Research Article

Association of serum sortilin and insulin resistance in patients with gestational diabetes mellitus

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Article Info

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Keywords

Gestational Diabetes Mellitus, Insulin resistance, HOMA-IR, Sortilin

Abstract

Introduction: Gestational diabetes mellitus is a condition in which glucose intolerance develops during pregnancy. Sortilin is a type I transmembrane protein, that belongs to the VPS10 family of post-Golgi trafficking receptors that is involved in signaling, intracellular sorting, and transport of proteins. Sortilin is required for the storage of glucose and co-expressed with the glucose transporter GLUT4 in differentiated adipocytes. This study aimed to evaluate serum sortilin level in individuals with GDM and to elucidate its relation with insulin resistance.

Methodology: This was a case-control study. It involved 80 pregnant women, 40 with GDM (case group) and 40 healthy pregnant women (control group). Fasting blood glucose, HbA1c, insulin, HOMA-IR, and sortilin were analyzed in all the participants. Statistical analysis was performed with SPSS, version 26.0.

Results: Age, gestational week, and blood pressure showed no significant difference in both groups. Body mass Index (BMI), fasting blood glucose, glycated hemoglobin (HbA1c), fasting insulin, homeostasis model assessment of insulin resistance (HOMA-IR), and sortilin were significantly higher in the GDM group. Maternal serum sortilin showed a statistically significant positive correlation with BMI, fasting plasma glucose, serum insulin, HOMA-IR, and HbA1c. (r:0.37, p:<0.05; r:0.64, p:<0.001; r:0.38, p:<0.001; r:0.42, p<0.001, r:0.68, p<0.001 respectively). The Receiver Operating Characteristics (ROC) curve indicated sortilin as a potential biomarker for the prediction of cases with an area under a curve of 0.98 (p-value<0.001) and for the cut-off point value of >2.6ng/ml, the sensitivity was 97.5%, specificity was 97.5%, false negative rate was 2.5% and false positive rate was 2.5%. The Youden's index was 0.95, thus indicating the diagnostic accuracy of sortilin.

Conclusion: This study aimed to evaluate serum sortilin level in individuals with GDM and to elucidate its relation with insulin resistance. In this study, we observed that serum sortilin concentration was significantly higher in individuals with gestational GDM than in healthy pregnant women. Also, serum sortilin had a statistically significant positive correlation with fasting blood glucose, fasting insulin, HOMA-IR, and glycated hemoglobin. The area under the curve of ROC and the Youden's index shows the impeccable diagnostic accuracy of sortilin.

Introduction

Gestational diabetes mellitus is a condition in which glucose intolerance develops during pregnancy [1]. Globally, the prevalence of Gestational diabetes mellitus is around 14% of pregnancies. The prevalence of GDM in India is 0.80% of pregnancies in 2020 [2].

Several risk factors are implicated in the development of gestational diabetes mellitus namely, increased maternal age, obesity, family history of type 2 diabetes mellitus etc. In a normal gestation, the insulin sensitivity increases in the early gestation, but in the mid-2nd and 3rd trimester, the surge of local and placental hormones like oestrogen, prolactin, placental lactogen and growth hormone will elevate the blood glucose level. This increase in blood glucose level is associated with a compensatory increase in insulin secretion. The beta cells compensate for this increased metabolic demand by hypertrophy or hyperplasia. In gestational diabetes mellitus, the beta-cells inadequately compensates for the increased demand. Also, gestational diabetes mellitus is associated with decrease in insulin sensitivity of the tissues [3].

Previous studies have demonstrated a marked- reduction in insulin mediated glucose transport in the skeletal muscles of patients with gestational diabetes mellitus. This reduction in glucose transport is more severe in obese gestational diabetes mellitus individuals. Insulin mediates the transport of glucose across membranes via GLUT 4 transporters. GLUT 4 proteins are downregulated in the adipose tissue of pregnant women and this decrease is more profound in women with gestational diabetes mellitus. Also, the insulin induced translocation of GLUT4 to plasma membrane is abnormal in individuals with gestational diabetes mellitus [4].

Various proteins are involved in the translocation of GLUT 4 between the surface of plasma membrane and trans-Golgi network (TGN). The GLUT4 receptors from the plasma membrane are internalised into peripheral endosomes. From the peripheral endosomes, GLUT 4 is retrieved into trans-Golgi network, a perinuclear compartment. This prevents GLUT 4 from being degraded by the lysosomes [5]. Sortilin is a sorting protein which is involved in the export of GLUT4 from endosomes to TGN. It is a single-pass type 1 transmembrane glycoprotein encoded by the SORT1 gene. The luminal VPs 10 (vacuolar protein sorting 10 protein) domain of sortilin interacts with the first luminal loop of GLUT4, thereby rerouting it from entering the degradative pathway to recycling pathway. Hence sortilin plays an important role in insulin resistance. A case-control study done by Ozalp et al in 87 pregnant women showed an elevated level of serum sortilin in women with gestational diabetes mellitus [6,7,8,9].

This study was aimed to compare the level of serum sortilin between normal pregnant women and gestational diabetes mellitus women and to correlate the level of serum sortilin with insulin resistance. To our knowledge, this is the first study investigating sortilin levels specifically in an Indian ethnic population, highlighting its regional and demographic uniqueness compared to prior research on GDM.

Materials and Methods

Study design and Participants

This case-control study was conducted in the Department of Biochemistry & Department of Obstetrics & gynaecology, Sri Ramachandra Medical College & Research Institute, Chennai. The sample size was calculated with the power of 95% and α error of 5%. The study included 80 pregnant women of Indian ethnicity, with 40 healthy pregnant women above 18 years of age with singleton pregnancy in the control group and 40 women with GDM above 18 years of age with singleton pregnancy in the case group. The study was carried out over a one-year period, spanning from January 2023 to December 2023.

All the participants in the study underwent 75g oral glucose tolerance test between 24-28 weeks of gestation. The diagnostic criteria of International Association of Diabetes and Pregnancy Study Groups was used to interpret the oral glucose tolerance test. Pregnant women with hypertension, overt diabetes mellitus, multiple gestation, chronic hepatic, or renal diseases were excluded from the study. The study was conducted after obtaining ethical clearance from the Institutional Ethics Committee (REF: CSP/23/JUL/131/577).

Informed consent was obtained from all the participants. Baseline characteristics like age, gestational age, systemic blood pressure and body mass index were obtained from the study participants. Venous blood sampling was carried out by a trained phlebotomist. Blood samples for fasting blood glucose (Cobas e 6000 clinical chemistry analyser), glycated hemoglobin (Tosoh Automated Glycohemoglobin Analyzer HLC-723G8 analyser), serum insulin (Cobas e 602 immunoassay analyser) were processed within 3 hours of collection., and were processed in automated platforms. Serum samples for sortilin measurement were stored at –20°C and were analyzed collectively using a sandwich enzyme-linked immunosorbent assay (Human SORT1 ELISA Kit, catalogue number EH15347). The assay's detection range was 0.156–10 ng/mL, with a sensitivity of 0.094 ng/mL, and both intra-assay and inter-assay coefficients of variation were below 6%.

Statistical analysis

The statistical analysis was carried out by using the software

Statistical Package for the Social Science (SPSS) Version 26.0. The normality of the data was tested using Shapiro-wilk's test. Data showed normal distribution and hence was expressed as mean ± standard deviation. Independent sample t test was performed and a two-tailed p-value of <0.05 was considered statistically significant. The p-value for serum maternal sortilin levels was adjusted for BMI using regression analysis. Correlation analysis between the various parameters was assessed using Pearson's correlation.

Result

Table 1: Comparison of demographic and clinical characteristics between control (normal pregnant women) and case group (women with Gestational diabetes mellitus).

Parameters	Control group (n=40)	Case group (n=40)	p-value
Age	26.88±4.32	27.38±3.26	0.56
SBP (mmHg)	107.35±10.41	108.70±7.96	0.51
DBP (mmHg)	67.95±8.29	70.00±8.47	0.27
G. weeks	23.90±4.48	23.90±6.34	1
BMI (Kg/m2)	24.15±3.89	28.39±4.92	<0.001* *
FBG (mg/dL)	77.22±6.11	95.40±10.35	<0.001* *
HbA1c (%)	5.04±0.40	5.78±0.22	<0.001* *
Fasting Insulin (mU/ml)	10.30±5.60	24.11±19.26	<0.001* *
HOMA-IR	2.04±1.18	5.74±4.85	<0.001* *
Sortilin (ng/mL)	1.24±0.41	7.40±2.5	<0.001* *

Data represented as Mean ± standard deviation (SD). Comparison is done via independent sample t-test. * Statistically significant (p<0.05); * * Statistically significant (p<0.001)

BMI – body mass index; SBP – Systolic Blood pressure; DBP-Diastolic blood pressure; G. weeks- Gestational weeks; FBG – Fasting blood glucose; HbA1c – Glycated Hemoglobin; HOMA-IR: homeostatic model assessment of insulin resistance

Age, systemic blood pressure and gestational age did not show any statistically significant difference between the groups. But body mass index was significantly higher in women with gestational diabetes mellitus when compared with control group. Fasting blood glucose, HbA1c, fasting insulin, HOMA-IR and sortilin were significantly higher in women with gestational diabetes mellitus.

Table 2: Correlation of body mass index, HbA1c, fasting blood glucose, fasting insulin and HOMA-IR with sortilin.

Correlation coefficient (r value) with sortilin		P value
BMI	0.37	<0.05*
HbA1c	0.68	<0.001**
Fasting blood glucose	0.64	<0.001**
Fasting insulin	0.38	<0.001**
HOMA-IR	0.42	<0.001**

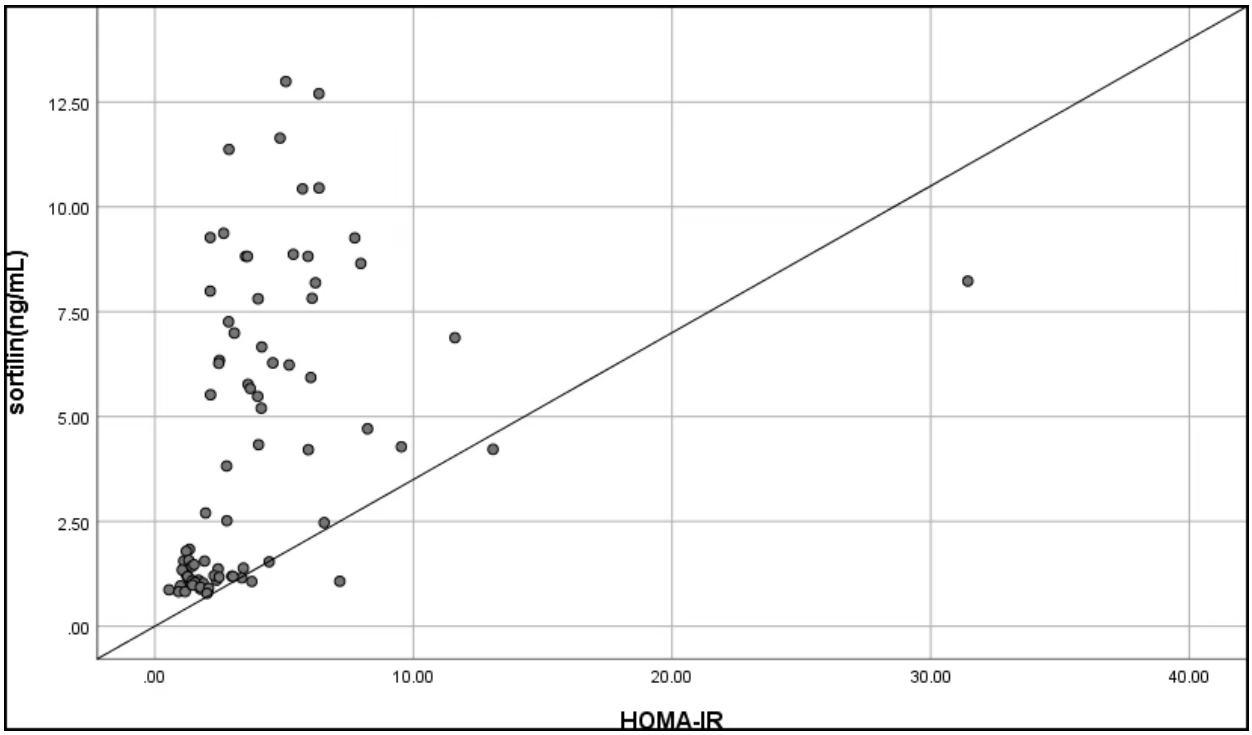
The correlation was done by using the Pearson correlation test

* Statistically significant (p<0.05)

* * Statistically significant (p<0.001)

Sortilin had a significant correlation with body mass index, glycated hemoglobin, fasting blood glucose, fasting insulin and HOMA-IR.

Figure 1: Scatter Plot Representing Correlation between HOMA-IR and Sortilin level in the case group.



Sortilin level and HOMA-IR showed a strong positive association (correlation coefficient=0.42), which was statistically significant (p-value<0.001).

Figure 2: ROC curve of serum Sortilin.

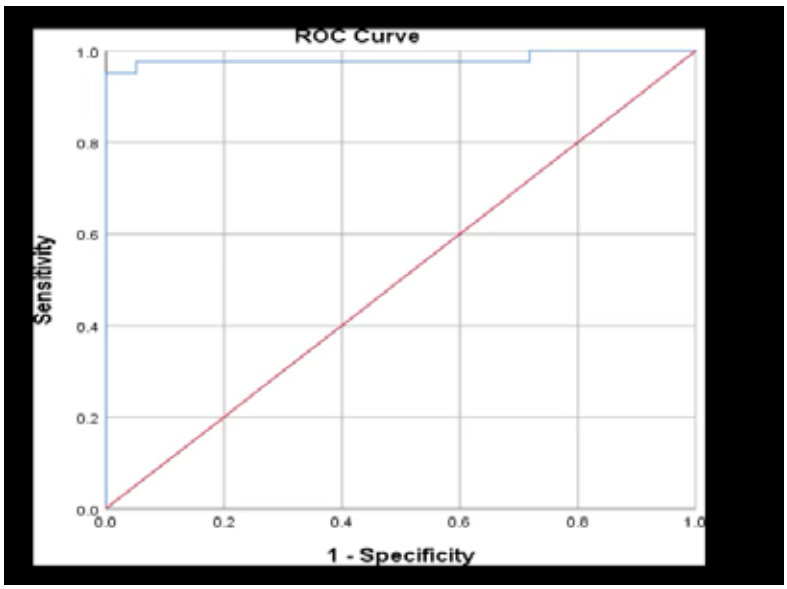


Table 3: ROC curve metrics.

Metrics	Value
Are under the curve (AUC)	0.98
Cut-off point value	>2.6 ng/mL
Youden's index	0.95
Sensitivity (2.6 ng/mL)	97.50%
Specificity (2.6 ng/mL)	97.50%

The Receiver Operating Characteristics (ROC) curve indicated sortilin as a potential biomarker with an area under a curve of 0.98 (p-value<0.001) and for the cut-off point value of >2.6ng/ml, the sensitivity was 97.5%, specificity was 97.5%, false negative rate was 2.5% and false positive rate was 2.5%. The Youden's index was 0.95, thus indicating the diagnostic accuracy of sortilin.

Table 4: 95% confidence interval for the ROC curve metrics.

Metrics	Value	95% confidence interval
Are under the curve (AUC)	0.98	0.95 – 1.00
Sensitivity (2.6 ng/mL)	97.50%	86.8% - 99.9%
Specificity (2.6 ng/mL)	97.50%	91.0% – 100%

Discussion

Sortilin is a post-Golgi trafficking receptor that is involved in signalling, intracellular sorting, and transport of proteins. It is highly expressed in metabolically active tissues such as the brain, liver, skeletal muscle, and adipose tissue. In adipocytes, sortilin plays an important role in the GLUT 4 pathway, affecting the peripheral transport of glucose into the cells [10,11].

In this study, BMI was significantly higher in the GDM group (p-value<0.001) with a mean of 28.39 kg/m2. Individuals with GDM have a higher body mass index when compared to healthy pregnant women. This is in consistent with the previously published studies [12]. The high pre-pregnancy BMI of the mother is an established risk factor for GDM (12). According to Lee et al, the prevalence of GDM was highest among Asian women with BMI ≥30 kg/m2 (13.8%) followed by women with BMI ≥25 kg/m2 (10.2%) [13]. Seshiah et al. also reported a significantly higher prevalence of GDM at higher BMI [14].

The significantly elevated fasting blood glucose and HbA1c level in this study are in alignment with Yanqin Lou et al., in which early-pregnancy FBG and HbA1c of pregnant women with GDM were higher when compared with the control group [15].

The fasting insulin and HOMA-IR level were significantly elevated in the GDM group when compared to the control group (p value<0.001). There is evidence to suggest that insulin and C-peptide values are good predictors of GDM [16]. The concentrations of fasting insulin and C-peptide are significantly higher in pregnant women with GDM than in healthy pregnant women [17].

Homeostatic model assessment for insulin resistance (HOMA-IR) is calculated from the values of fasting glucose and fasting insulin or C-peptide. The homeostatic model assessment for insulin resistance has mostly been reported to be significantly more abundant in pregnant women with GDM and is a good predictor of GDM [18].

However, some studies have downplayed the significance of HOMA-IR when compared to other parameters. Some studies have suggested that there is no difference in HOMA-IR between pregnant women with GDM and healthy pregnant women [19]. So, it can be concluded that the significance of HOMA-IR is questionable and HOMA-IR alone is insufficient for use as a predictive marker for GDM [20].

In early gestation, insulin sensitivity increases, promoting the uptake of glucose into adipose stores in preparation for the energy demands of later pregnancy. As the pregnancy progresses, there is an increase in local and placental hormones, namely estrogen, progesterone, leptin, cortisol, placental lactogen and placental growth hormone which together promote a state of insulin resistance. Also, the systemic and placental inflammatory responses associated with normal pregnancy are exaggerated by obesity. This is also reflected in elevated maternal circulating level of proinflammatory cytokines and increased mRNA expression of IL-1β, IL-8 and monocyte chemoattractant protein (MCP) 1 in the placenta. The increase in placental inflammatory mediators may be secondary to infiltration of maternal macrophages, which are elevated in the maternal circulation in obesity and known to release the proinflammatory cytokines IL-1, IL-6 and TNFα. [21].

Pro-inflammatory cytokines are known to impair insulin signalling and inhibit insulin release from β-cells. These factors induce insulin resistance either by diminishing insulin receptor (IR) tyrosine kinase activity, increasing serine phosphorylation of IRS-1, or through the STAT3-SOCS3 pathway, which degrades IRS-1. Hence, both increased concentration of placental hormones and inflammatory conditions together contribute to insulin resistance in GDM [21].

Sortilin had a normal distribution in the study and was expressed as mean and standard deviation. The mean Sortilin level in the control group was 1.24 ng/mL and, in the case, group was 7.40 ng/mL (Table 6). The Sortilin level was significantly higher in the GDM group when compared to the control group (p-value < 0.001). Also, sortilin had a statistically significant positive correlation with fasting blood glucose, insulin, HOMA-IR and HbA1c. This observation was consistent with already published articles. Mirac Ozalp et al. in their study revealed that serum sortilin level was significantly higher in the GDM group as compared to non-GDM [22].

This study also revealed that there was a positive correlation between serum sortilin, insulin, HOMA-IR and glycated hemoglobin.

On the contrary to the above-observed findings, Demir et al. compared the level of sortilin in newly diagnosed T2DM

patients with individuals having normal glucose tolerance and found that serum sortilin level were low in the T2DM group. Also, serum sortilin level are negatively correlated with fasting blood glucose, insulin, and HOMA-IR [23].

The differences between our findings and those of Demir et al. might be attributed to several factors. Variations in the characteristics of study populations, such as ethnicity, duration of diabetes, glycemic control, and presence of other health conditions, can influence serum sortilin levels differently. Additionally, methodological differences including assay types, sample storage, and timing of measurements may affect results. Sortilin is involved in diverse processes like lipid metabolism and inflammation, which might vary depending on the stage. Finally, disparities in study design, sample size, and statistical analysis could also contribute to the contrasting observations.

The relationship of sortilin with age, gestational age, BMI, FBG, HbA1c and HOMA-IR was analyzed in the GDM group. Sortilin did not show any statistically significant correlation with age or gestational age. However, sortilin had a statistically significant positive relationship with fasting blood glucose, HbA1c and HOMA-IR.

The Receiver Operating Characteristics (ROC) curve indicated sortilin as a potential biomarker for the prediction of cases with an area under a curve of 0.98 (p-value <0.001); and for the cut-off point value of >2.6ng/ml, the sensitivity was 97.5%, specificity was 97.5%, false negative rate was 2.5% and false positive rate was 2.5%. The Youden's index was 0.95, thus indicating the diagnostic accuracy of sortilin.

As sortilin plays an important role in this retrograde traffic of GLUT4 from endosomes and the reformation of IRVs; sortilin protein is a target of insulin signalling through the Insulin/PI3K/AKT signalling cascade and insulin increases sortilin protein expression.

Sortilin also plays an important role in intracellular lipid metabolism. In the hepatocytes, sortilin promotes the lipolysis of VLDL, through apolipoprotein B-100, resulting in elevated low-density lipoprotein concentration in the circulation. In the macrophages, it modulates the LDL uptake and foam cell formation, thereby playing an important role in atherosclerosis [24]. Sortilin is also linked to endothelial dysfunction and hypertension by exerting its effect through the S1P pathway; augmenting the production of Reactive Oxygen Species. This increased ROS production leads to impaired endothelium relaxation [25].

Conclusion

Hence, in this study, serum sortilin concentration was significantly higher in GDM individuals. The Receiver Operating Characteristics (ROC) curve indicated sortilin as a potential biomarker for the prediction of cases with an area under a curve of 0.98 (p-value<0.001) and a cut-off value of >2.6ng/ml. Also, serum sortilin had a statistically significant positive correlation with BMI, FBG, HbA1c and HOMA-IR, reflecting its role in the pathogenesis and later implication of GDM.

Limitations

The study was limited by its single-centre design, which may affect the wider applicability of the results. Additionally, the research included only participants of Indian ethnicity, restricting the generalizability to other populations. Furthermore, sortilin levels were not assessed during the postpartum period, leaving potential changes in this timeframe unexplored.

Author Contributations

Conceptualization: Rupa Thakur, Leena Chand, Anjana Vinod, K Sowmya; Methodology: Rupa Thakur, Leena Chand, Anjana Vinod, K Sowmya; Material preparation, data collection: Rupa Thakur, Leena Chand, Anjana Vinod, K Sowmya; Formal analysis and investigation: Rupa Thakur, Leena Chand, Anjana Vinod, K Sowmya; Writing - original draft preparation: Rupa Thakur, Leena Chand, Anjana Vinod, K Sowmya; Writing - review and editing: Rupa Thakur, Leena Chand, Anjana Vinod, K Sowmya; Resources: Rupa Thakur, Leena Chand, Anjana Vinod, K Sowmya; Supervision and final approval: Rupa Thakur, Leena Chand, Anjana Vinod, K Sowmya; Accountability for the research: Rupa Thakur, Leena Chand, Anjana Vinod, K Sowmya.

Ethics Approval

The study was approved by Sri Ramachandra Institute of Higher Education and Research Institutional Ethics Committee (CSP/23/JUL/131/577). This study was conducted in compliance with the ethical principles for medical research involving human subjects, in accordance with the Declaration of Helsinki.

Funding

No funding was received for the conduct of this project.

Data Availability

The datasets used and/or analysed during the current study are not available because of the Institutional policy.

Disclosure of Conflict of Interest

The authors declare that there is no conflict of interest concerning this study.

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