



## ORIGINAL ARTICLE

# ASSOCIATION OF SERUM IRISIN WITH GESTATIONAL DIABETES MELLITUS

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**Background:** Gestational diabetes mellitus (GDM) is a condition in which there is intolerance to glucose with first recognition in pregnancy with an elevated risk of perinatal morbidity. Irisin has a role in the metabolism of glucose and lipids which may prove to be an early diagnostic marker for future GDM development. The aim of this study was to compare the levels of irisin in pregnant women having GDM and healthy controls, for any correlation between glycaemic factors and irisin. **Methods:** This case-control study was performed at the Gynaecological OPD, National Medical Centre, Karachi between January and June 2023. Eighty-eight pregnant women were recruited in the study. Serum-irisin levels of both the case and control groups were estimated with ELISA kit collected at 24<sup>th</sup> to 28<sup>th</sup> weeks of gestation. The correlations were evaluated using statistical tests such as *t*-test and Pearson's correlation coefficient. **Results:** There were significant differences in fasting blood glucose and postprandial glucose levels between control and GDM groups. The average serum irisin level in control group was substantially greater than the GDM group. There was a significant inverse linear association between serum irisin levels and fasting and postprandial glucose levels. Fasting insulin and HOMA-IR levels were negatively correlated with serum irisin. **Conclusion:** Lower serum irisin levels may be connected to the development of GDM. This study confirms the potential of serum irisin as an early diagnostic marker and clarifies its function in the pathophysiology of GDM.

**Keywords:** GDM, Gestational diabetes mellitus, Glucose, Insulin, Irisin, Metabolic, Metabolism

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## INTRODUCTION

Gestational diabetes mellitus or (GDM) is defined by the American Diabetic Association as any degree of intolerance to glucose along with its onset or recognition, primarily during pregnancy.<sup>1</sup> The prevalence of GDM ranges from 1% to 14% among all pregnancies, based on the population that is under study as well as the diagnostic test applied.<sup>2</sup> One of the leading causes of maternal and foetal morbidity as well as mortality is GDM along with its complications worldwide.<sup>3</sup> GDM has a multi-factorial pathogenesis and may include genetic and environmental factors. Gestational diabetes mellitus stands to be a predictor for future development of type-2 Diabetes Mellitus (T2DM).<sup>4</sup>

Gestation in humans is evidently characterized by features like weight gain along with a progressive decline in the sensitivity for insulin, which in turn coincides with foeto-placental-unit growth and insulin resistance in pregnant women during later months of gestation.<sup>5</sup> The low insulin-sensitivity is mainly due to a post-receptor defect which results in poor insulin capability in order to cause mobilization of GLUT4 from the cell interior to the surface of the cell.<sup>6</sup> Resistance to insulin hormone in pregnancy could be a potential cause of a number of pathogenic effects such as development of GDM, compromised utero-placental circulation, Pregnancy Induced-Hypertension (PIH) and intrauterine growth retardation (IUGR) etc.<sup>7</sup>

Irisin, a 22 kD protein, is a newly discovered hormone which has lately been characterized as a product formed due to cleavage of the cell membrane protein (transmembrane) fibronectin type-III domain containing protein-5 (FNDC5).<sup>8</sup> In the year 2012, a study demonstrated the role of physical exercise in the increased expression on skeletal muscles of various genes which are involved in the expenditure of energy, particularly the metabolism of glucose and lipids; one of the prominent genes discussed was FNDC5 gene, which is located on the locus 1p35.1, expressed due to consequential activation of PGC-1 $\alpha$  (transcription co-activator of PPAR- $\gamma$ ); also, the FNDC5 protein (32 kD) is further cleaved and released as irisin in the circulation.<sup>9</sup> A number of studies suggest that the heart as well the skeleton release irisin molecules in response to exercise which in turn act as tissue messengers, including skeletal tissue, heart, liver, and the brain.<sup>10</sup> Expression of FNDC5 gene by PGC1- $\alpha$  mediates a variety of biological actions which are related to metabolism and energy and modulates the expression of a protein known as uncoupling protein-1 (UCP1) along with its role in thermogenesis in brown fat. PGC1- $\alpha$  is also a source of resistance to dystrophy of skeletal muscles, age related obesity, diabetes and longevity as shown by increased expression in transgenic mice; it in turn suggests the stimulation of the secretion of certain skeletal muscle factors which are responsible for affecting other tissue functions.<sup>11</sup>

Multiple studies suggest that irisin plays a significant role in diseases of metabolism such as obesity, coronary artery diseases, lipid metabolism, T2DM, non-alcoholic fatty liver disease, and polycystic ovary syndrome etc.<sup>12</sup> Therefore, in the context of a common metabolic disease of pregnancy, it may play a role in becoming an early diagnostic marker or a strong predictor of gestational diabetes mellitus. Wang *et al*<sup>13</sup> associated the lower circulating irisin levels in the first trimester with the higher risk of GDM, suggested that it might be help in early identification of women at risk for the future development of GDM, which ultimately could be an early prevention strategy.<sup>13</sup>

This study has compared concentrations of serum irisin in the sera of pregnant women with and without gestational diabetes mellitus to check if irisin could prove to be an early diagnostic tool for GDM.

## METHODOLOGY

The protocol was approved by the ethical research committee of Bahria University of Health Sciences Karachi. It was a case control study conducted in Gynaecology OPD, National Medical Centre, Karachi, for a period of 6 months (Jan–Jun 2023). Pregnant women (age 20–40 years) diagnosed with GDM as per WHO diagnostic criteria between 24–28 weeks of gestation were included as cases and without GDM were selected as controls. Females with known diabetes mellitus, multiple pregnancies, glucose intolerance and comorbidities were excluded. The sample size was calculated considering a maximum acceptable error of 5% power of 80% equal to 1.0 ratio between the two groups using Epi Info Version 3.01. The calculated sample size came out to be 44 patients in each of the Case group and Control group, whereas the sampling technique was non-probability convenient sampling.

Pregnant women visiting the OPD of National Medical Center Karachi, underwent oral-glucose tolerance test (OGTT, 75 g 2 h) in routine, out of which, 44 patients diagnosed with GDM and 44 healthy women with normal glucose tolerance (NGT), matched for age and week of gestation, were recruited for this study. Diagnosis of GDM was made if the plasma levels of glucose increased during a 75 g, 2 h OGTT as per the diagnostic criteria of WHO. Written informed consent was obtained from all participants before enrolment and subject evaluation forms were filled via interviews and physical assessment. Overnight fasting venous blood samples were obtained from all participants to analyse serum irisin and insulin levels in the second trimester (24<sup>th</sup>–28<sup>th</sup> weeks of gestation). All samples were stored at room temperature for at least 30 min to allow the blood to clot, followed by centrifugation at 2,500 rpm, for 15 min, at 4 °C in order to separate serum. Serum specimens were aliquoted and stored at -80 °C until the analysis. Insulin levels were determined using a

chemiluminescent assay (AccessDxI800; Beckman Coulter, Inc., Fullerton, CA). Homeostatic model assessment of insulin resistance (HOMA-IR) was calculated using fasting glucose (mmol/L)×fasting insulin (IU/mL)/22.5. Serum irisin and insulin levels were quantified using commercially available ELISA kits. The sensitivity of the assay was 23 ng/mL, and inter- and intra-assay coefficients of variation both were ≤10%. All samples were analysed in duplicate. Results were expressed as ng/mL.

Data were analysed using SPSS-20. Independent samples *t*-test was used to compare serum irisin levels and other factors among GDM and control groups. The Pearson's correlation coefficients were calculated to explore the direction and strength of linear relationship between the irisin levels and other factors and  $p \leq 0.05$  was considered statistically significant. The multiple linear regression model was used for building a model for irisin levels on the basis of several other factors.

## RESULTS

The ages of the subjects were 20–40 years in both groups. The mean age in the GDM group (30.36±5.13 Years) was slightly higher than that in control group (28.10±4.87 Years). Minimum and maximum number of pregnancies ranged from 1 to 5 in the control group and 1 to 4 in the GDM group. Majority (59, 74.4%) of previous deliveries were performed via LSCS, while 17 (21.3%) had spontaneous vaginal delivery (SVD) and 3 (4.3%) had SVD with assistance of a vacuum extractor (SVD TAP). Only a small number (9, 11.5%) had a history of GDM in the previous pregnancies. The BMI ranged from 22.21 to 39.41 in control group, while in GDM group, it ranged from 19.81 to 42.46. The BMI appeared to be less scattered in the control group compared to GDM group. The average BMI was higher in the GDM group (29.67±5.00) compared to the control group (27.98±4.22).

There were significant differences between control and GDM groups in fasting blood glucose and glucose levels at 1 and 2 hours postprandial. The average glucose levels were consistently and significantly higher in the GDM group. In comparison to the control group, the mean values of serum insulin and HOMA-IR were greater in the GDM group. It was discovered that the control group's average serum irisin level was substantially greater than the GDM group (Table-1). There was an inverse link between irisin levels and fasting blood glucose in this study, proving a significant inverse linear association between serum irisin levels and fasting blood sugar, postprandial glucose after 1 and 2 hours. The fasting insulin and HOMA-IR levels were found to be negatively correlated with serum irisin, with a non-significant inverse link between them (Table-2).

**Table-1: Comparison of factors between control and GDM group using independent samples *t*-test**

| Factors                  | Control      | GDM          | <i>p</i> |
|--------------------------|--------------|--------------|----------|
| Age                      | 28.10±4.87   | 30.36±5.13   | 0.042    |
| BMI                      | 27.98±4.22   | 29.67±5.00   | 0.491    |
| Pulse                    | 102.90±15.73 | 104.55±14.31 | 0.000    |
| Blood Pressure Diastolic | 82.75±7.84   | 80.91±7.09   | 0.000    |
| Blood Pressure Systolic  | 126.65±11.30 | 124.77±13.38 | 0.000    |
| Fasting Blood Glucose    | 78.23±7.92   | 97.23±12.53  | 0.000    |
| Glucose (1 Hr)           | 123.70±21.02 | 178.64±21.34 | 0.000    |
| Glucose (2 Hr)           | 102.15±19.29 | 152.93±23.12 | 0.000    |
| Serum Irisin             | 13.53±6.40   | 8.80±7.39    | 0.002    |
| Fasting Insulin Level    | 1.08±0.53    | 1.63±0.72    | 0.002    |
| HOMA-IR                  | 6.53±6.10    | 15.02±11.53  | 0.000    |

**Table-2: Correlation of serum irisin with other factors using Pearson's correlation coefficient and multiple regression coefficient**

| Factors               | Correlation Coefficient | <i>p</i> | Multiple Regression Coefficient | <i>p</i> |
|-----------------------|-------------------------|----------|---------------------------------|----------|
| BMI                   | -0.130                  | 0.237    | -0.170                          | 0.309    |
| Fasting Blood Glucose | -0.349                  | 0.001    | -0.024                          | 0.793    |
| Glucose (1 Hr)        | -0.323                  | 0.003    | -0.030                          | 0.300    |
| Glucose (2 Hr)        | -0.269                  | 0.013    | -0.016                          | 0.578    |
| Fasting Insulin Level | -0.046                  | 0.675    | 0.200                           | 0.108    |
| HOMA-IR               | -0.120                  | 0.277    | -0.834                          | 0.134    |

## DISCUSSION

The findings of this study reinforce the significance of early identification and prevention for GDM owing to the potential hazards it presents to both the mother and foetus. The mean age of participants in the GDM group was noticeably greater than that of participants in the control group, indicating that being older may be linked to a higher chance of developing GDM. This result is consistent with a cross-sectional study in Peshawar, that found a greater prevalence of GDM in older mothers.<sup>14</sup> BMI was not found to differ significantly between the two groups in the present study. However, the mean value was higher among the cases as compared to the control group, consistent with another study.<sup>15</sup> It has also been reported that obesity is linked to an increase in the number of Type-2-Diabetes Mellitus and GDM which are related to excess body weight.<sup>16</sup> In comparison to the control group, the GDM group had reduced mean values for both diastolic and systolic blood pressure. These results go against earlier research that claimed GDM was linked to higher blood pressure.<sup>17</sup>

The present study also found significant differences between control and GDM groups, which were seen in fasting blood glucose and postprandial glucose levels at 1 hour and 2 hours. These average glucose levels were consistently higher in the GDM group. These results are in concordance with a study that showed that glycaemic variability in pregnant women with GDM was higher than in normal gravid women. The detected variations lend credence to the reduced insulin sensitivity and poor glucose control linked to GDM.<sup>18</sup>

In comparison to the control group, the mean values of serum insulin and HOMA-IR were greater in the GDM group, these results support another study.<sup>19</sup>

It was discovered that the control group's average serum irisin level was substantially greater than the GDM group, similar to findings of another study<sup>4</sup> that revealed maternal serum irisin levels significantly lower in patients with GDM compared to the levels in healthy pregnant controls. It may be a possibility that GDM may affect the expression of PGC-1 $\alpha$  or functions in muscles, which supports the existence of irisin as a possible marker for the early identification and prognosis of GDM.<sup>20</sup> However, contrasting results proving no significant difference between GDM and control group in terms of serum irisin level, fasting blood glucose, oral glucose tolerance test, insulin, insulin resistance index as well as BMI were reported by another study.<sup>21</sup> Recently, various studies have suggested that circulating irisin levels in plasma may be related to obesity or increased BMI.<sup>22</sup>

There is an inverse link between the irisin levels and fasting blood glucose in this study, proving a significant inverse linear association between the serum irisin levels and fasting blood sugar, postprandial glucose in 1 and 2 hours. These results suggest that fasting and postprandial blood glucose levels tend to rise when serum irisin levels drop. These results are in accordance with a study in China which revealed that fasting insulin, HbA1c along with the albumin/globulin ratio were negatively associated with serum irisin level with statistical significance.<sup>17</sup> Some reported a negative association between irisin and postprandial glucose in patients with type 2 diabetes.<sup>23</sup>

The fasting insulin levels and HOMA-IR levels were found to be negatively correlated with serum irisin, with a non-significant inverse link between them in the present study. Another study also found the serum irisin levels negatively correlated with fasting insulin, HOMA-IR and the metabolic parameters including Waist Circumference, Waist Hip Ratio, and serum creatinine.<sup>24</sup> The negative association between irisin and HOMA-IR could be because of the secondary results of impaired PGC-1 $\alpha$  function.<sup>25</sup>

These results have significant implications for identification and management of GDM. The sharp fall in irisin levels seen in the GDM group suggests that it may be useful as a diagnostic tool to identify women who are at risk of developing GDM, enabling early intervention and therapy.<sup>4</sup>

## CONCLUSION

The findings have highlighted the potential of serum irisin as a diagnostic marker for GDM as well as its therapeutic implications. The significant differences in serum irisin levels between the GDM and the control groups suggest that lower serum irisin levels may be connected to the development of GDM.

## FUTURE RECOMMENDATIONS

- Conduct long-term research to evaluate how serum irisin levels and glycaemic markers vary over time in pregnant women with GDM.
- Examine the underlying processes through which irisin influences insulin sensitivity and glucose metabolism in GDM.

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Authors approved the draft and are accountable in ensuring that questions related to accuracy or integrity of the work are duly investigated and resolved.

**KA:** Concept, study design, data acquisition, analysis and interpretation

**KN:** Final approval of the version to be published

**ZTL:** Interpretation of data

**SAS:** Manuscript writing and critical review for intellectual content

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