Original Article

Preptin and Irisin as a Metabolic Biomarkers in Juvenile Diabetes

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Abstract

Background: Type 1 diabetes is a multifactorial metabolic disorder characterized by hyperglycemia due to reduced or absent insulin secretion. It is widely spread among children with a prevalence increased worldwide in recent years. Preptin is a novel peptide hormone secreted concomitantly with insulin from the pancreatic β-cells. Irisin is a novel exercise-induced myokine secreted from skeletal muscle which will have a great role in regulating glucose homeostasis and energy expenditure. **Objective:** As patients with type 1 diabetes are known to have reduced or absent insulin secretion and metabolic syndrome. The present work aims to evaluate the levels of preptin and irisin and determine their correlation to the disease. **Materials and Methods:** A total of 100 children participated in this study who divided into 50 patients with T1D and 50 were of controls. The patients who developed diabetic complications during sample collection were excluded. Preptin and irisin were determined using a commercial enzyme-linked immunosorbent assay kit. **Results:** Slightly decreased levels of preptin were found in patients compared with control group ($P > 0.05$). Irisin was slightly increased in the patients group ($P > 0.05$). There was a significant positive correlation between preptin with irisin and random blood sugar (RBS) with P-value ($r = 0.762$, $P \leq 0.001$), ($r = 0.345$, $P = 0.025$), respectively. In addition, there was a significant positive correlation between irisin and RBS ($r = 0.352$, $P = 0.022$). **Conclusion:** Preptin was correlated positively and significantly with irisin in all individuals. Preptin and irisin correlated significantly with RBS only in the patients group, which indicates a strong association with hyperglycemia. Irisin was a significant predictor for preptin and thus residual β-cells; therefore, it can be used as a prognostic marker for T1DM.

Keywords: Irisin, preptin, RBS, type 1 diabetes

Introduction

Type 1 diabetes is a chronic autoimmune disorder caused by the destruction of pancreatic beta cells by autoreactive T-lymphocytes. Reduced insulin secretion results in prolonged hyperglycemia which requires a lifelong insulin therapy.[1] Several risk factors are implicated in the development of the disease, including genetic predisposition, environmental factors, and immunologic dysregulation.[2] The incidence and prevalence of the disease have increased in recent years due to different etiologies, with incidence rate of 3%–4% in the past three decades.[3] The reduced insulin levels in diabetic patients result in hyperglycemia that makes excess glucose shunted into alternative metabolic pathways such as the polyol pathway, protein kinase-C pathway, hexose amine pathway, and advanced glycation end products pathway. All these pathways have been shown to produce reactive oxygen species and propagate oxidative stress and osmotic pressure which in turn causes cell damage.[4,5] Osmotic stress is believed to play a key role in the development of micro- and macrovascular complications of diabetes such as retinopathy, nephropathy, neuropathy, cerebrovascular disease, cardiovascular disease, foot ulcers, and amputations.[5,6] As the disease is characterized by metabolic derangements, it is critical to find an alternative cure that helps in metabolic regulation with insulin.

Irisin is a novel exercise-induced myokine mainly secreted from the skeletal muscle in response to physical activity and exercise, mediating the beneficial effects of

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exercise. Irisin plays a critical role in metabolic regulation particularly glucose homeostasis through the mitogen-activated protein kinase pathway.[7] It is produced from the proteolytic cleavage of the membrane-bound protein fibronectin type-III domain-containing protein 5 (FNDC5) [Figure 1].

The expression and synthesis of FNDC5 are stimulated by peroxisome proliferator-activated receptor-γ co-factor 1α (PGC1α), a master regulator of genes involved in metabolism and energy expenditure. As a result of exercise and shivering, the expression of PGC-1α increased. This in turn induces FNDC5 expression, which is enzymatically cleaved and released as irisin into circulation.[9] It is still unclear which exact protease enzyme cleaves FNDC5; however, it has been proposed that a disintegrin and metalloproteinase family (ADAM) specifically ADAM 10 is the candidate enzyme that cleaves FNDC5 to release irisin.[10]

Irisin has numerous beneficial functions especially on metabolism as it can induce glucose uptake by the adipose tissues and skeletal muscle, reduce oxidative stress, induce β-cells regeneration and insulin secretion, promote browning of white adipose tissues, and enhance insulin sensitivity, metabolism, osteogenesis, and cognition.[7]

Preptin is a peptide hormone composed of 34 amino acids synthesized primarily in the pancreatic β-cells and stored with insulin in the same vesicle. It is derived from proinsulin-like growth factor-II (Pro-IGF-II) and secreted with insulin and C-peptide at the same time in response to hyperglycemia.[11] Preptin can also be secreted from the salivary gland, mammary tissues, and kidneys.[12] Preptin is reported to be involved in mineral metabolism, but it also has another critical function as it can bind to the insulin-like growth factor-II receptor on β-cells augmenting insulin secretion through a Ca+ dependent pathway, as shown in Figure 2.[13]

Materials and Methods

This case–control study involved 100 participants divided into two groups, each comprised 50 participants. The patients were taken from the Diabetes Centre in Marjan City Hospital and Babylon Teaching Hospital for maternity and children of Babylon province. Venous blood samples were taken from the participants and the blood collected in a gel tube, centrifuged at 3000×*g* for 20 min. The serum samples were stored at -70°C. Random blood sugar was measured manually with a glucose kit using a spectrophotometer (Taytec, Canada). HbA1c was assayed using an automated analyzer (HbA1c Turbidimetric, Linear, Cromatest, Barcelona, Spain). Irisin and preptin were measured using enzyme-linked immunosorbent assay technique (Bioassay Technology Laboratory, China).

A. Inclusion criteria:
   1. T1DM without diabetic complications.
   2. Age ≤ 18 years.

B. Exclusion criteria:
   1. Patients with diabetic complications (micro or macrovascular complications).
   2. Nephrotic syndrome.
   3. Growth hormone deficiency.
   4. Thyroid dysfunction.
   5. Cushing syndrome.
   6. Patients with T2DM.

In addition, the control group were taken without any apparent disorder of renal, liver, skin, and celiac disease.

Ethical approval

All participants in this study were informed before collecting samples, and verbal agreement was obtained from each of them. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to document number 14 on July 6, 2022 to get this approval.

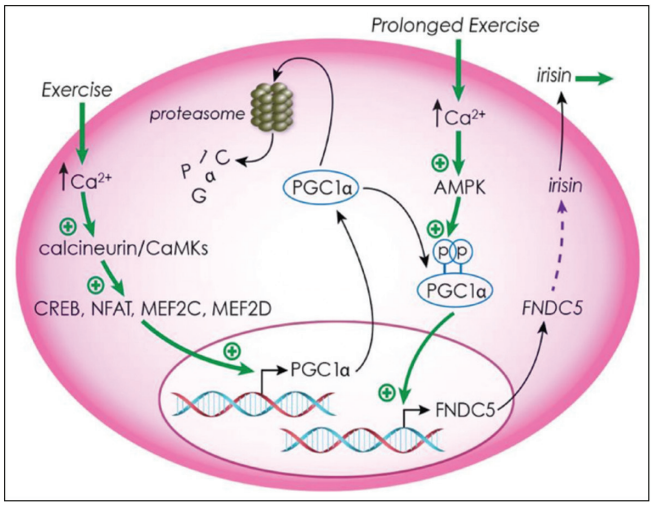

Figure 1: Synthesis of irisin controlled by PGC-1α[8]

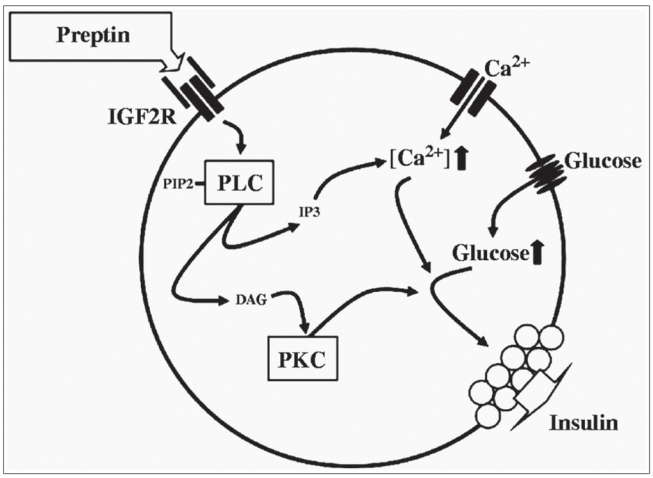

Figure 2: Candidate pathway for the regulation of insulin secretion by preptin[13]

Statistical analysis

Statistical analysis was performed using SPSS, version 28.0 (IBM). The normality of data distribution was tested by the Kolmogorov–Smirnov and Shapiro–Wilk tests. Normally distributed continuous data are expressed as mean ± standard deviation (SD), while non-normally distributed data are expressed as median (minimum–maximum). Mann–Whitney *U* test and Student's *t* test were applied to compare the means between groups for non-normal and normally distributed data respectively. Correlations between variables were performed using Spearman correlation, because the data are not-normally distributed. Partial coefficient was used for binary correlations adjusted for potential confounders, in order to remove the effect of other variables. Simple linear regression analysis was used to determine the predictors of preptin. A *P*-value < 0.05 was considered statistically significant.

Results

Demographic and biochemical characteristics of patients and control

The demographic and biochemical characteristics of the studied groups are shown in Table 1. The range of age in the patients and control group was 2–16 years. The studied groups were matched regarding age and body mass index to reduce their effect on the studied parameters with *P*-values (0.984) and (0.214), respectively.

Among the patients, there were (52%) boys and (48%) girls, while in the control group, there were (57%) boys and (43%) girls.

As well, the distribution of patients according to residence showed that the majority (62%) of patients came from rural areas, while only (38%) came from urban areas. This distribution is related to the higher risk factors for developing the disease in rural areas, such as exposure to environmental factors (e.g. viral infection, chemicals, etc.).[12]

A total of 62% of the patients had a family history of T2DM, 19% had no family history, 14% had both T1D and T2DM, and only 5% had a family history of T1D. In the control group, (64%) had a family history of T2D, whereas 36% had no family history.

The median duration of the disease was 2 years. The mean of HbA1c in patients was (9.95 ± 2.6). Patients with T1D have higher levels of random blood sugar (RBS) compared with the control group ($P < 0.001$), as shown in Table 1.

Serum levels of preptin and irisin in the studied groups

The current work showed a statistically non-significant difference in the preptin level between groups ($P > 0.05$) [Table 1]. Regarding gender, there was non-significant difference in preptin levels between female and male participants in the patient's group ($P > 0.05$) [Table 2]. In contrast, preptin levels were slightly lower in diabetic patients with a duration of disease (≥5 years), whereas in patients with a duration of <5years it was higher with a non-significant difference ($P > 0.05$), as shown in Table 3.

Regarding irisin, there was a slightly higher level in diabetic patients with a non-significant difference compared with the control group ($P > 0.05$), as shown in Table 1. In addition, there was a non-significant difference between boys and girls in the patient's group ($P > 0.05$), as shown in Table 2.

Spearman correlation of preptin and irisin with other parameters

In patients with type 1 diabetes, there was a positive significant correlation between preptin and irisin ($P < 0.001$, $r = 0.762$), as well as preptin was positively correlated with RBS ($P < 0.05$, $r = 0.346$). A non-significant negative correlation was found between preptin and BMI, duration of disease and no correlation with HbA1c ($P > 0.05$), as shown in Table 4. Regarding irisin, there was a significant positive correlation with RBS ($P < 0.05$, $r = 0.352$). However, when the correlation was adjusted regarding gender, irisin correlated negatively with the duration of disease ($P > 0.05$), and not correlated with HbA1c, as shown in Table 4.

Table 1: Demographic and biochemical characteristics of the studied groups (patients and control)

	T1DM group Median (Min–Max)	Control group Median (Min–Max)	*P*-value
Gender (male/female) (%)	52%/48%	57%/43%	0.906
BMI (kg/m^2)	17.1 (13.9–25)	18.6 (13.8–27)	0.214
Preptin (ng/mL)	297.1 (117.1–985.7)	307.5 (119.1–644.9)	0.783
Irisin (ng/mL)	8.1 (3.2–25.99)	7.1 (3.3–29.9)	0.8
Duration of disease (years)	2 (0.02–14)	–	–
Residence (rural, urban)	62%, 38%	12%, 88%	–
Family history (T1D, T2D, T1 & T2DM, No)	5%, 62%, 14%, 19%	T2D (64%), No (36%)	–
	Mean ± SD	**Mean ± SD**	
Age (years)	10.1 ± 3.6	10.1 ± 3.9	0.984
RBS (mmol/dL)	14.4 ± 7.1	4.2 ± 1	<0.001
HbA1c (%)	9.95 ± 2.6	–	–

Table 2: Comparison of the preptin and irisin levels in the patient group according to gender using Mann–Whitney *U* test

Study groups	Gender	Preptin (ng/mL) Median (Min–Max)	*P*-value
Patients	Girls	304.1 (139.2–542.9)	0.640
	Boys	286.0 (117.1–985.7)	
	Gender	**Irisin (ng/mL) Median (Min–Max)**	***P*-value**
Patients	Girls	7.2 (3.7–12.3)	0.770
	Boys	7.1 (3.2–25.9)	

Table 3: Comparison of preptin levels in patient group according to the duration of the disease

Patient subgroup	Preptin (ng/mL) Median (Min–Max)	*P*-value
Group I (<5 years)	303.9 (117.1–985.7)	0.5
Group II (≥5 years)	296.3 (211.7–395.6)	

Table 4: Spearman correlation of preptin and irisin with other parameters in T1DM patients

	Preptin	*P*-value	Irisin	*P*-value
	r		*r*	
Age (years)	0.054	0.734	0.085	0.592
BMI (kg/m^2)	–0.155	0.328	0.056	0.725
Duration	–0.028	0.858	–0.060	0.706
RBS	0.346*	0.025	0.352*	0.022
Irisin	0.762**	<0.001	–	–
Preptin	–	–	0.762**	<0.001
HbA1c	0.139	0.379	0.214	0.174

*Correlation is significant < 0.05

**Correlation is significant at the 0.01 level (2-tailed)

Table 5: Partial correlation between irisin and HbA1c

	Partial correlation irisin	
	r	*P*-value
HbA1c	0.314	0.048

Table 6: Linear regression analysis with preptin as a dependent variable

Study parameters	*β*-coefficient	*P*-value
Irisin	0.840	<0.001
RBS	0.071	0.460

Partial correlation between irisin and HbA1c

In partial correlation between irisin and HbA1c with adjustment for preptin and RBS, the study concluded a significant positive association, as shown in Table 5.

Linear regression analysis

In linear regression analysis with preptin as a dependent variable, only irisin was determined as an independent predictor for the prediction of preptin levels, as shown in Table 6.

Discussion

The present study demonstrated the comparison of irisin and preptin between patients with juvenile diabetes and apparently healthy controls. The results showed that preptin levels slightly decreased in diabetic patients with a non-significant difference in the levels between patients and the control group ($P > 0.05$). However, another study found a significant decrease in preptin levels in diabetic patients,[14] whereas in another study, preptin was significantly increased in patients with T1D.[15] This discrepancy in the results might be related to the difference in ethnicity and sample size between studies. In addition, there was non-significant difference in preptin levels between girls and boys in the patient's group ($P > 0.05$), as shown in Table 2. This result comes in agreement with Wafaa Fathy Mohamed Elsaeed *et al.*[14]

Contrarily, preptin levels slightly decreased when the duration of the disease increased, as shown in Table 3. This result might be due to the fact that in T1D, beta cell mass decreased as the duration of the disease increased,[14] which in turn may result in the declined preptin levels.

Regarding irisin, results demonstrated a slightly higher level in diabetic patients compared with the control group. This result was in agreement with another study done by Faienza *et al.*[16] However, we could not find a significant difference between the studied groups which may be related to a large number of patients (96 T1D) in Faienza study compared with only 50 patients in the present study. In addition, numerous studies suggest that the commercially available enzyme-linked immunosorbent assay kits may have different qualifications for detecting irisin levels.[17] There is still a debate about the increased levels of irisin in patients with T1D in both children and adults. ATP deprivation in skeletal muscles that is increased in T1D patients is considered a stimulus for irisin synthesis and secretion. It was found that there is a hyperactive Ca+ kinetics which increases Ca+ exposure occurring in the muscles of diabetic patients,[18] and thus irisin synthesis increased from skeletal muscles through Ca+-AMPK-PGC-1α or Ca+-calcineurin/CaMKs-CREB, NFAT, MEF2C, MEF2D pathways, as shown in Figure 1.

Regarding gender, there was no difference between boys and girls in levels of irisin in the patient's group ($P > 0.05$), and this is in agreement with other study done by Faienza *et al.*,[16] as shown in Table 2.

The main finding of the current results is the significant correlation between irisin and preptin in the studied groups ($P < 0.001$), as shown in Figure 3. To the best of our knowledge, this is the first study that determines the correlation between irisin and preptin in patients with type 1 diabetes. These results support the study of Zhang *et al.*[19] who found that irisin has the ability to promote the

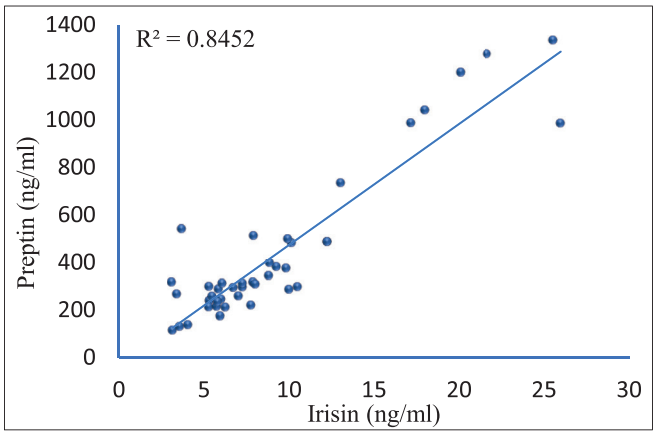

Figure 3: Correlation between preptin and irisin

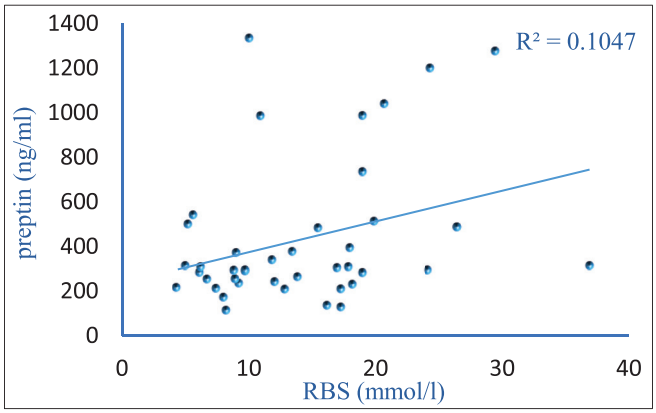

Figure 4: Correlation between preptin and RBS

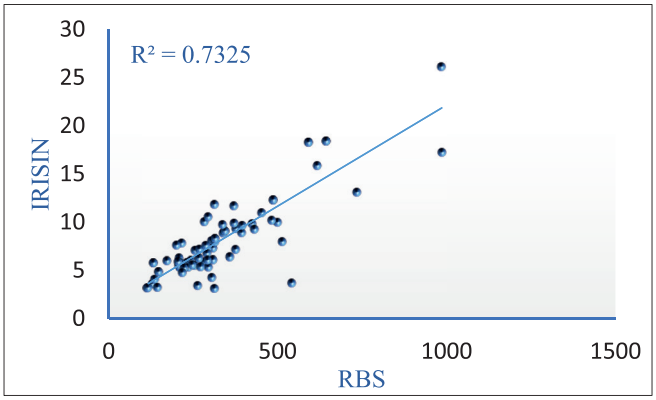

Figure 5: Correlation between irisin and RBS

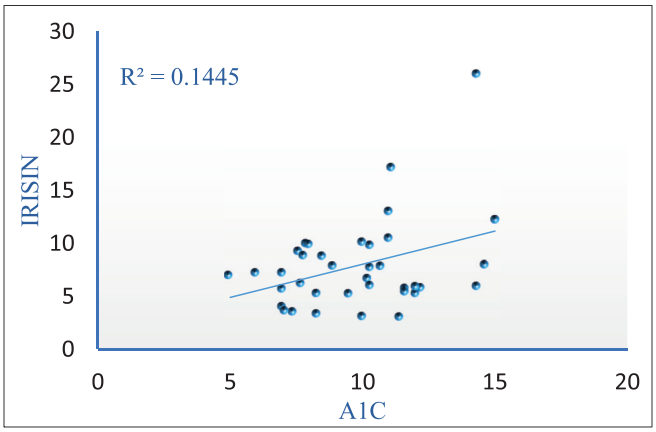

Figure 6: Correlation between irisin and HbA1c

expression and synthesis of betatrophin, another newly discovered hormone in the liver which promotes β-cells regeneration and proliferation through the p38-PGC-1α pathway.[20] Thus, irisin promotes preptin secretion indirectly from pancreatic β-cells.

In contrast, a significant positive correlation was found between preptin and random blood sugar (r = 0.346, P = 0.025), which is similar to the result of Kalayci *et al.*,[21] as shown in Figure 4.

In addition, there was a positive significant correlation between irisin and RBS (r = 0.352, P = 0.022); this finding is similar with Li *et al.*,[22] as shown in Figure 5. One of the important roles of irisin as a metabolic hormone is to increase glucose uptake by skeletal muscle and adipose tissue. Therefore, its secretion might be related to hyperglycemia as a compensatory mechanism.[23] Irisin was also correlated positively with BMI (P > 0.05), and this finding is in agreement with a study done by Li *et al.*[22] There was no correlation between irisin and HbA1c in spearman correlation, however; after adjustment for preptin and RBS in partial correlation, a positive significant correlation observed (P = 0.048, r = 0.314), as shown in Figure 6. This result is similar with studies done by Yücel *et al.*[24] and El Dayem *et al.*[25] Since there is a strong correlation between hyperglycemia associated with poor glycemic control in T1D patients[26] and HbA1c as observed in Jenan study,[27] the positive correlation between irisin and HbA1c is not a surprising result. In addition, the positive correlation between irisin and RBS in the present findings supports this correlation; thus, irisin might be released as a result of increased glucose levels.

Conclusion

Irisin correlated significantly with preptin, and this result supports previous studies that assumed the relationship between irisin and β-cells. Irisin is a strong predictor for preptin levels, and thus residual β-cells. Preptin and irisin are both related to glucose levels in patients with T1DM.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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