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Original Research Article

Association of serum irisin with gestational diabetes mellitus

Abeda Sultana[1]*, M. Akhtanur Rahman Joarder[2], Khadiza Begum[3], Nafisa Shamsunnahar[1], Sharmin Ferdous[1], Tabassum Parveen[1]

[1]Department of Fetomaternal Medicine, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh
[2]Department of Cardiovascular Surgery, Square Hospital Ltd., Dhaka, Bangladesh
[3]Department of Obstetrics and Gynecology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh

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***Correspondence:**
Dr. Abeda Sultana,
E-mail: dr.abeda79@gmail.com

ABSTRACT

Background: Gestational diabetes mellitus (GDM) is a condition characterized by glucose intolerance with onset during pregnancy, increasing risks to both mother and child. Recent studies have focused on irisin, a hormone linked to energy metabolism and insulin sensitivity, to understand its role in GDM. This study aimed to explore the relationship between serum irisin levels and the incidence of GDM.
Methods: This prospective diagnostic accuracy study was conducted at the outpatient Department of Fetomaternal Medicine and the Department of Obstetrics and Gynecology at BSMMU in Dhaka from July 2021 to June 2022. According to the inclusion criteria, 65 pregnant women who were non-GDM at 11-14 weeks were selected purposively. Serum irisin levels were measured in these non-diabetic participants using an enzyme-linked immunosorbent assay (ELISA) kit. The participants were divided into two groups: those with reduced irisin levels and those with normal irisin levels. Data were then analyzed using statistical package for the social sciences (SPSS) version 23.0 software.
Results: Among the low irisin group, 36.4% were diagnosed with GDM, while 63.6% remained euglycemic. In the high irisin group, 97.7% remained euglycemic, and 2.3% developed GDM. Overall, 14% of respondents were with GDM across both groups. The ROC analysis for detecting GDM based on irisin levels showed statistically significant results with an AUC of 0.834. A cut-off value of ≤0.287 had 88.9% sensitivity and 75% specificity, leading to 76.9% accuracy. The PPV was 36.4%, and the NPV was 97.7%. The mean serum irisin level was significantly lower in mothers with GDM compared to non-GDM mothers (p=0.001).
Conclusions: The maternal serum irisin level is found to be lower in pregnant women with GDM compared to those without GDM. Therefore, in pregnancy, maternal serum irisin levels may be useful as a biomarker for detection of GDM.

Keywords: Gestational diabetes mellitus, Insulin-like growth factor, Irisin, Pregnancy

INTRODUCTION

Gestational diabetes mellitus (GDM) is a common metabolic disorder during pregnancy, defined as glucose intolerance diagnosed during pregnancy that was not pre-existing diabetes.[1] Most guidelines recommend screening for GDM at 24 to 28 weeks of gestation, while FIGO suggests universal screening during the booking visit. According to the World Health Organization (WHO) (2015), GDM is diagnosed when fasting blood sugar levels are 5.1-6.9 mmol/l, or when 2-hour plasma glucose levels are 8.5-11.0 mmol/l following a 75-gm oral glucose load.[2] In a normal pregnancy, weight gain and progressive decrease in insulin sensitivity occur, paralleling the growth of the fetoplacental unit.[3] This change is due to increased levels of hormones such as human chorionic somatotrophin, cortisol, prolactin, progesterone, and estrogen. The β cells in the pancreas typically undergo

hypertrophy and hyperplasia to release more insulin in response to increased insulin resistance.[4] GDM occurs when there is delayed or insufficient insulin secretion despite increasing peripheral resistance.[5] Irisin is a novel myokine composed of 112 amino acid residues, with a molecular weight of 12,587 kDa, and is secreted from skeletal muscle.[6] Recent studies have shown that circulating irisin levels are significantly lower in pregnant women with GDM compared to those without the condition.[7] Known as an antidiabetic hormone, Irisin is believed to enhance insulin sensitization, though its exact mechanism remains unclear.[8] A probable mechanism is that physical activity leads to the activation of the peroxisome proliferator-activated receptor-gamma co-activator-1α (PGC-1α) gene in human skeletal muscle.[9] PGC-1α acts as a co-transcriptional regulator, facilitating the action of multiple transcription factors to regulate a complex network of genes.[10] Activation of PGC-1α increases the level of fibronectin type III domain-containing protein 5 (FNDC5), a membrane protein in muscle tissue.[11] During physical activity, FNDC5 is cleaved and released into the bloodstream as irisin.[12] Irisin plays a critical role in signalling white adipose tissue to increase the expression of uncoupling protein 1 (UCP1) in the mitochondrial inner membrane through an unknown mechanism.[13] This process converts white adipose tissue to brown adipose tissue, resulting in increased total energy expenditure rather than ATP production. This energy expenditure leads to weight loss, improved glucose tolerance, and enhanced insulin sensitization.[14]

METHODS

This prospective diagnostic accuracy study was conducted at the outpatient Department of Fetomaternal Medicine and the Department of Obstetrics and Gynecology at BSMMU, Dhaka, for one year from July 2021 to June 2022. The study included 65 pregnant women aged 18 to 40 years in their 11-14 weeks of gestation with normal oral glucose tolerance test (OGTT), utilizing purposive sampling based on availability and inclusion criteria.

Data were collected through semi-structured questionnaires, and serum irisin levels of patients were assessed at 11-14 weeks to explore its association with the development of GDM. Blood samples were taken under aseptic conditions, and processed for serum separation, and irisin levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit. The participants were divided into two groups: those with reduced irisin levels and those with normal irisin levels.

The study employed descriptive and inferential statistical analyses using the statistical package for the social sciences (SPSS) version 23.0 program, employing Chi-square and unpaired t-tests to assess significance, with a p value threshold of <0.05 for statistical significance. Participants were informed about the study procedures, and consent was obtained before data collection.

RESULTS

In our study, most participants were aged 18 to 25 years (46.2%) and had completed higher secondary education or more (73.8%). A significant portion of the participants were housewives (72.3%). The mean BMI of the participants was 20.00±2.89 kg/m², with most falling within the normal BMI range. Fasting blood sugar (FBS) at 24-28 weeks of gestation averaged 4.62±0.67 mmol/l, while blood sugar levels measured 2 hours after a 75 g glucose load at the same gestational age averaged 6.93±1.32 mmol/l. The mean serum Irisin level among participants was 0.463±0.358 µg/ml. In our study, 14% of participants developed GDM. While there wasn't a statistically significant relation between parity and GDM status (p>0.05), there was a significant difference in serum irisin levels between those who developed GDM and those who did not (p<0.05). The mean serum Irisin level was significantly lower in pregnant women who developed GDM (0.217±0.143 µg/ml) compared to those who remained non-GDM (0.502±0.367 µg/ml). In my study, fasting blood sugar (FBS) and blood sugar levels 2 hours after a 75 g glucose load were significantly higher in women diagnosed with GDM during the second trimester (p<0.001). There was also a significant difference in BMI between women with GDM (26.05±3.27 kg/m²) and those without GDM (23.56±2.70 kg/m²). ROC analysis of serum irisin levels yielded an AUC of 0.834 (95% CI: 0.676-0.993), indicating its utility in predicting GDM, which was statistically significant (p<0.05). The study determined that a serum irisin cutoff value of ≤0.2875 µg/ml provided the highest Youden index (0.639), with sensitivity at 88.9% and specificity at 75%. The overall accuracy was 76.9%. At this cutoff, the positive predictive value (PPV) was 36.4%, and the negative predictive value (NPV) was 97.7%. According to cross-tabulation, 8 out of 9 GDM cases had serum irisin levels below this cutoff, suggesting that the threshold is effective in identifying GDM with about 77% accuracy.

Table 1: Body weight/BMI distribution (n=65).

Body weight/BMI	N	%
Underweight	1	1.5
Normal	44	67.7
Overweight	17	26.2
Obese	3	4.6
Mean±SD BMI (kg/m²)	20.00±2.89	

Table 2: Distribution of laboratory parameter (n=65).

Characteristics	Mean±SD
Serum irisin (µg/ml) at 11-14 weeks of gestation	0.463±0.358
FBS (at 24-28 weeks of gestation)	4.62±0.67
Blood sugar 2 hours after 75 gm glucose (at 24-28 weeks of gestation)	6.93±1.32

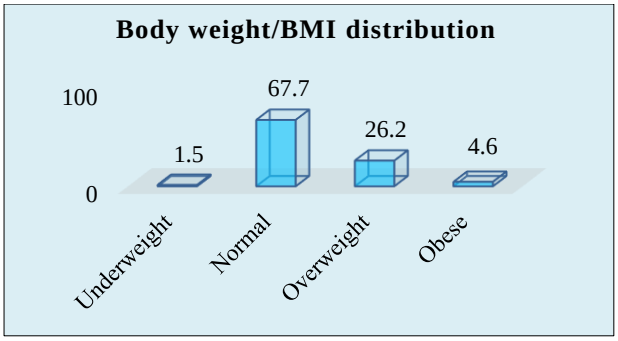

Figure 1: Column chart showed body weight/BMI among participants (n=65).

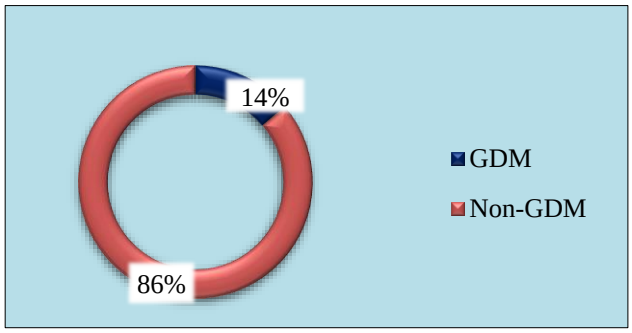

Figure 2: Pie chart showed frequency of GDM among participants (n=65).

Table 3: Gravidity status of GDM and non-GDM samples (n=65).

Parity	GDM	Non-GDM	P value
Primi	6 (66.7)	44 (78.6)	>0.05
Multi	3 (33.3)	12 (21.4)	

Table 4: Comparison of serum irisin among GDM and non-GDM samples (n=65).

GDM	N	Serum irisin (µg/ml)		P value
		Mean	SD	
GDM	9	0.217	0.143	0.001
Normal	56	0.502	0.367	

Table 5: Comparison of BMI, FBS, and blood sugar 2 hours after 75 gm glucose among GDM-developed and non-GDM sample (n=65).

Parameters	GDM	Non-GDM	P value
BMI	26.05± 3.27	23.56±2.70	0.015
FBS (at 24-28 weeks of gestation)	5.79± 0.50	4.43±0.47	<0.001
Blood sugar 2 hours after 75 gm glucose (at 24-28 weeks of gestation)	9.73± 0.61	6.48±0.69	<0.001

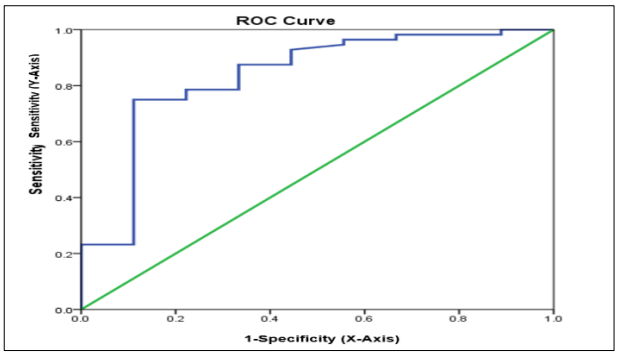

Figure 3: ROC curve of irisin for prediction of GDM.

Table 6: Area under the curve (n=65).

Area	Std. error	P value	95% confidence interval	
			Lower bound	Upper bound
0.834	0.081	0.001	0.676	0.993

Table 7: Determination of cut-off value with Youden index (n=65).

Cut-off value	Sensitivity	Specificity	PPV	NPV	Accuracy	Youden index (j=sen+spe-1)
0.2815	0.778	0.75	0.333	0.955	0.754	0.528
0.2875	0.889	0.75	0.364	0.977	0.769	0.639
0.293	0.889	0.714	0.333	0.976	0.738	0.603

Table 8: Cross-tabulation of GDM development with serum irisin value based on the derived cut-off value (n=65).

Parameters	GDM development		Total
	Yes	No	
≤0.2875 (µg/ml)	8	14	22 (TP+FP)
>0.2875 (µg/ml)	1	42	43 (FN+TN)
Total	9 (TP+FN)	56 (FP+TN)	65 (TP+FP+FN+TN)

Table 9: Sensitivity, specificity, PPV, NPV, and accuracy gained by the derived cutoff of serum irisin with 95% confidence interval (n=65).

Statistic	Value (%)	95% CI (%)
Sensitivity	88.89	51.75 to 99.72
Specificity	75.00	61.63 to 85.61
PPV	36.36	25.57 to 48.74
NPV	97.67	86.80 to 99.63
Accuracy	76.92	64.81 to 86.47

DISCUSSION

GDM can lead to several adverse health consequences for both the mother and fetus. Insulin resistance plays a critical role in the pathophysiology of both type 2 DM and GDM, where insulin mediates its effects via the phosphorylation of the insulin receptor. In pregnant women with GDM, irisin levels are significantly lower, which is associated with increased insulin resistance.[7] Our study divided participants into two groups based on serum Irisin levels during the first trimester: those with high irisin levels (>0.2875 µg/ml) and those with low Irisin levels (≤0.2875 µg/ml). In the low irisin group, 8 out of 22 respondents developed GDM, while 14 remained euglycemic. In the high irisin group, only 1 out of 43 respondents developed GDM, with the remaining 42 staying euglycemic. Overall, 9 participants (14%) developed GDM, which aligns with the prevalence range reported by Jesmin et al and is slightly lower than the 25% prevalence reported by the IDF for the Southeast Asia region.[15] In our study there is significant role of maternal BMI as a risk factor for developing GDM. We observed that participants who developed GDM had a mean BMI of 26.05±3.27 kg/m^2, compared to 23.56±2.70 kg/m^2 in the non-GDM group. This aligns with findings from Yue et al, who reported a mean pre-pregnancy BMI of 22.1±1.8 kg/m^2 in the non-GDM group and 24.1±3.8 kg/m^2 in the GDM group.[16] Similar results were observed in studies by Zhu et al highlighting the association between higher BMI, increased insulin resistance in GDM.[17] In our study, we found that among the participants, 15 were multigravid and 50 were primigravid. Of these, 6 primigravid mothers (66.7%) and 3 multigravid mothers (33.3%) developed GDM. However, the relationship between parity and GDM status wasn't statistically significant (p>0.05). This differs from the findings of Heija et al, who reported a steady increase in GDM incidence with higher parity, ranging from 3.5% in nulliparous women to 14.6% in those with parity ≥4.[18] In our study, the ROC analysis of serum irisin levels for detecting GDM showed an AUC of 0.834 (95% CI: 0.676–0.993), which was statistically significant (p<0.05). A cutoff value of ≤0.2875 showed the highest Youden index (0.639), with 88.9% sensitivity and 75% specificity, and an accuracy of 76.9%. Additionally, the PPV was 36.4%, and the NPV was 97.7%. The mean serum irisin level in mothers with GDM (0.217±0.143 µg/ml) was significantly lower than in non-GDM mothers (0.502±0.367 µg/ml). The reference range for irisin in the first trimester of pregnancy is 0.257–0.811 µg/ml, as noted by Khorasani et al.[19] In comparison to our findings, Ural et al reported serum irisin levels as significantly lower in their GDM group (1.04±0.3 µg/ml) compared to the non-GDM group (1.3±0.2 µg/ml).[20] The variations in mean serum irisin levels between our study and theirs might be attributed to factors like different ethnicities, laboratory setups, or ELISA kits used for measurement. Piya et al also noted an inverse correlation between BMI and serum irisin levels.[21] In our study, it was observed that low irisin levels are associated with the development of GDM. These findings suggest that serum irisin could serve as a biomarker to predict the risk of development of GDM. However, to fully understand this association, further large-scale prospective studies are necessary. These future studies should aim to include diverse groups of subjects and explore the relationship between first-trimester serum irisin levels and other potential biomarkers for detecting GDM.

Limitations

The respondents were limited to pregnant women from a single hospital in Dhaka, which may not accurately reflect the broader population of the country. To ensure that the sample represents the population, a larger, more extensive study across a wider area would be necessary, but this was not feasible within the limited timeframe. As a result, the study outcome cannot represent the entire population. Conducted over a short period, a prospective follow-up study is needed to assess the effect of irisin levels on the development of GDM. Furthermore, the serum irisin levels of all samples were measured in a single setting.

CONCLUSION

This study suggests that lower maternal serum irisin levels are observed in pregnant women with GDM compared to those without. These findings imply that irisin could serve as a potential biomarker for early detection and management of GDM. Utilizing irisin levels as a biomarker might enhance diagnostic accuracy and enable timely interventions, thus improving maternal and fetal outcomes. Further research is warranted to validate these findings and explore the clinical applications of irisin in managing gestational diabetes.

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