

# Circulating Galectin-3 Levels Associated with Insulin Resistance in Gestational Diabetes Mellitus: A Cross-sectional Study

LAKSHMI VIJUKUMAR<sup>1</sup>, P RENUKA<sup>2</sup>, VM VINODHINI<sup>3</sup>, KARTHIGA J PRABHU<sup>4</sup>,  
ASHISH KUMAR<sup>5</sup>, ARYAN KUMAR SINGH<sup>6</sup>



## ABSTRACT

**Introduction:** Gestational Diabetes Mellitus (GDM) is a prevalent pregnancy complication with significant health implications for both the mother and offspring. Galectin-3, a protein expressed in various cells, contributes to cellular and systemic insulin resistance and is secreted into extracellular fluid. However, the link between Galectin-3 and insulin resistance in the development of GDM has not been firmly established.

**Aim:** To estimate the circulating Galectin-3 levels in diagnosed GDM patients and compare them with those of healthy pregnant women.

**Materials and Methods:** This cross-sectional study was conducted in the Obstetrics and Gynaecology Outpatient Department (OPD) at SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India, from July 2023 to December 2023, including 40 pregnant women aged  $\geq 18$  years in each group. The parameters measured between both groups included the diabetic profile, lipid profile and Galectin-3 levels. The case group consisted of

individuals diagnosed with GDM whose Oral Glucose Challenge Test (OGCT) value was  $\geq 140$  mg/dL, whereas the control group comprised pregnant women with OGCT values below 140 mg/dL {selected using Diabetes in Pregnancy Study Group of India (DIPSI) criteria}. Independent t-tests, Mann-Whitney U tests and Pearson Correlation were performed using Statistical Package for the Social Sciences (SPSS) (27.0).

**Results:** The mean age of the patients was  $27.78 \pm 3.84$  years in the GDM group and  $26.88 \pm 3.89$  years in the normal pregnancy group. The mean Galectin-3 levels were higher in GDM patients compared to normal pregnant women ( $4.84 \pm 0.75$  ng/mL vs.  $3.34 \pm 0.78$  ng/mL;  $p < 0.001$ ). Additionally, GDM patients exhibited significant increases in Fasting Plasma Glucose (FPG), fasting insulin, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR), Triglycerides (TyG) index and Glycated Haemoglobin (HbA1c) compared to normal pregnant women.

**Conclusion:** The present study confirmed the presence of insulin resistance and elevated Galectin-3 levels in pregnancies affected by GDM but did not find a correlation between them.

**Keywords:** Glycated haemoglobin, Homeostatic model assessment for insulin resistance, Triglycerides index

## INTRODUCTION

The GDM is a prevalent metabolic condition that develops during pregnancy. It is a temporary type of diabetes that arises due to insulin resistance and the malfunction of pancreatic  $\beta$ -cells during pregnancy. GDM causes an increased propensity for adverse pregnancy effects for both the mother and the offspring [1-4]. The effects can be both short-term as well as long-term [5]. Women diagnosed with GDM are prone to experiencing health issues throughout the postnatal period. In addition, they are more likely to develop diabetes and cardiovascular disease in the future. Many factors contribute to the risk of GDM [6,7]. These factors may include maternal characteristics such as advanced maternal age, pre-pregnancy overweight or obesity, excessive gestational weight gain, dietary patterns, passive smoking, parity, family history of diabetes and socioeconomic status [8]. The prevalence of GDM varies depending on population characteristics and diagnostic criteria. A cohort study conducted in the UK and Ireland in 2010 indicated that 1-3% of pregnancies are affected by GDM. In the early 1980s, the prevalence of GDM was 2% in India [9]. However, a 2008 study revealed higher rates, with urban areas experiencing a prevalence of 17.8%, rural areas 9.9% and semi-urban regions 13.8% [10]. There is considerable geographical variation in GDM prevalence in India, ranging from 3.2% in Kashmir [11] to 16.2% in Tamil Nadu [10,12]. Galectin-3 is a protein found in various types of cells and can be released into the extracellular fluid in its soluble form [13]. It serves various functions, including regulating cell adhesion, differentiation,

proliferation and promoting inflammation [14-16]. In women with a history of GDM, insulin resistance is present before pregnancy and progresses during gestation [17,18]. Hyperglycaemia occurs when an increase in insulin secretion is unable to compensate for insulin resistance [19]. Because Galectin-3 has been associated with insulin resistance, there is a possibility that circulating Galectin-3 mediates insulin resistance, which might be a factor in the pathogenesis of GDM [20]. Literature focusing on Galectin-3 levels in Indian women with GDM is scarce. An Israeli study comparing Galectin-3 levels between normal healthy pregnant women and GDM participants identified significantly elevated levels in women with GDM [21]. A recent study found that Galectin-3 was significantly related to adverse pregnancy outcomes in Chinese mothers with GDM [22]. In the present study, an attempt was made to estimate circulating Galectin-3 levels in pregnant women with GDM and in normal healthy pregnant women and to investigate whether circulating Galectin-3 is associated with insulin resistance in GDM within the Indian context.

## MATERIALS AND METHODS

A cross-sectional study was carried out at OPD SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, located in Kattankulathur, Chennai, Tamil Nadu, India, from July 2023 to December 2023. Following the study protocol, the authors obtained written informed consent from each participant after receiving approval from the Institutional Ethics

Committee (SRMIEC-ST0323-437). The present study comprised 80 gestational age-matched pregnant women, of whom 40 had GDM and 40 were normal, healthy pregnant women.

#### Inclusion criteria:

- For GDM patients: Pregnant women aged 18 years and older with singleton gestation diagnosed with GDM using the Diabetes in Pregnancy Study Group India (DIPSI) criteria [23], with a gestational age between 24 and 36 weeks, were included in the case group.
- For normal pregnancy: Pregnant women aged 18 years and older with singleton gestation and a gestational age between 24 and 36 weeks were included in the control group.

**Exclusion criteria:** Pregnant women with a history of Diabetes Mellitus (DM), polyhydramnios, Polycystic Ovary Syndrome (PCOS), chronic hypertension, chronic renal disease, coronary heart disease, heart failure, infectious diseases and liver disease were excluded from both the case and control groups.

**Sample size calculation:** The sample size was calculated using the formula:

$N = \frac{(z_{\alpha/2} + z_{1-\beta})^2 (\sigma_1^2 + \sigma_2^2)}{(\mu_1 - \mu_2)^2}$  where [21],

$$N = \frac{(1.96 + 0.84)(252 + 39.7922)}{(100 - 124.6)^2} = \frac{(2.8)^2(625 + 1583.375)}{(24.6)^2} = \frac{(7.84)(2208.375)}{(605.16)} = \frac{17380.173}{605.16} = 28.7$$

**N=29**  
**N1=29 N2=29**

N: Sample size required for the case and control groups in the gestational age of 24 to 36 weeks.  $z_{\alpha/2}$ : z-score corresponding to the desired significance level ( $\alpha$ ) for a two-tailed test.  $z_{1-\beta}$ : z-score corresponding to the desired power (1- $\beta$ ) for the test.  $\sigma_1^2$  and  $\sigma_2^2$ : variances of the two populations.  $\mu_1$  and  $\mu_2$ : means of the two populations.

$\mu_1 = 100$ , standard deviation  $\sigma_1 = 25\%$  of 100;  $\sigma_1 = 0.25 \times 100 = 25$

$\mu_2 = 124.6$ , standard deviation  $\sigma_2 = 32\%$  of 124.6;  $\sigma_2 = 0.32 \times 124.6 = 39.792$ .

Using this formula, the minimum sample size required was  $N_1 = 29$  and  $N_2 = 29$ . However, in the current study, the sample size was 80, with  $N_1 = 40$  and  $N_2 = 40$ , where  $N_1$  and  $N_2$  are the sample sizes required for GDM patients and normal pregnancy groups, respectively.

#### Study Procedure

The GDM was diagnosed using the DIPSI criteria [23] for gestational ages between 24 and 36 weeks. Pregnant women attending the antenatal Outpatient Department (OPD) were given 75 g of anhydrous glucose dissolved in 250-300 mL of water, regardless of their fasting state and plasma glucose levels were estimated after two hours. A two-hour plasma glucose level of  $\geq 140$  mg/dL was considered a criterion for diagnosing GDM. Biochemical parameters like FPG, fasting insulin, HbA1c, HOMA-IR, HOMA- $\beta$ , TyG index and Galectin-3 were measured. HOMA-IR was calculated using the formula:  $\text{HOMA-IR} = (\text{fasting insulin } (\mu\text{IU/mL}) \times \text{fasting blood glucose (mg/dL)}) / 405$  [24]. The TyG index was calculated using the formula:  $\text{TyG index} = \ln(\text{TyG (mg/dL)} \times \text{FPG (mg/dL)}) / 2$  [25]. The Homeostatic Model Assessment for  $\beta$  cell function (HOMA- $\beta$ ) was

calculated using the formula:  $\text{HOMA-}\beta = \{20 \times \text{fasting insulin } (\mu\text{IU/L}) / \{(\text{FPG (mg/dL)} \times 0.0555) - 3.5\}$  [24]. Following aseptic protocol, a 4 mL fasting venous blood sample was collected in plain vacutainer, sodium fluoride and Ethylenediamine Tetraacetic Acid (EDTA) tubes. (The plain vacutainer tubes were centrifuged at 3000 rpm for 10 minutes and the serum sample was separated). Samples were analysed for various parameters, like glucose and HbA1c. The remaining samples were aliquoted and stored daily at  $-80^\circ\text{C}$  until the analysis of Galectin-3 and fasting insulin. The samples can be stored at  $-80^\circ\text{C}$  for one year and the validity of the kits is also one year. Galectin-3 and fasting insulin were estimated using a Bio-Rad Enzyme-linked Immunosorbent Assay (ELISA) reader and washer, while HbA1c was analysed using a Bio-Rad D10.

#### STATISTICAL ANALYSIS

The statistical analysis was performed utilising SPSS version 27.0 software. Data are expressed as mean  $\pm$  SD for parametric variables and as median (interquartile ranges) for non parametric variables. An independent samples t-test was used to determine the significant difference between the means of two independent groups: pregnant women with GDM and normal healthy pregnant women. The Mann-Whitney U test was used to compare the medians between the groups. The Pearson correlation coefficient was used to analyse the correlation between serum Galectin-3 levels and insulin resistance in GDM patients.

#### RESULTS

The Body Mass Index (BMI) was higher in GDM patients compared to normal, healthy pregnant women. The diabetic profiles, such as FPG, OGCT and HbA1c, showed a significant increase in GDM patients compared to healthy, non diabetic pregnant women. Galectin-3 levels and HOMA-IR values were significantly higher in GDM patients compared to those with normal pregnancies [Table/Fig-1]. There is no correlation between Galectin-3 and the indices of insulin resistance, including HOMA-IR and the TyG index [Table/Fig-2].

Parameters	GDM patients (n=40)	Normal pregnant women (n=40)	p-value
Gestational age (weeks)	30.73 $\pm$ 6.07	30.73 $\pm$ 6.07	1.00
Patient age (years)	27.78 $\pm$ 3.84	26.88 $\pm$ 3.89	0.307
BMI (current) kg/m <sup>2</sup>	29.5 $\pm$ 5.4	27.0 $\pm$ 4.7	<b>0.035*</b>
FPG (mg/dL)	84.5 (74.5-97.25)	77 (73.25-83.75)	<b>0.005*</b>
OGCT (mg/dL)	158 (158-183)	104 (94-111.75)	<b>0.001*</b>
HbA1c (%)	5.4 (5.1-5.8)	5.0 (4.82-5.2)	<b>0.002*</b>
Fasting insulin (micro IU/mL)	17.42 (9.89-27.38)	12.65 (7.48-20.0)	0.061
Total cholesterol (mg/dL)	217.5 (197-234)	229 (202.25-254.25)	0.137
TGL (mg/dL)	226 (184-281.75)	189.5 (150.75-226.75)	<b>0.005*</b>
LDL (mg/dL)	135.56 $\pm$ 31.16	150.63 $\pm$ 36.29	0.053
VLDL	43.5 (35-56.2)	37.9 (30.15-45.35)	<b>0.037*</b>
HDL (mg/dL)	63.75 $\pm$ 8.87	64.1 $\pm$ 13.08	0.890
Galectin-3 (ng/mL)	4.84 $\pm$ 0.75	3.34 $\pm$ 0.78	<b>0.001*</b>
HOMA IR	3.78 (2.00-5.76)	2.46 (1.30-3.83)	<b>0.019*</b>
HOMA- $\beta$	311.29 (179.63-427.14)	330.98 (162.17-583.80)	0.672
TyG index	4.95 $\pm$ 0.20	4.78 $\pm$ 0.15	<b>&lt;0.001*</b>

**[Table/Fig-1]:** Demographic and biochemical characteristics of both GDM and normal healthy pregnant women. BMI: Body mass index; FPG: Fasting plasma glucose; OGCT: Oral glucose challenge test; HbA1c: Glycated haemoglobin; HOMA-IR: Homeostatic model assessment for insulin resistance; HOMA- $\beta$ : Homeostatic model assessment for  $\beta$  cell function; TGL: Triglycerides; LDL: Low density lipoprotein; VLDL: Very low density lipoprotein; HDL: High density lipoprotein. Data are expressed as mean  $\pm$  SD for parametric variables and median (interquartile ranges) for non parametric variables. Independent student's t test: \*p-value <0.05 is considered significant. Mann-Whitney U Test: \*p-value 0.05 is considered significant

Parameters		HOMA IR	TyG index
Galectin-3	r value	-0.075	-0.057
	p-value	0.645	0.729

**[Table/Fig-2]:** Correlation between Galectin-3 and insulin resistance in GDM patients. HOMA-IR: Homeostatic model assessment for insulin resistance; r value: Correlation coefficient Pearson's correlation: \*p-value <0.05 is considered significant

## DISCUSSION

The GDM poses adverse health effects not only to the mother in the form of future T2DM risk but also for the newborn. The present study comparing women with GDM and those with normal pregnancies showed that women with GDM had a higher current BMI. By analysing National Family Health Survey data, comprising nearly 30,000 pregnant women, Chakraborty A and Yadav S identified BMI as one of the strong risk factors for GDM in Indian women [26]. Another recent study from Rajasthan concurred that a strong association exists between higher BMI and the development of GDM [27]. Elevated FPG and OGCT values suggest impaired glucose regulation and tolerance in GDM, while higher HbA1c levels indicate suboptimal long-term glycaemic control. Rajput R et al., suggested that OGTT should be performed in pregnant women with HbA1c levels between 5.45% and 5.95% for the diagnosis of GDM [28]. The TyG index, which is considered a surrogate marker of insulin resistance, was significantly increased in women with GDM. This strengthens the evidence for the potential role of insulin resistance in the pathogenesis of GDM [29]. These distinct metabolic characteristics associated with GDM emphasise the importance of early detection and targeted management strategies to mitigate adverse pregnancy outcomes. The presence of GDM suggests an altered metabolic profile during pregnancy, reflecting a potential predisposition to diabetes [30]. HOMA- $\beta$ , an indicator of insulin secretion, was comparable between the two groups. Similar findings were reported by Zhang Z et al., [31].

In contrast to the present findings, Baldane S et al., showed lower HOMA- $\beta$  levels in GDM patients but did not find a correlation with Galectin-3 levels and concluded that this lectin may not be involved in the impairment of insulin secretion [32]. However, the authors found no correlation between Galectin-3 and HOMA- $\beta$ , aligning with the findings of Zhang Z et al., [31]. This suggests the potential existence of alternative metabolic pathways through which Galectin-3 may directly influence GDM. Heusler I et al., observed higher Galectin-3 mRNA expression in the maternal circulation and placenta of GDM patients [33]. Elevated levels of Galectin-3 in individuals with GDM indicate a potential association with an increased risk of developing the condition. This observation underscores the possibility that increased Galectin-3 levels may contribute to the onset of insulin resistance and subsequent DM [34]. HOMA-IR levels were elevated in pregnant women with GDM. The malfunctioning of beta cells, coupled with persistent insulin resistance throughout pregnancy, leads to impaired beta cell function and tissue insulin resistance. These factors are pivotal aspects of GDM pathophysiology [35].

Galectin-3 gene knock-out mice did not develop insulin resistance following a high-fat diet, indicating a potential link between Galectin-3 and insulin resistance [33]. Although markers of insulin resistance, like HOMA-IR and the TyG index, were significantly increased in GDM patients in our study, we could not establish a significant correlation between Galectin-3 and insulin resistance markers. In-vitro studies on 3T3-L1 adipocytes treated with Galectin-3 showed a reduction in insulin-stimulated Glucose Transporter type 4 (GLUT4) translocation [36]. A positive correlation between Galectin-3 and insulin resistance was also reflected in women with PCOS [37]. In contrast, Freitag N et al., did not identify any differences in Galectin-3 levels between normal and GDM pregnancies in the first and second trimesters and found a decrease in Galectin-3 levels in the third trimester [38]. Talmor-Barkan Y et al., recommended the utility of Galectin-3

levels in the first trimester to screen for GDM. Early detection of GDM plays a crucial role in implementing lifestyle modifications and treatments to prevent morbidity [21]. Literature findings suggest that Galectin-3 acts as a positive regulator of trophoblast functions and may be disrupted in GDM [38]. Authors who evaluated trophoblastic functions through exogenous Galectin-3 stimulation in cell culture combined these findings with serum results, suggesting a potential link between GDM and elevated serum Galectin-3 levels in late gestation [38]. Therefore, further research is needed to explore this association.

## Limitation(s)

Due to the cross-sectional nature of the study, a causal relationship could not be derived between Galectin-3 and development of GDM. The lack of a significant correlation between insulin resistance and Galectin-3 could be due to the limited sample size.

## CONCLUSION(S)

The present study established the existence of insulin resistance and elevated Galectin-3 levels in pregnancies affected by GDM, but it could not demonstrate an association between them.

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**PARTICULARS OF CONTRIBUTORS:**

1. Postgraduate Student, Department of Biochemistry, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India.
2. Professor, Department of Biochemistry, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India.
3. Professor and Head, Department of Biochemistry, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India.
4. Professor, Department of Obstetrics and Gynaecology, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India.
5. Undergraduate Student, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India.
6. Undergraduate Student, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, Kattankulathur, Chengalpattu, Tamil Nadu, India.

**NAME, ADDRESS, E-MAIL ID OF THE CORRESPONDING AUTHOR:**

Dr. P Renuka,  
Professor, Department of Biochemistry, SRM Medical College Hospital and Research Centre, SRM Institute of Science and Technology, SRM Nagar, Kattankulathur, Chengalpattu District, Chennai-603203, Tamil Nadu, India.  
E-mail: [renukap@srmist.edu.in](mailto:renukap@srmist.edu.in)

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