

The Relationship between Serum Levels of Irisin and Gestational Diabetes

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Abstract

Background: Hyperglycemia often occurs in pregnant women with a significant increase in the global prevalence of diabetes. This phenomenon provides a large amount of research data for studying the relationship between pregnancy and blood glucose. Irisin is a myokine first identified for its ability to induce the browning of white adipose tissue, to increase energy expenditure, and to protect against insulin resistance and obesity. **Objectives:** The aim is to assess the relationship between serum levels of irisin and gestational diabetes mellitus (GDM). **Materials and Methods:** A case-control study was conducted at the Department of Obstetrics and Gynecology at Al-Imamain Al-Kadhemain Medical City, from the first of January 2020 to the end of October 2020. Pregnant women at the second trimester ($n = 100$) were divided into two groups: women with GDM previously diagnosed as case group ($n = 50$) and healthy pregnant women as control group ($n = 50$). **Results:** Mean serum level of irisin for the case group was 707.5 ± 167.2 ng/mL, and 892 ± 123.8 ng/mL for the control group, with a highly significant decrease in the case group than that in the control group ($P < 0.001$). The validity test of the serum irisin level at cutoff value of 702 shows that sensitivity was 94%, specificity was 90%, negative predicted value was 94%, positive predicted value was 90%, and the accuracy of the test was 92%. **Conclusion:** Serum levels of irisin were significantly lower in patients with GDM.

Keywords: Gestational diabetes, irisin, serum levels, the relationship

INTRODUCTION

In recent years, hyperglycemia often occurs in pregnant women with a significant increase in the global prevalence of diabetes. This phenomenon provides a large amount of research data for studying the relationship between pregnancy and blood glucose. A systematic review shows that pregnant women with hyperglycemia have a higher risk of adverse pregnancy outcomes. Positive and correct treatment of gestational diabetes mellitus (GDM) has a very large effect on reducing adverse birth outcomes.^[1] GDM is easily overlooked, but its complications and adverse effects on mothers and children are very serious. Nearly half of the women who have had GDM will develop type 2 diabetes within 5–10 years.^[2] The definition of GDM is evolving. Until recently, the accepted definition was “any degree of glucose intolerance with onset or first recognition during pregnancy”; hyperglycemia first detected at any time during pregnancy should be classified either as diabetes mellitus in pregnancy or GDM.^[3] The prevalence of GDM worldwide

is unclear and apparently has been steadily increasing with the increase in obesity and type 2 diabetes. It is estimated that GDM affects 1%–4% of all pregnancies each year. The incidence of GDM is more common during 24–28 weeks of gestation. It is closely related to genetic characteristics, living environment and area, screening and diagnostic criteria, and the incidence of type 2 diabetes. GDM affects 1% of pregnant women under age 20 and 13% of pregnant women over 44 years old.^[4] Irisin is a myokine first identified for its ability to induce the browning of white adipose tissue, to increase energy expenditure, and to protect against insulin resistance and obesity.^[5] Irisin is an adipomyokine secreted mainly by skeletal muscles as well as subcutaneous and visceral adipose tissues. Immunohistochemical studies showed that

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smaller amounts of irisin are also produced by testes, liver, pancreas, brain, spleen, heart, and stomach.^[6,7] In normal pregnancy, serum irisin levels are altered. Garces *et al.* found serum irisin levels to be higher in pregnancy. Kuzmicki *et al.* reported a significant decrease in irisin levels 3 months postpartum in both women with GDM and controls with normal glucose tolerance.^[8] These two studies suggest that the placenta and the pregnant state may contribute to an increase in circulating irisin levels. Irisin has been localized via immunohistochemical staining to the cytoplasm of decidual, cytotrophoblast, and syncytiotrophoblast of the placenta.^[9] The placental expression of irisin raises questions as to whether it is secreted into the fetal circulation, where it could have important effects on the growth and development of the fetus. This needs further exploration.^[10] The aim of study is to assess the relationship between serum levels of irisin and GDM.

MATERIALS AND METHODS

This is a case-control study, conducted at the Department of Obstetrics and Gynecology at Al-Imamian Al-Kadhemain Medical City, from January 1, 2020 to October 31, 2020. The council of Iraqi Board of Medical Specializations approved it. The study included 100 pregnant women in the second trimester, and they were divided into two groups: GDM group included 50 pregnant women with GDM previously diagnosed. Control group included 50 healthy pregnant women, with no GDM; they had uneventful antenatal progress with normal glucose tolerance test. Inclusion criteria were singleton viable pregnancy 2, and gestational age = 14–28 weeks; exclusion criteria were women with twin pregnancy and pregnant with other diseases, e.g., hypothyroidism, prepregnancy diabetes mellitus, pregnancy-induced hypertension, preeclampsia, and acute or chronic inflammation. The purpose and procedures were explained to all participants, and they were given the right to participate or not, and verbal consent was taken with reassurance that the information will be kept confidentially. For all included women, full history was taken including maternal age, parity, gestational age, body mass index (BMI), previous history or family history of diabetes, and history of GDM in previous pregnancies. Gestational age was determined by the last menstrual period and confirmed by ultrasonographic examination performed during the first trimester of pregnancy. BMI measured using the following formula: weight (kg)/height (m²). An overnight fasting venous blood sample was obtained from all participants to assess irisin levels and other biochemical parameters. All samples were stored at room temperature for at least 30 minutes to allow the blood to clot, followed by centrifugation (3000rpm) for 15 minutes to separate serum. Serum specimens were aliquoted and stored at –80°C until irisin levels were analyzed. Irisin serum concentrations were determined

with an enzyme-linked immunosorbent assay according to the manufacturer's instructions. Moreover, fasting insulin (FI) was determined with a two-site chemiluminescent enzyme immunometric assay for the automated analyzer. Glycosylated hemoglobin A1c (HbA1c), glucose levels, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and triglycerides (TG) were measured by standard laboratory methods in the hospital. $HOMA-IR = FI (\mu U/L) \times \text{fasting glucose (mg/dL)} / 405$. The normal HOMA-IR value of a healthy human ranges from 0.5 to 1.4. Less than 1.0 means you are insulin-sensitive, which is optimal. Above 1.9 indicates early insulin resistance. Above 2.9 indicates significant insulin resistance. All patients' data were entered using computerized statistical software; Statistical Package for Social Sciences (SPSS) version 23 used in this study. Descriptive statistics presented as mean $\pm$ standard deviation and frequencies as percentages. Multiple contingency tables were conducted, and appropriate statistical tests were performed; chi-square used for categorical variables (Fishers exact test used when expected variable was less than 20% of total) and t-test used to compare between two means. One-way ANOVA was used to compare between more than two means. In all statistical analysis, a level of significance (*P* value) was set at ≤ 0.05 , and the result was presented as tables and/or graphs.

Ethical approval

The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki. It was carried out with patients' verbal and analytical approval before the sample was taken. The study protocol and the subject information and consent form were reviewed and approved by a local ethics committee according to the document number 155 (including the number and the date in 12/12/2019) to get this approval.

Table 1: Demographic characteristics of the included women

Parameters	No.	%
Age group	<20	11
	20–29	44
	30–39	40
	≥ 40	5
Total	100	100.0
Gestational age (weeks)	≤ 20	23
	21–24	20
	25–28	57
Total	100	100.0
BMI	Normal	0
	Overweight	13
	Obese	71
	Morbid	16
Total	100	100.0

RESULTS

As shown in Table 1, 100 pregnant women were enrolled in the current study, and the main age groups were 20–29 years old (44%), with the mean age of 30.97 ± 5.3 years; multigravida was presented in 77%, and primigravida was in 23%; for the parity, it was found that 83% were with 1–3 parity, and 17% with >3.

As shown in Table 2, the mean age of patients was 25.76 ± 5.2 years and 26.01 ± 4.3 years for the control group with no significant differences ($P = 0.7$), the mean of BMI in the GDM group was $29.4 \pm 2.8 \text{ kg/m}^2$, and $28.03 \pm 3.7 \text{ kg/m}^2$ for the healthy group with significant differences ($P = 0.03$), and the mean of gestational age for the GDM group was 22.31 ± 1.2 weeks, and 22.4 ± 1.7 weeks for the healthy group with no significant differences ($P = 0.7$).

Table 3 shows that the mean of Fasting blood sugar (mg/dL) for patients was 124.6 ± 12.8 and 95.3 ± 10.7 for the control group with highly significant differences ($P < 0.001$), FI ($\mu\text{U/L}$) of the GDM group was 104.8 ± 11.3 , and 92.5 ± 12.1 for the healthy group with

highly significant differences ($P < 0.001$), and the mean of HOMA-IR for the GDM group was 3.5 ± 0.2 , and 1.7 ± 0.4 for the healthy group with highly significant differences ($P < 0.001$). HbA1c for the GDM group was $5.7\% \pm 1.1\%$, and $4.9\% \pm 0.6\%$ for the healthy group with highly significant differences ($P < 0.001$).

The mean of LDL (mg/dL) for patients was 70.21 ± 13.51 and 72.21 ± 14.89 for the control group with no significant differences ($P = 0.48$), HDL (mg/dL) of the GDM group was 45.21 ± 10.32 , and 47.13 ± 12.06 for the healthy group with no significant differences ($P = 0.39$), and the mean of TG (mg/dL) for the GDM group was 95.82 ± 14.31 , and 94.22 ± 16.31 for the healthy group with no significant differences ($P = 0.6$). Cholesterol (mg/dL) for the GDM group was 150.01 ± 16.52 , and 153.21 ± 17.34 for the healthy group with no significant differences ($P = 0.34$). All these were given in Table 4.

Table 5 shows that the mean serum level of irisin (ng/mL) for patients was 707.5 ± 167.2 and 892 ± 123.8 for the control group with highly significant decrease in patients than that in the control group ($P < 0.001$).

Table 2: Relation between demographic parameters of the studied groups

Variables (mean $\pm$ SD) + range	GDM (patients), $n = 50$	Control group, $n = 50$	<i>P</i> value
Age (years)	25.76 ± 5.2 (19–41)	26.01 ± 4.3 (17–40)	0.7
BMI (kg/m^2) at sampling	29.4 ± 2.8 (27–33)	28.03 ± 3.7 (27–35)	0.03
Gestational age (weeks)	22.31 ± 1.2 (15–28)	22.4 ± 1.7 (14–26)	0.7
$P \leq 0.05$ (significant)			

Table 3: Differences between glucose profiles of the studied groups

Variables (mean $\pm$ SD) + range	GDM group	Control group	<i>P</i> value
Fasting blood sugar (mg/dL)	124.6 ± 12.8 (110.1–153.5)	95.3 ± 10.7 (72.1–118.0)	<0.001
FI ($\mu\text{U/L}$)	104.8 ± 11.3 (89.4–137.2)	92.5 ± 12.1 (77.8–103.2)	<0.001
HOMA-IR	3.5 ± 0.2 (3.1–3.9)	1.7 ± 0.4 (1.02–1.9)	<0.001
HbA1c (%)	5.7 ± 1.1 (5.1–9.6)	4.9 ± 0.6 (4.3–6.2)	<0.001

Table 4: Differences between lipid profiles of the studied groups

Variables (mean $\pm$ SD) (mg/dL) + range	GDM ($n = 50$)	Control ($n = 50$)	<i>P</i> value
LDL	70.21 ± 13.51 (60–82)	72.21 ± 14.89 (65–97)	0.48
HDL	45.21 ± 10.32 (34–53)	47.13 ± 12.06 (39–59)	0.39
TG	95.82 ± 14.31 (82–99)	94.22 ± 16.31 (85–101)	0.6
Cholesterol	150.01 ± 16.52 (133–179)	153.21 ± 17.34 (141–188)	0.34

Table 5: Differences in serum irisin level between studied groups

Statistics	Irisin (ng/mL)		<i>P</i> value
	GDM	Control group	
Mean	707.5 ± 167.2	892 ± 123.8	<0.001
Range	634–756	778–931	
Median	705.0	900.5	<0.001
IQR	685–749	873–918	

IQR = interquartile range

Table 6: Correlation between irisin and different parameters in the GDM group

Variables	Irisin (ng/mL)	
	GDM	
	r	P value
Age (years)	0.193	0.284
BMI (kg/m ²)	0.352	0.31
FI (μU/L)	0.655	<0.05 [S]
HOMA-IR	0.457	0.003 [S]
HbA1c (%)	0.342	0.01 [S]
Cholesterol (mg/dL)	0.256	0.5
LDL (mg/dL)	0.164	0.407
HDL (mg/dL)	0.119	0.452
TG (mg/dL)	0.038	0.841

HbA1c = hemoglobin A1c, HOMA-IR = homeostasis model assessment of insulin resistance, r = correlation coefficient, [S] = significant

Table 6 shows the relation between irisin in GDM patients and some of the demographic characteristics; it shows no significant correlation between irisin and age, BMI, cholesterol, LDL, HDL, and TG ($P \geq 0.05$) and significant association with correlation between irisin and FI, HOMA–HbA1c in patient with GDM ($P \leq 0.05$).

DISCUSSION

GDM is a metabolic disorder during pregnancy leading to acute and chronic complications in both mother and newborn. Thus, GDM patients have an increased risk of comorbidities during pregnancy, e.g., preeclampsia, pregnancy-induced hypertension, and shoulder dystocia with impeded delivery.^[11] Furthermore, chronic complications might occur after delivery including type 2 diabetes mellitus (T2DM) and cardiovascular disease.^[12,13] Therefore, early diagnosis and appropriate treatment of GDM is helpful in reducing the adverse maternal and fetal outcomes and in protecting mothers and infants from long-term complications.^[14] Irisin has been proposed to be involved in mediating the beneficial effects of exercise on the metabolism, and an increase in levels of irisin induces the browning of subcutaneous adipocytes and thermogenesis.^[15] It was shown that irisin, a myokine potentially induced by acute exercise, thus plays an important role in obesity and metabolic disorders.^[16,17] In the present study, we evaluate the serum irisin level between GDM women and healthy pregnant women and found that maternal serum irisin levels were significantly lower in pregnant women with GDM as compared to controls, which is in agreement with Ural *et al.* study, which revealed that maternal serum irisin levels were significantly lower in pregnant women with GDM as compared to controls.^[18] Our results are also consistent with the findings of Yuksel *et al.*,^[19] who also reported a decrease in circulating irisin in women with GDM; however, in this study, irisin levels were measured

in late pregnancy. In contrast, Ebert *et al.*^[20] found no difference in circulating irisin between pregnant women with and without GDM; this may be due to difference in sample size collection, although 4 years after childbirth, irisin concentrations were significantly higher in patients with previous GDM than in women with normal glucose tolerance. Aydin *et al.*^[21] showed decreased serum irisin in lactating women with prior GDM in comparison with healthy lactating women. Piya *et al.*^[22] show that there was no significant difference between nonobese, obese, and GDM groups, although a negative correlation between BMI and serum irisin was noted. The current study shows highly significant increase in fasting glucose, FI, and HOMA-IR in the GDM group than that in the control group. In agreement with Sancak *et al.*, the study presented that fasting glucose and insulin levels and HOMA-IR are significantly higher in pregnant women with GDM than healthy pregnant women in early pregnancy are, but there was no relationship between HOMA-IR and irisin.^[23] Circulating plasma lipid patterns during normal pregnancy have been widely evaluated, and most researchers have found that serum TG, HDL, LDL, and total cholesterol (TC) levels are clearly raised during the pregnancy.^[24-26] In the current study, the TG were increased in patients with GDM but no significant differences were found between both groups. Consistent with Shen *et al.*'s study,^[27] this indicated that the elevation of lipid concentrations is a physiologic requirement for maintaining stable energy storage for the fetus. It is also similar to that found by Ryckman *et al.*, which revealed that TG levels were significantly elevated in women with GDM compared with those without GDM.^[28] However, it is difficult to ascertain which level of lipid elevation is physiologic or pathologic, and there are no worldwide standard criteria of lipid levels during pregnancy because of the heterogeneity of the population. Wang *et al.* report that lipid profile alters significantly in patients with GDM, and there are no significant differences in TC and LDL concentrations in the first, second, and third trimesters between the GDM group and the control group.^[24] In the present study, we found a significant correlation between maternal serum levels of irisin with fasting glucose, FI, and HOMA-IR. Huh *et al.* showed that irisin correlated with fasting glucose.^[16] Stengel *et al.* demonstrated that circulating plasma irisin is also correlated with FI level.^[29] Other studies revealed that after adjusting for BMI, lipids, and glucose, irisin levels were significantly correlated with fasting glucose, insulin, and HOMA-IR.^[22]

CONCLUSION

Serum levels of irisin were significantly lower in patients with GDM.

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Conflicts of interest

There are no conflicts of interest.

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