transition stage between normal glycemia and diabetes**.**

pre-DM is diagnosed through laboratory measurements of fasting blood glucose (FBG) and glycosylated hemoglobin (HbA1c). The expression pre-DM is used to identify those who are at risk of developing diabetes in the future (11). The most significant hazard reasons for T2DM and pre-DM in adults are being overweight and obese (12). Irisin is a novel myokine that was found to be produced by skeletal muscle and enters the bloodstream during exercise. Irisin increases the browning of white adipose tissue, which improves glucose metabolism and thus increases energy expenditure (13). Irisin improves insulin resistance and T2DM by growing sensitization for the insulin receptor in skeletal muscle and heart by improving hepatic glucose and lipid metabolism, promoting pancreatic β cell functions (14). This study aims to estimate irisin levels in diabetic patients and subjects with pre-DM compared to healthy persons to know whether it can be applied as an early predictor for the studied cases **.**

2. Materials and Methods

2.1. Study subjects

In the current study, levels of irisin and some relevant biochemical parameters were measured. All the studied samples were collected from patients in the National Diabetes Center/ Mustansiriyah University, Baghdad, Iraq. A total of 138 participants, 46 healthy individuals, 46 people with T2DM, and 46 people with pre-DM in the age range of (30-65) years, were included in this study. A questionnaire presents the anthropometric and biochemical features of each group. Patients were divided into two groups based on their FBG and HbA1c levels. Group 1 included 46 T2DM patients with FBG of more than 126 mg/dl and HbA1c of more than (6.4%). Group 2 included 46 pre-diabetic patients with FBG between (100 -125) mg/dl and HbA1c between (5.7-6.4) percent. The insulin and retinol-binding protein 4 concentrations were evaluated using a My BioSource manufactured enzyme-linked immunosorbent test ELISA kit, USA. The levels of total cholesterol, triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), and very low-density lipoprotein (VLDL) were measured using a Linear Chemicals S.L kit.

2.2. Exclusion criteria

Patients with diabetic neuropathy, diabetic nephropathy, and diabetic retinopathy were excluded, as well as patients over 65 years of age. Also, patients treated with insulin, non-fasting diabetic patients, and chronic thyroid patients.

2.3. Inclusion criteria

Clinical screening signals were used to determine the presence of metabolic syndrome (MetS) in patients. Patients with T2DM, aged 30 to 65, who are also diabetic and who should be fasting according to their medical history and physical examination.

2.4. Blood samples collection

Five milliliters (mLs) of venous blood were collected from each patient and controlled in serum-separating tubes. Sera were obtained by centrifuging 4 mLs of blood at 3000 rpm for 10 minutes. After it had been allowed to clot for approximately 30 minutes at room temperature, the obtained serum was divided between two Eppendorf tubes. It was stored at -20 ºC until being used for subsequent analysis. The first section has been utilized to determine FBG, CHOL, TG, HDL, irisin, and insulin levels in the second component, which was kept at a temperature of minus 20°C and was evaluated by an enzyme-linked immunosorbent assay kit (ELISA). Additionally, 1 mL of whole blood in EDTA tubes was analyzed for HbA1c assay.

2.5. Statistical analyses

The Statistical Analysis System- SAS (2018) program was applied to categorize the influence of numerous factors on research parameters. Thus, for statistical comparison between means, a Least Significant Difference (LSD) test (Analysis of Variation ANOVA) was employed. The ROC curve was used to assess the accuracy of markers as indicators of diabetes.

3. Results

Table 1 shows the values of age, BMI, and waist-to-hip ratio (WHR) for all the studied groups. Age results in mean ± SD for T2DM, pre-DM, and control groups [(53.21 ± 1.20), (51.00 ± 1.35) and (42.30 ±1.12)] respectively, the results revealed considerable differences (P=0.0001) between the T2DM group and control group as well as the pre-DM and control groups. Still, there is no significant variance between the T2DM and pre-DM groups.

The results of BMI in patients with T2DM, subjects with pre-diabetes, and healthy persons in terms of mean ± SD were found to be [(28.61 ± 0.94), (27.41 ± 0.64) and (24.78 ± 0.19)] respectively. The results revealed highly significant differences (P =0.0003) between the T2DM, pre-diabetes groups, and the control group, while there was no significant difference between T2DM and pre-DM. Also, **Table 1** records the WHR for the T2DM, pre-DM, and control groups and finds them to be [(0.958 ± 0.01), (0.915 ± 0.009), and (0.917 ±0.004)], respectively. The results revealed a significant difference between the T2DM, pre-DM, and control groups. In contrast, there was no difference between the pre-DM and control groups.

Table 1. Age, BMI and WHR for the study groups.

Groups	Mean ±SD			
	Age (Years)	BMI (kg/m^2)	WHR	Duration of DM (Years)
T2DM (n =46)	53.21 ± 1.20 a	28.61 ± 0.94 a	0.958 ± 0.01 a	6.73 ± 0.69
Pre-DM (n =46)	51.00 ± 1.35 a	27.41 ± 0.64 a	0.915 ± 0.009 b	0.726 ± 0.06
Control (n =46)	42.30 ± 1.12 b	24.78 ± 0.19 b	0.917 ± 0.004 b	-
LSD	3.44 **	1.870 **	0.0262 **	1.393 **
p-value	0.0001	0.0003	0.0016	0.0001

The different letters in the same column Mean that they are differed significantly, ** (P ≤ 0.01), T2DM: Type 2 Diabetes Mellitus, Pre-DM: Pre-Diabetes Mellitus.

Table 2 shows the effect of gender on the studied parameters, including BMI, WHR, FBG, and HbA1c, in both T2DM and pre-DM groups. The results revealed that gender does not affect the mentioned parameters in the case of pre-DM. While BMI is significantly affected (P=0.0071) in the case of T2DM, no other parameters are noted.

Table 2. Effect of gender in parameters for the study groups**.**

Parameters	Mean ±SD					
	Pre-DM group			T2DM group		
	Male	Female	P-value	Male	Female	P-value
BMI (kg/m^2)	27.03 ± 0.89	27.72 ± 0.94	0.604 NS	26.45 ± 1.22	31.43 ± 1.22	0.0071 **
WHR	0.914 ± 0.01	0.916 ± 0.02	0.922 NS	0.956 ± 0.02	0.961 ± 0.02	0.849 NS
FBG (mg/dL)	116.08 ± 1.15	112.94 ± 1.76	0.158 NS	194.15 ± 14.29	198.74 ± 10.21	0.806 NS
HbA1c (%)	6.03 ± 0.05	6.01 ± 0.04	0.790 NS	7.84 ± 0.29	8.45 ± 0.36	0.184 NS

The different letters in the same column Mean that they are differed significantly, ** (P ≤ 0.01), NS: Non-Significant, T2DM: Type 2 Diabetes Mellitus, Pre-DM: Pre-Diabetes Mellitus.

Table 3 shows the results of irisin and insulin for all the studied groups; irisin data revealed a significant difference (P =0.0001) between the T2DM, pre-diabetes, and control groups. Irisin values of the mentioned groups were found to be [(34.69 ± 1.47) (18.51 ± 0.76) (17.58 ±1.30)] respectively. On the other hand, the insulin results of the studied groups, including T2DM, pre-DM, and control, were found to be [(4.02 ± 0.20) (2.14 ±0.13), (1.838 ± 0.05)] respectively. They revealed a significant difference (P=0.0001) between the T2DM group and the other two groups, including pre-DM and control groups, but no significant differences between pre-DM and control groups.

The results of FBG, HbA1,c, and HOMA-IS in all the mentioned groups were found to be [(196.14 ± 9.14), (114.37 ±1.10) and (93.49 ±0.76)] respectively for FBG, [(8.11 ± 0.23), (6.02 ± 0.03)], [(4.69 ± 0.03), respectively for HbA1c and [(0.597 ±0.02),(1.89 ±0.11) and (2.36 ± 0.09)] respectively for HOMA-IS. At the same time, the FBG, HbA1c, and HOMA-IS results revealed significant differences (P=0.0001) among the studied groups. The values of HOMO-IR for the mentioned groups were recorded to be [(1.97 ± 0.15), (0.603 ± 0.04), and (0.453 ± 0.02)]

respectively. The results of HOMA-IR showed a significant difference (P=0.0001) between the T2DM group and both the pre-DM and control groups, as shown in **Table 4**.

Table 3. Irisin and insulin levels for the study groups.

Groups	Mean ±SD	
	Irisin (ng/mL)	Insulin (µu/mL)
T2DM (n =46)	34.69 ± 1.47 a	4.02 ± 0.20 a
Pre-DM (n =46)	18.51 ± 0.76 b	2.14 ± 0.13 b
Control (n =46)	17.58 ± 1.30 b	1.838 ± 0.05 b
LSD	3.412 **	0.402 **
p-value	0.0001	0.0001

The different letters in the same column Mean that they are differed significantly,** ($P \leq 0.0001$), T2DM: Type 2 Diabetes Mellitus, Pre-DM: Pre-Diabetes Mellitus.

Table 4. The FBG, HbA1c, HOMA-IR and HOMA-IS values for the study groups.

Groups	Mean ±SD			
	FBG (mg/dL)	HbA1c (%)	HOMA-IR	HOMA-IS
T2DM (n =46)	196.14 ± 9.14 a	8.11 ± 0.23 a	1.97 ± 0.15 a	0.597 ± 0.02 c
Pre-DM (n =46)	114.37 ± 1.10 b	6.02 ± 0.03 b	0.603 ± 0.04 b	1.89 ± 0.11 b
Control (n =46)	93.49 ± 0.76 c	4.69 ± 0.03 c	0.453 ± 0.02 b	2.36 ± 0.09 a
LSD	14.907 **	0.380 **	0.258 **	0.242 **
p –value	0.0001	0.0001	0.0001	0.0001

The different letters in the same column Mean that they are differed significantly, ** ($P \leq 0.01$), T2DM: Type 2 Diabetes Mellitus, Pre-DM: Pre-Diabetes Mellitus.

Values of cholesterol, TGs, HDL, LDL, and VLDL in groups of T2DM, pre-DM, and control were [(182.81 ±6.62) (191.22 ±5.33) (162.67 ±5.32)], respectively, for cholesterol, [(171.82 ± 13.46), (168.56 ±11.46) and (110.84 ±4.28), respectively for TGs, [(44.98 ±1.62), (46.87 ±1.96) and (49.78 ±1.61)] respectively, for HDL, [(34.36 ±2.69), (33.71 ±2.29) and (22.53 ±0.98)] respectively for VLDL and [(103.46 ±5.39), (110.63 ±4.78) and (94.14 ±4.21)] respectively for LDL as noticed in **Table 5**.

The results showed that cholesterol, TGs and VLDL in both groups of T2DM and pre-DM possess high significant differences ($P \leq 0.01$) of both T2DM and pre-DM groups in comparison with control group. Whereas there is no significant difference among all the studied in case of HDL. Also, the results of LDL revealed significant difference between control and both of T2DM and pre-DM groups as recorded in **Table 5.**

In **Table 6**, data revealed the effect of gender on lipid profile in both T2DM and pre-DM groups. The results showed significant differences between males and females for only TGs, HDL, and VLDL parameters in Pre-diabetes. In contrast, gender does not affect any lipid profile parameter in T2DM.

Table 5. Lipid profile of the study groups.

Groups	Mean ±SD				
	Cholesterol	TG	HDL	LDL	VLDL
T2DM (n =46)	182.81 ± 6.62a	171.82 ± 13.46a	44.98 ± 1.62	103.46 ± 5.39ab	34.36 ± 2.69a
Pre-DM (n =46)	191.22 ± 5.33a	168.56 ± 11.46a	46.87 ± 1.96	110.63 ± 4.78a	33.71 ± 2.29a
Control (n=46)	162.67 ± 5.32b	110.84 ± 4.28b	49.78 ± 1.61	94.14 ± 4.21b	22.53 ± 0.98b
LSD	16.201 **	29.384 **	4.864 NS	13.48 *	5.927 **
p-value	0.0022	0.0001	0.148	0.050	0.0001

The different letters in the same column Mean that they are differed significantly,** (P≤0.01), *(P≤0.05), T2DM: Type 2 Diabetes Mellitus, Pre-DM: Pre-Diabetes Mellitus, TG: triglycerides, HDL: high density lipoprotein,LDL: low density lipoprotein, VLDL: very low density lipoprotein.

Table 6. Effect of gender in lipid profile in the study groups.

Parameters	Mean ±SD					
	Pre- DM group			T2DM group		
	Male	Female	P-value	Male	Female	P-value
Cholesterol (mg/dL)	192.66 ± 8.05	190.01 ±7.25	0.807 NS	184.02 ±9.28	181.25 ±9.53	0.838 NS
TG (mg/dL)	200.30±16.18	141.88 ±4.32	0.0095 **	171.45±19.63	172.30±18.12	0.975 NS
HDL (mg/dL)	41.76 ±3.58	51.16 ±1.60	0.021 *	44.90 ±2.51	45.10 ±1.90	0.952 NS
LDL (mg/dL)	110.83 ±7.30	110.47±6.44	0.970 NS	104.83 ±7.34	101.69 ±8.11	0.776 NS
VLDL (mg/dL)	40.06 ±3.23	28.38 ±2.86	0.0096 **	34.29 ±3.92	34.46 ±3.62	0.975 NS

The different letters in the same column Mean that they are differed significantly ** (P≤0.01) *(P≤0.05) NS: Non-Significant, TG: Triglycerides, HDL: High Density Lipoproteins, LDL: Low Density Lipoproteins, VLDL: Very Low Density Lipoproteins, Pre-DM: Pre-Diabetes Mellitus, T2DM: Type 2 Diabetes Mellitus

The ROC test for the irisin marker showed an obvious cut-off value (>18.57) with AUC of 0.987, 0.978 for sensitivity, and 0.087 for 1-specificity indicated irisin is considered an excellent diagnostic marker for diagnosis of the study case, as shown in **Table 7** and **Figure 1**.

Table 7. The ROC data analysis for irisin.

Characteristics	Test result variable
IrIsin (ng/mL)	> 18.57
Asymptotic Sig.[b]	0.001
SE[a]	0.010
Sensitivity	0.978
1-Specificity	0.087
AUC	0.987
(95% CI)	(0.968-1.000)

CI: Confidence interval, AUC: Area under curve.

Data of ROC analysis for HOMA-IS showed high AUC (0.901) with cut-off (> 1.95), sensitivity (0.891) and specificity (0.217). Accordingly, as shown in **Table 8** and **Figure 2**, HOMA-IS represented an excellent diagnostic marker.

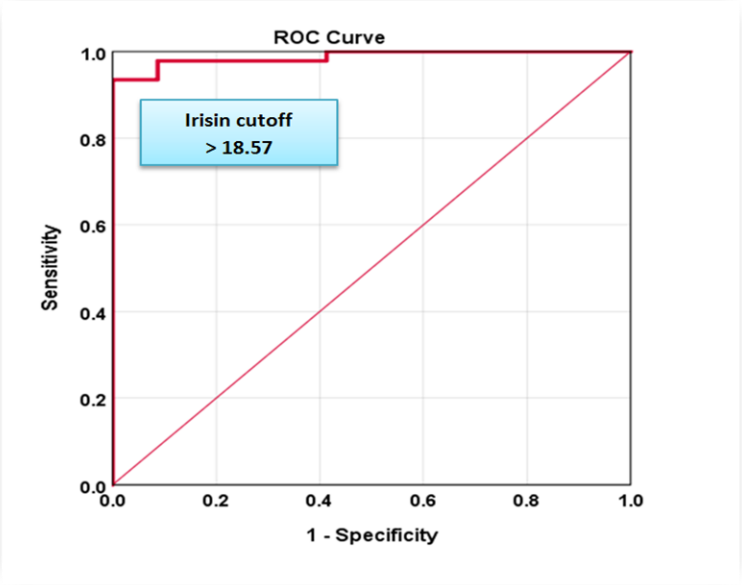

Figure 1. The ROC of irisin.

Table 8. The ROC data for HOMA-IS.

Characteristics	Test result variable
HOMA IS	< 1.95
Asymptotic Sig.[b]	0.001
Std. Error[a]	0.029
Sensitivity	0.891
1-Specificity	0.217
AUC	0.901
(95% CI)	(0.847- 0.951)

CI: Confidence interval, AUC: Area under curve

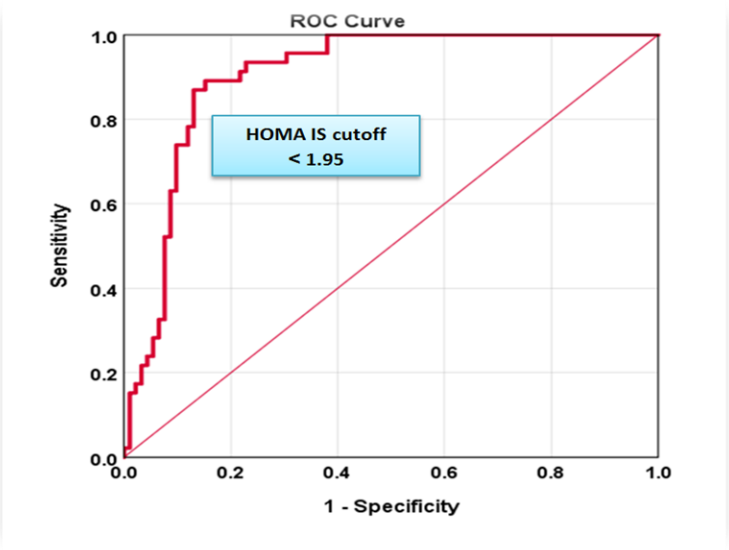

Figure 2. The ROC curve of HOMA-IS.

4. Discussion

In the current study, the age distribution results showed a significant difference between the control group and both groups of T2DM and pre-DM. This result may be attributed to the slow progression of T2DM, which frequently does not occur in the early stages for the patient to detect the symptoms of typical DM. It is well known that T2DM often begins for many years without being diagnosed significantly since the risk of T2DM increases with age, obesity, and inactivity (15).

The BMI results confirmed the existence of significant differences between the patients and healthy groups, which enhances the consistency of the current study with previous studies. The progression of DM and obesity has gained substantial attention in many studies (16).

Obesity exceeds 30 kg/m^2 of BMI value, while it falls within the normal BMI range of 18.5-24.9 kg/m^2 (17). According to Joshi et al., who discovered that diabetic patients' BMI was significantly higher than that of non-diabetic patients (18).

The current study's WHR results agreed with those of other studies, which found that this ratio is high in patient groups relative to healthy people. This ratio is also associated with MetS and high blood pressure (19). Furthermore, other studies have indicated that the WHR is better than BMI in obesity in people with cardiovascular disease. In addition, each WHR and BMI are critical sensitive indicators in the case of diabetes (20).

International standards were adopted in collecting the current study models, which are based on the levels of FBG and HbA1c to describe the condition of patients with T2DM and pre-DM. Subsequently, the results of the current study are consistent with previous studies (21,22). The current study showed a significant increase in the level of insulin hormone and HOMO-IR in the patients group with T2DM compared to the healthy group. In contrast, no significant difference was found between pre-DM and control groups. At the same time, the HOMA-IS level revealed highly significant differences among the three studied groups. This result agrees with the study of Mohsen et al. (23), who showed that patients with T2DM had elevated HOMA-IR together with insulin and low levels of HOMA-IS compared to the control group. This result can be explained by the fact that IR is most likely the initial metabolic aberration in T2DM. Raised serum glucose levels brought on by IR led to the pancreas's overproduction of insulin. When hyperglycemia is continuous and chronic, the pancreatic cells are damaged and cease functioning (24).

Current lipid profile levels showed highly significant differences in cholesterol and TG. In contrast, the serum HDL-C level was lower in T2DM than in the control group, but there was no significant difference between the two groups of DM and pre-DM compared to the control group. This result agrees with previous studies (26, 27).

In the current study, the results of irisin levels showed a statistically significant increase in the group of patients with T2DM compared with the control group and the pre-DM group. The presence of higher circulating levels of Irisin in T2DM subjects may indicate irisin dysregulation. However, a few studies have suggested that metabolic disease states have low Irisin levels (28-30). Other studies revealed that T2DM and other metabolic disorders have higher irisin levels (31,32). Recently, it has been found that people with MetS have considerably greater irisin levels than those without. They proposed that the uncontrolled release of irisin may

have been caused by compromised irisin signaling in MetS (33).

5. Conclusion

According to the current study, irisin is an excellent marker for diagnosing the case studied. This result was supported by ROC data analysis, which showed the value of AUC equal to 0.987. The patient's group had a significantly higher level of insulin hormone and HOMO-IR than the healthy group. At the same time, the HOMA-IS level revealed highly significant differences among the three studied groups. ROC data analysis supported this result, which showed the value of AUC equal to 0.901.

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Conflict of Interest

The authors declare that they have no conflicts of interest.

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Ethical Clearance

This study was approved by a local ethics committee at the Department of Chemistry/ College of Science for Women/ University of Baghdad. They reviewed and approved the study protocol, subject information, and consent form according to document number 6364/22 on 5/ December /2022.

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