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Research Article
Serum Irisin, Level and Validity in Gestational Diabetes Mellitus in Iraqi Women: A Pilot Study

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Abstract

Background and Objective: Gestational diabetes mellitus (GDM) is a common metabolic complication of pregnancy and associated with increase rates of maternal and perinatal problems. Irisin is a novel adipomyokin which plays a role in carbohydrate and fat metabolism, insulin response and inflammatory response. To assess serum level of irisin, cut off level and its correlation with different anthropometric and biochemical parameter in pregnant women with GDM. **Materials and Methods:** case control study conducted at AL-Yarmouk teaching hospital/Al-Mustansiriyah medical college in the period from April, 2017-April, 2018. One hundred pregnant women with comparable age, gestational age and body mass index were enrolled, 50 pregnant women with GDM (study group) and 50 normal pregnant women (control group). Serum irisin level was measured by enzyme-linked immunosorbent assay kit at 24-28 weeks of pregnancy and assessed in correlation with BMI, Hb A1c, fasting insulin and Oral Glucose Tolerance Test (OGTT). **Results:** Serum Irisin level was significantly lower in gestational diabetic women in comparison with healthy pregnant women (1.6 ± 0.4 vs. 2.6 ± 0.7 μg L^{-1}) with p-value <0.001.It was independently low in correlation with BMI, serum insulin and OGTT. The cutoff value of serum Irisin in determining gestational diabetes was 2.145 μg L^{-1} with overall 87.0% accuracy. **Conclusion:** Serum irisin was significantly and independently low in women with GDM. Its cutoff level may be used as biochemical marker in the diagnosis and screening of GDM.

Key words: Gestational diabetes mellitus, serum irisin, pregnant women, biochemical parameter, healthy pregnant women

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Data Availability: All relevant data are within the paper and its supporting information files.

INTRODUCTION

Gestational diabetes mellitus (GDM) refers to diabetes diagnosed in the second or third trimester of pregnancy that is not obviously frank diabetes[1]. Screening and diagnosis of GDM and treating it effectively prevent adverse maternal and perinatal outcome and universal screening is recommended in area with high prevalence[2]. Nguyen *et al.*[3] study revealed that the prevalence of GDM in Eastern and southeastern Asia was high, approximately one in 10 pregnant women and it was greater than results reported in western countries including Europe, US and Australia and recommended the need for international uniformity in screening strategies and diagnostic criteria for GDM[3].

To date, at least 8 associations have developed their own diagnostic criteria for GDM[4,5]. The diagnosis of GDM is generally assured by the 75 or 100 g oral glucose tolerance test (OGTT). In previous study International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria is used for the diagnosis of GDM because recently it becomes more accepted worldwide[6,7].

Screening of GDM commonly involves a one-step approach in which all patients afford the diagnostic OGTTor a two-step approach in which screening is done by determining high risk women or preforming 50 g oral Glucose challenge test (GCT). The presence of one of them indicates performing OGTT[8]; although all proficient panels recommend universal screening using OGTT, this strategy is burdensome on patients and health care institutes and simpler alternative screening test is required.

Many studies tried to find the predictive biomarkers for GDM, the search for such biomarkers was carried out in the biochemical activities including the dynamic of insulin, handling of glucose by the body, beside the oxidation and inflammatory process[9] and several markers have been discovered for metabolic disorders, one of them is the irisin[10].

Irisin is a recently recognized myokine molecule, with increasing evidences about its role in increasing the response of tissues to insulin. However, the current studies cannot clarify the importance of irisin in the metabolic process, but its role in a number of conditions characterized by decreasing response to insulin cannot be ignored[11].

Investigations of circulating irisin in women with GDM had drawn the attention of many researchers. Zhao *et al.*[12] did cross-sectional study and meta-analysis to display that circulating irisin is significantly lower in GDM women[12].

On the other hand many studies had measured irisin in different people but it is still unsettled what normal extent of irisin[13] is and it level in GDM also varies but summed up results indicated a lower level of circulating irisin in subjects with GDM[12].

Erol *et al.*[14] study showed that Irisin may be a helpful biomarker in early pregnancy to predict the development of GDM[14]. Moreover, Wang *et al.*[15] study showed that reduced circulating irisin in first trimester was associated with the increased risk of GDM and might be helpful in identifying women at risk for GDM for early prevention strategies[15].

Ural *et al.*[16] study serum irisin in the second trimester in GDM women and end up in a conclusion that irisin might be introduced as a novel marker for GDM, with decreased levels of irisin being indicative of GDM.

The aims of this study were to evaluate serum irisin in three important aspects, first to assess serum level of irisin, second its cut off level and finally its correlation with different anthropometric and biochemical parameter in pregnant women with GDM hoping that at the end this study may help to possibly justify using serum irisin as a predictive and diagnostic biochemical marker in GDM.

MATERIALS AND METHODS

This case-control study was carried out at Department of Obstetrics and Gynecology, Al-Yarmouk teaching Hospital/ Al-Mustansiriyah medical college, Baghdad, Iraq between April, 2017-April, 2018 after approval of the study by the ethical and scientific Committee of Obstetrics and Gynecology Department and written informed consent was obtained from all participants. Fifty pregnant women with GDM (study group) and 50 normal pregnant women (control group) were enrolled with matched age, BMI and gestational age. The exclusion criteria were maternal age above 40, BMI above 30 and women complaining of hypertension.

Full history and examination was done and body mass index was calculated at the same time according to the equation:

$$\text{BMI} = \frac{\text{Weight (kg)}}{\text{Squared height (m)}}$$

Oral 75 mg OGTT was done after overnight fasting at 24-28 weeks gestation and the diagnosis of GDM was based on the IADPSG criteria which depended on the basis of the following glucose levels: Fasting 100 mg dL^{-1} (5.5 mmol L^{-1}), 1 h 180 mg dL^{-1} (10.0 mmol L^{-1}) and 2 h 140 mg dL^{-1} (7.8 mmol L^{-1}).

Fasting maternal serum irisin was measured 3 days after OGTT using enzyme-linked immunosorbent assay (Human Irisin ELISA kit, Shanghai Yehua Biological Technology Co, China).

Fasting insulin and glycosylated hemoglobin A1C (HbA1c) were also measured meanwhile and the correlation between maternal serum irisin levels and OGTT reading, HbA1c and fasting insulin (FI) were analyzed.

Statistical analysis: The data analyzed using Statistical Package for Social Sciences (SPSS IBM, Chicago) version 24.

The data presented as mean and standard deviation. Student's t-test (two tailed) was used to compare the continuous variables between study groups.

Assessment of type and degree of relationship between serum Irisin with age, BMI, systolic and diastolic blood pressure as well as with laboratory parameters of diabetic patients was done by Pearson's correlation test. The correlation coefficient (r) ranges from -1 to +1, where the positive number indicated positive relationship and the negative relationship was reflected by negative number. The more was the level of positive (r), the more was the power of correlation.

Receiver operator (ROC) curves was used to assess the sensitivity and specificity of serum Irisin in determining diabetic patients. A level of p-value less than 0.05 was significant.

RESULTS

A total of 100 eligible women were included in the study, 50 pregnant women with GDM (study group) vs. 50 normal pregnant women (control group) as shown in Table 1 which clarified the demographic data of both groups. The two groups were matched in term of age, BMI, Systolic and Diastolic blood pressure (SBP, DBP); p-value of less than 0.05 considered significant.

The biochemical parameters including HbA1C, fasting insulin (μIU mL^{-1}) and the three OGTT readings (mg dL^{-1}), were significantly higher among diabetic group except serum Irisin which was significantly lower among them as shown in Table 2.

Serum irisin was independently low in GDM with no significant correlations with maternal age, blood pressure, FI, HbA1c and OGTT readings as shown in Table 3.

Receiver operator (ROC) curves was used to assess the sensitivity and specificity of serum Irisin in determining diabetic patients. The ROC-AUC analysis showed that with cutoff value of 2.145 μg L^{-1}; serum irisin had sensitivity 90.0 and specificity 84.0% in determining diabetic women this was demonstrated in Fig. 1, which also showed that the AUC was 0.93 (95% CI 0.883-0.977).

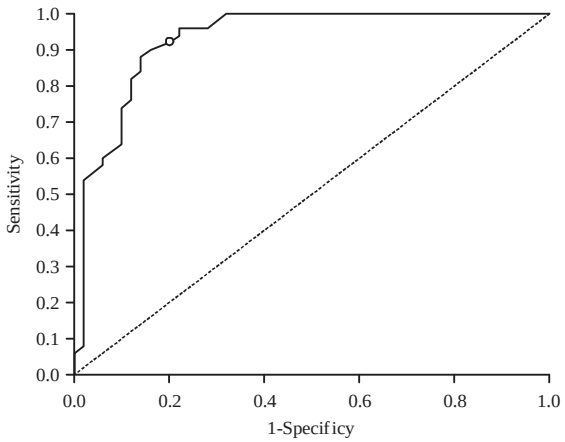

Fig. 1: ROC curve, plotting validity values of serum Irisin in determining diabetic patients (cutoff value2.145 μg L^{-1})

Table 1: Comparison of participants' parameters between the 2 group (study and control group)

	Study groups		
	Total No. = 100		
Variables	GDM Mean±SD	Controls Mean±SD	p-value
Age (years)	28.0±5	27.0±6	0.512
BMI (kg m^{-2})	26.2±3.6	26.0±3.7	0.874
Systolic BP (mm Hg)	106.0±11	106.0±11	0.661
Diastolic BP (mm Hg)	68.0±6	68.0±7	0.878

Table 2: Comparison of laboratory measures between study and control group

	Study groups		
Variables	GDM Mean±SD	Controls Mean±SD	p-value
HbA1C	6.5±0.7	4.6±0.5	<0.001*
Fasting plasma glucose (mg dL^{-1})	98.1±9.2	68.5±7.2	<0.001*
Plasma glucose 1 h post OGTT (mg dL^{-1})	186.5±16	108.5±9.1	<0.001*
Plasma glucose 2 h post OGTT (mg dL^{-1})	145.1±9.1	96.0±8.3	<0.001*
Fasting insulin (μIU mL^{-1})	8.5±0.6	6.2±1.8	<0.001*
Serum Irisin (μg L^{-1})	1.6±0.4	2.6±0.7	<0.001*

SD: Standard deviation, *Significant at 0.05 level by student's t-test

Table 3: Correlation of serum Irisin with other parameters of diabetic patients

	Serum Irisin (μg L^{-1})	
Variables	Pearson correlation	p-value
Age (years)	0.044	0.762
Body mass index (BMI)	-0.128	0.375
Systolic BP	-0.123	0.393
Diastolic BP	0.140	0.334
HbA1C	0.040	0.785
Fasting plasma glucose (mg dL^{-1})	0.117	0.419
Plasma glucose 1 h post OGTT (mg dL^{-1})	0.244	0.088
Plasma glucose 2 h post OGTT (mg dL^{-1})	0.216	0.132
Fasting insulin (μIU mL^{-1})	0.052	0.722

DISCUSSION

The GDM is a metabolic disease characterized by insulin resistance and as such, changes in irisin levels may happen. There is still contradictory regarding the exact changes that occur to irisin in GDM[17].

In the current study it was found that serum irisin was significantly and independently low in women with GDM with cutoff value of 2.145 μg L^{-1}.

Zhao *et al.*[12] published meta-analysis that includes 5 studies with 632 participants and end up in a conclusion that serum irisin was low in women with GDM and that was also recognized in our study.

The ROC-AUC analysis shows that with cutoff value of 2.145 μg L^{-1}; serum irisin has sensitivity 90.0 and specificity 84.0% in determining diabetic women and the AUC was 0.93 (95% CI 0.883-0.977). With such high predictive value, this study can be used as a base for further studies since there is no clear cutoff level seen in other literature. However, it should be alert to some limitations in this point; it had measured irisin level at 24-28 weeks of gestation and whether this cutoff level will be the same throughout the pregnancy or it will be changed, cannot be answered from this study, second limitation is the correlation with the duration of gestational diabetes and the adherence to treatment, where these two factors are obviously affect insulin sensitivity and may affect the results of the irisin levels in GDM women.

Many factors including age, BMI, blood pressure, fasting plasma glucose, fasting insulin, OGTT and Hb A1c had been studied and showed different correlation with blood irisin levels.

The current study showed that serum irisin decrease independently in GDM and irrespective to age, BMI, blood pressure, FI, Hb A1c and OGTT readings. This result was in agreements with Ural *et al.*[16].

Ebert *et al.*[18] in his study found that serum irisin decrease significantly in GDM and that FI was independently and positively associated with serum irisin in multivariate analysis.

When analyzing the correlation between body max index (BMI) and irisin levels, differences were also found. Some researchers observed a significant direct correlation between serum irisin and BMI, proposed that increased irisin level may be an adaptive response to compensate for metabolic disturbances associated with obesity[19,20], while other reported null[16] or even a negative correlation[21].

Huh *et al.*[22] study revealed that serum irisin were also positively correlated with BMI and with fasting glucose. On the contrary, Timmons *et al.*[23] found that serum irisin level was not correlated to BMI, FI and fasting glucose.

On the contrary to current results, Choi *et al.*[24] had found an inverse association between the HbA1c and plasma irisin. Stengel *et al.*[19] reported that irisin was positively related with BMI and FI. But not all studies confirm these findings[21].

CONCLUSION

Serum irisin was significantly and independently low in women with GDM. Its cutoff level of 2.145 μg L^{-1} in Iraqi women may be used as novel predictor biochemical marker in the diagnosis and screening of GDM.

SIGNIFICANCE STATEMENT

The study revealed that, being significantly and irrespectively low in GDM with clear and high predictive cutoff value on one hand and being easy one step test to be performed on another hand made serum irisin a possible promising new biochemical marker and a new theory on using it as novel biochemical marker in the diagnosis and screening of GDM may be arrived. Large sample size and heterogeneous groups of patients needed to be included in future study to strength that theory.

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