Original Article

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Comparison of WNT1-Inducible Signaling Pathway Protein 1 Levels in Gestational Diabetes Mellitus and Normoglycaemic Pregnancy: A Cross-sectional Study

Obstetrics and Gynaecology Section

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ABSTRACT

Introduction: Gestational Diabetes Mellitus (GDM) is a common condition that occurs in pregnancy with adverse outcomes. The Wingless and Int-1 (WNT) signaling pathway is related to adipogenesis as well as inflammatory processes during pregnancy. WNT Inducible Signaling Pathway Protein 1 (WISP-1) has recently been described as a novel adipokine, which may participate in impaired glucose homeostasis. WISP-1 plays a critical part in the pathogenesis of obesity- and inflammation-related diseases.

Aim: To estimate WISP 1 levels and their association with hepatic steatosis and insulin resistance in GDM.

Materials and Methods: The present cross-sectional study was conducted in the Obstetrics Antenatal Outpatient Department (OPD) of SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu District, Tamil Nadu, India, from December 2023 to May 2024. A total of 41 GDM patients and 41 normal healthy pregnant women between 12 to 28 weeks of pregnancy were included. Pregnant women were diagnosed as GDM, based on the Diabetes in Pregnancy Study Group India criteria (DIPSI). The biochemical analytes such as fasting plasma glucose, Glucose Challenge Test (GCT), Total Cholesterol (TC), Triglycerides (TGL), Low Density Lipoprotein (LDL), High Density Lipoprotein (HDL), Aspartate Transaminase (AST), Alanine Transaminase (ALT), Hepatic Steatosis Index (HSI), WISP-1 and C-peptide levels were analysed. C-peptide derived C-Peptide Immunoreactivity Insulin Resistance (CPR-IR) index, C-peptide based Homeostatic Model Assessment of Insulin Resistance (HOMA-IR CP) was calculated. Independent t-test was used for normal distribution and data was presented as mean±SD or the Mann-Whitney U test for skewed data and data presented as median (interquartile range). Correlation analysis was performed using Spearman's correlation between parameters in GDM group. Statistical significance was defined as probability value, $p<0.05$.

Results: The mean age was 27.17 years in GDM group while in the control group it was 25.58 years. WISP 1 levels were found to be increased in GDM patients, 114.54 (69.29, 174.7) compared to healthy pregnant women, 95.5 (67.39, 160.76), but this difference was not statistically significant ($p=0.366$). C peptide 0.46 (0.27, 0.88), HOMA-IR CP 1.51 (1.51, 1.53) were found to be significantly increased in GDM patients. WISP-1 does not correlate with hepatic steatosis ($\rho=-0.207$, $p=0.193$) and insulin resistance based on C peptide ($\rho=-0.219$, $p=0.170$) in GDM patients.

Conclusion: WISP-1 has no correlation with hepatic steatosis and insulin resistance based on C peptide in GDM patients.

Keywords: C peptide, Healthy Pregnancy, Hepatic steatosis, Obesity

INTRODUCTION

Globally, GDM affects about 3-25% of pregnancies [1], and its prevalence is on the rise in concordance with rise of obesity [2]. Maternal adipose tissue contributes to the increased insulin resistance in GDM [3]. Obesity during pregnancy alters the structure and function of the placenta with secretion of adipokines such as adiponectin, Fatty Acid Binding Protein (FABP), WISP-1 [4], leads to increase in inflammatory mediators in the placenta with obesity related gestational diabetes [5].

WISP 1, also known as Cellular Communication Network protein family (CCN 4), is a newly identified adipokine, secreted by adipocytes, that activates cytokine responses in adipose tissue-associated macrophages and plays role in adipose tissue dysfunction [6]. It has the potential to be trapped inside the extracellular matrix but the mechanism through which it enters is still unknown [7]. WISP-1/CCN4 is present in several parts of the body such as placenta, ovaries, small intestine, heart, kidney, lung, pancreas, spleen, and brain [8]. Studies have revealed that WISP-1 plays a part in pathogenesis of chronic inflammation related diseases such as fibrosis, dyslipidaemia, hypertension, obesity, metabolic disorders [9,10]. WISP-1 is found to be expressed in cell and tissue homeostasis via various autocrine and paracrine functions [11]. The effects of WISP-1 on glucose metabolism is mediated by its direct inhibition of insulin receptor phosphorylation in liver and muscle cells, which results in increased glucose level in liver and decreased glycogen synthesis in muscle [12], and it was found to be elevated in gestational diabetes and involved in several disease processes [13].

Jung TW et al., showed that WISP-1 may play a crucial role in obesity-induced insulin resistance and hepatic steatosis [9]. The role of WISP-1 in insulin resistance and hepatic steatosis in the development of GDM has not been substantially established in the Indian population. Therefore, the present study aimed to evaluate the circulating WISP 1 levels and to assess their relationship with insulin resistance and hepatic steatosis in GDM patients.

MATERIALS AND METHODS

The present cross-sectional study was conducted in the Obstetrics Antenatal OPD of SRM Medical College Hospital and Research Centre, Kattankulathur, Chengalpattu District, Tamil Nadu, India, from December 2023 to May 2024. The study protocol was approved by SRM Ethical Committee (EC NO: SRMIEC-ST0923-704), informed written consent was obtained from all the participants. Pregnant women with diabetes mellitus diagnosed by

DIPSI criteria, categorised into GDM as cases (n=41) and healthy pregnant women as controls (n=41), between 12 to 28 weeks of pregnancy form the sample population. (Second trimester is more suitable for diagnosing GDM, and metabolic markers like C peptide, HSI, and WISP-1, are detectable in this stage). Hormonal and liver enzyme fluctuations in the 1st or 3rd trimester can affect the HSI. WISP-1 is involved in metabolic regulation and may be influenced by HSI and C peptide.

Oral Glucose Challenge Test (OGCT) using 75g anhydrous glucose in 250-300 ml of water and plasma glucose (after 2 hr) ≥140 mg/dl was considered as GDM. The maternal prepregnancy weight was self-reported information collected from the patient. The height of the patient was measured using the stadiometer. Pre pregnancy Body Mass Index (BMI) was calculated as weight before gestation over height squared. We followed the BMI classification according to Asia-pacific cut off, Body Mass Index in Kg/m^2 (underweight = 18.5, normal weight = 18.5 - 22.9, overweight = 23.0 - 24.9, obese ≥ 25) [14].

Inclusion criteria:

- For the GDM group - pregnant women aged 18 years or older with a confirmed diagnosis of GDM using DIPSI criteria and carrying a singleton pregnancy were included;
- For control group- healthy pregnant women aged 18 years or older with singleton pregnancy were included.

Exclusion criteria: Multiple pregnancies, coronary heart disease, heart failure, infectious disease, immunosuppressive treatment, pre-eclampsia, pre-existing glucose intolerance, chronic or generalised inflammation, polycystic ovarian syndrome were excluded from both GDM and control group.

Sample size calculation: The sample size was calculated using the formula [15]:

$$n = \frac{(Z\alpha/2 + Z1 - \beta)^2 (\sigma1 + \sigma2)^2}{(\mu1 - \mu2)^2}$$

Where, N - Sample size required for the case and control groups, Z α/2 - Z score corresponding to the desired significance level (α), Z (1-β) - Z score corresponding to the desired power (1-β), σ1 and σ2 - variances of two populations, μ1 and μ2 - means of two populations

Zα/2 (90%) = 1.645

Z1-β (90%) = 1.282

μ1 = 934, μ2 = 692

σ1 = 449, σ2 = 286

$$n = \frac{(z\alpha/2 + z1 - \beta)^2 (\sigma1 + \sigma2)^2}{(\mu1 - \mu2)^2}$$

$$= \frac{\{1.645 + 1.282\}^2 \{(449)^2 + (286)^2\}}{(934 - 692)^2}$$

$$= \frac{(2.927)^2 (201601 + 81796)}{(242)^2}$$

$$= \frac{(8.567)(283397)}{58564}$$

$$= \frac{2427862.099}{58564}$$

$$= 41.4 \sim 41$$

n1 = 41

n2 = 41

n1 = normal healthy pregnant women

n2 = pregnant women with GDM

Study Procedure

Laboratory analysis: Fasting venous blood samples were collected. Routine serum biochemical parameters such as lipid profile- TC, TGL, LDL and HDL (HDL-C), liver function test- AST, ALT were analysed on Beckman coulter AU480 auto analyser. Fasting glucose was determined using hexokinase method.

CP, WISP-1 were determined by monoclonal antibody-based Enzyme Linked Immunosorbent Assay (ELISA) immunochemical kit (Sandwich method), according to the instructions given by the manufacturer. Concentrations of WISP-1 were measured in the serum sample stored at -80°C, no longer than six months. Hepatic Steatosis Index (HSI) was calculated using the formula [16]:

$$HSI = 8 \times \frac{ALT}{AST} + BMI + 2\,(if\ type\ 2\ diabetes) + 2\,(if\ female)$$, with values >36 determining the presence of steatosis.

Insulin resistance indices were calculated using the following formulae [17,18]:

$$CPR - IR = \frac{20}{fasting\ C-peptide\ (ng/ml) \times fasting\ glucose\ (mg/dl)}$$

$$HOMA - IR\ CP = 1.5 + \frac{fasting\ glucose\ (mg/dl) \times fasting\ C-peptide}{2800\ (ng/ml)}$$

STATISTICAL ANALYSIS

Statistical analyses were performed using the Microsoft excel. Normal distribution of the data was investigated by Shapiro Wilk test. Comparison between two groups were analysed by Independent t-test was used for normal distribution and data was presented as mean±SD or the Mann-Whitney U test for skewed data and data presented as median (interquartile range). Correlation analysis was performed using Spearman's correlation between parameters in GDM group. Statistical significance was defined as probability value, p<0.05.

RESULTS

A total of 82 women participated in this study, categorised into 41 healthy pregnant women as controls and 41 pregnant women with GDM as cases The mean age was 27.17 years in GDM group while in the control group it was 25.58 years.Age,Height,Prepregnancy weight and BMI were comparable between the groups. Diabetic profile like OGCT, fasting C peptide and HOMA-IR CP, showed a significant increase in GDM patients compared to healthy pregnant women [Table/Fig-1].

WISP-1 was found to be significantly increased in GDM with HSI ≤36 compared to GDM with HSI >36. No significant differences were observed in control group between HSI ≤36 and HSI >36 [Table/Fig-2]. There is no correlation of WISP-1 with HSI, C peptide, CPR-IR, HOMA-IR CP [Table/Fig-3]. C peptide levels were positively correlated with cholesterol, TGL, LDL levels [Table/Fig-4]. HOMA IR CP levels were positively correlated with FPG, OGCT, cholesterol, TGL, LDL levels but not with HDL [Table/Fig-5].

DISCUSSION

The study findings revealed a significant increase in glucose levels, C-peptide in GDM patients when compared with healthy pregnant women, suggesting impaired glucose tolerance and insulin resistance in the GDM group. C-peptide is not cleared by the liver, like insulin. But the peripheral venous blood concentration of C-peptide is more accurate to determine the pancreatic insulin secretion than the peripheral venous blood concentration of insulin [19].

C peptide has higher and more stable blood level than insulin, primarily due to slower metabolic clearance rate, lack of hepatic extraction, and absence of cross-reactivity with insulin antibodies [20]. These features establish circulating C-peptide levels as a reliable marker of beta-cell secretory activity and a valuable tool for predicting the risk of GDM.

Parameter	GDM (n=41)	Healthy pregnancy (n=41)	t	U	p- value
Age	27.17±4.04	25.58±3.44	1.618	-	0.110
Height (cm)	155.57±6.70	155.05±6.48	0.362	-	0.718
Pre pregnancy weight (Kg)	63.84±10.90	63.13±14.70	0.250	-	0.803
BMI (Kg/m2)	26.36±3.97	26.07±5.38	0.274	-	0.785
FPG (mg/dl)	85 (79.5,90)	82 (77.5,88)	-	690.5	0.164
OGCT (mg/dl)	159 (148.5,171)	101 (88,117.5)	-	<0.0001	<0.0001
Cholesterol (mg/dl)	216.51±49.55	220.24±42.22	0.367	-	0.715
TGL (mg/dl)	189 (150.5,238)	170 (124.5,198)	-	662.5	0.098
LDL (mg/dl)	133.32±41.21	144.10±31.65	-	693.5	0.188
HDL (mg/dl)	63.68±13.99	62.07±10.71	0.585	-	0.560
ALT (mg/dl)	11 (10,15)	11 (8,14)	-	711.5	0.230
AST (mg/dl)	16 (13,19)	16 (14,20.5)	-	800	0.706
HSI	34.80±4.32	33.31±5.69	1.334	-	0.186
WISP 1 (pg/ml)	114.54 (69.29,174.7)	95.5 (67.39,160.76)	-	743	0.366
C peptide (ng/ml)	0.46 (0.27,0.88)	0.23 (0.17,0.36)	-	400	<0.0001
CPR-IR	0.53 (0.25,0.82)	1.14 (0.66,1.42)	-	514	<0.0001
HOMA-IR CP	1.51 (1.51,1.53)	1.51 (1.51,1.51)	-	596	<0.0001

[Table/Fig-1]: Comparison of demographic profile and other biochemical parameters included in the study.
Parametric variables- Age; Height; Pre-pregnancy weight; BMI: Body mass index; Cholesterol; LDL: Low density lipoprotein; HDL: High density lipoprotein; HSI: Hepatic steatosis index.
Non-Parametric variables – FPG: Fasting plasma glucose; OGCT: Oral glucose challenge test; TGL: Triglycerides; ALT: Alanine transaminase; AST: Aspartate transaminase; WISP-1: WNT-inducible signaling pathway protein 1; CPR-IR: C-peptide immunoreactivity insulin resistance index; HOMA-IR CP-C peptide based homeostatic model assessment of insulin resistance.
Parametric data were analysed by Independent t test, presented as mean±SD and non -parametric data were analysed by Mann-Whitney U test, presented as median (Q1, Q3). *p-values <0.0001, indicates the significance level.

	Group	HSI category	n	Median(IQR)	U	p-value
WISP-1	GDM	HSI ≤ 36	23	132.92(90.12,178.63)	129	0.040*
		HSI > 36	18	92.36(56.59,123.41)		
	Healthy pregnancy	HSI ≤ 36	29	92.37(59.85,137.03)	134.5	0.258
		HSI > 36	12	103.50(87.52,169.57)		

[Table/Fig-2]: Comparison of WISP-1 levels among study subjects categorised by HSI values of ≤36 and >36.
HSI: Hepatic steatosis index; WISP-1: WNT-inducible signaling pathway protein 1 Non-parametric data are presented median, interquartile range (IQR), Mann-Whitney U test was used for statistical comparison between subgroups. *p-values <0.05, indicates the significance level.

Parameters	ρ value	p-value
HSI	-0.207	0.193
C peptide	-0.219	0.170
CPR-IR	0.203	0.202
HOMA-IR CP	-0.143	0.373

[Table/Fig-3]: Correlation of WISP-1 with HSI, insulin resistance based on C- peptide indices in GDM patients.
HSI: Hepatic steatosis index; CPR-IR: C-peptide immunoreactivity insulin resistance; HOMA-IR CP-C peptide based homeostatic model assessment of insulin resistance. *p-values <0.05 indicates the statistical significance. Spearman correlation analysis was used for non- parametric distribution.

Parameters	ρ value	p-value
FPG	0.290	0.066
OGCT	0.264	0.095
Cholesterol	0.353	0 .024*
TGL	0.445	0 .004**
LDL	0.401	0 .009**
HDL	0.212	0 .184

[Table/Fig-4]: Correlation of C peptide with diabetic profile, lipid profile in pregnant women with GDM.
FPG-Fasting plasma glucose; OGCT: Oral glucose challenge test; TGL: Triglycerides; LDL: Low density lipoprotein; HDL: High density lipoprotein. *p-values <0.05, indicates the statistical significance. Spearman correlation analysis was used.

A recent study conducted in Bangladesh revealed significantly higher levels of C peptide in GDM when compared to healthy pregnant women [21], and it has been reported that C peptide levels will be reduced in the pregnant women with normal glucose tolerance in the second trimester [22].

Parameters	ρ value	p-value
FPG	0.413	0.007**
OGCT	0.418	0.006**
Cholesterol	0.415	0.007**
TGL	0.398	0.010**
LDL	0.440	0.004**
HDL	-0.029	0.856

[Table/Fig-5]: Correlation of HOMA-IR CP with diabetic profile, lipid profile in pregnant women with GDM.
FPG-Fasting plasma glucose; GCT: Glucose challenge test; TGL: Triglycerides; LDL: Low density lipoprotein; HDL: High density lipoprotein. *P-values < 0.05 indicates the statistical significance. Spearman correlation analysis was used.

In the present study, WISP-1 levels were found to be elevated in GDM patients but did not differ significantly. Studies have shown increased WISP-1 levels in GDM patients, suggesting a potential role in increasing insulin resistance [13,23]. Additionally WISP-1 levels were found to be increased in obese individuals with gestational diabetes [13], who exhibit insulin resistance and radiological indications of visceral adipose tissue fibrosis [24].

Non-Alcoholic Fatty Liver Disease (NAFLD) is a metabolic syndrome linked to insulin resistance, leading to hepatic steatosis due to change in lipid metabolism. Pro-inflammatory cytokines are secreted by macrophages and other immune cells in the liver. The resulting inflammation, known as Non-Alcoholic Steatohepatitis (NASH), can progress to cirrhosis [25]. While NAFLD is often associated with obesity, its causal role in the development of insulin resistance remains unclear. However, NAFLD is recognised as a risk factor for GDM, as hepatic steatosis contributes to insulin resistance [26]. The HSI, which includes BMI, ALT, and AST, serves as a useful marker for NAFLD and is less influenced by dyslipidemia [27].

A retrospective cohort study was conducted on women who delivered singleton pregnancies they found that elevated HSI was more likely to associate with the development of GDM during pregnancy [28]. WISP-1 levels were found to be significantly decreased in patients with hepatic steatosis and GDM. This suggests a potential link between hepatic steatosis and WISP-1

levels in GDM. Higher HSI level is associated with the increased risk of GDM, and it has also been reported that infant birth weight increased with an increased level of maternal HSI [29].

In The present study, circulating levels of WISP-1 shows no association with HSI, C peptide and C peptide based insulin resistance indices. A study that measures the circulating levels of adipokines in women with GDM and Type 2 Diabetes Mellitus (T2DM) has concluded that WISP-1 was not significantly associated with cholesterol, HDL, LDL, C peptide, CPR-IR [30]. In contrast, Liu L et al., observed that WISP-1 was positively correlated with weight, BMI, fasting plasma glucose, cholesterol, TGLs [10], and Sahin Ersoy G et al., observed significantly higher levels of WISP-1 in GDM and its positive correlation with FPG, BMI, fasting insulin, and TGL [13]. Circulating WISP-1 levels were associated with insulin resistance and adipose tissue inflammation [31]. In vitro studies on mouse hepatocyte AML12 showed that recombinant WISP-1 impairs insulin action by inhibiting Akt signalling pathway. WISP-1 inhibits insulin mediated glycogen synthesis in human myotubes and suppression of gluconeogenic gene expression in human hepatocytes [31].

The present study determined that C-peptide levels were positively correlated with cholesterol, TGL, LDL. Insulin resistance in pregnant women with GDM is more pronounced compared to normal healthy pregnant women and shows signs of dyslipidemia. C-peptide stimulates Peroxisomal Proliferator-Activator Receptor gamma (PPAR-γ), leading to lipid accumulation and gene expression changes, potentially causing inflammation, metabolic regulation, adipose tissue differentiation disorders, insulin resistance, and damaged β cell function [32]. CPR-IR, an indicator of insulin resistance, has a stronger correlation with Glucose Disposal Rate (GDR) in T2DM patients with high hepatic insulin clearance, suggesting minimal impact on GDR [18].

HOMA-IR CP is positively correlated with fasting glucose, GCT, cholesterol, TGL, and LDL. A cross-sectional study has observed that C-peptide-based HOMA model had higher sensitivity and specificity for detecting insulin resistance compared to the insulin-based HOMA-IR in diabetes mellitus [33]. HOMA model using C-peptide is more beneficial to assess the insulin resistance and β-cell function for patients undergoing exogenous insulin therapy [33].

There was no link between WISP-1 and insulin resistance based on C peptide. These findings highlight the complexity of WISP-1 pleiotropic effects, suggesting that its role in pregnancy, hepatic steatosis and insulin resistance may differ depending on tissue specific mechanism. To support these findings, further studies are required with a larger sample and more detailed analysis on its role in fat deposition and liver function.

Limitation(s)

Due to cross-sectional nature of the study a causal relationship between WISP-1, C peptide and HSI could not be established. The lack of significant correlation could be due to the limited sample size.

CONCLUSION(S)

Although WISP-1 levels were increased in GDM patients they did not differ significantly from the healthy controls. C-peptide was significantly higher in GDM patients, indicating insulin resistance; however, there was no correlation with WISP-1 levels.

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