LEPG2548A gene variant and metabolic parameters in Gestational Diabetes Mellitus (GDM)

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Abstract

Gestational diabetes mellitus (GDM) is a pregnancy-related condition characterized by impaired glucose tolerance due to insulin resistance. The objective of this study was to investigate the potential association between a specific variant of the leptin gene (LEP G2548A/rs7799039) with leptin levels, insulin resistance, and lipid profile in GDM patients compared to pregnant women with normal glucose tolerance.In this cross-sectional study, we enrolled 100 GDM patients and 100 healthy pregnant women with matched gestational age and BMI. Genotyping for the leptin gene variant LEPG2548A/rs7799039 was conducted using PCR-RFLP. Various biochemical parameters were assessed, and insulin resistance models were calculated using the homeostasis model assessment formulae. Statistical analysis involved the use of the chi-square test to explore associations, the Mann-Whitney U test to compare biochemical parameters, and Spearman's correlation test for correlation analyses. Odds ratios were computed to assess the risk associated with leptin gene polymorphism in the development of GDM. A significance level of 'p' < 0.05 was considered statistically meaningful. Our findings did not reveal any significant association between the leptin gene polymorphism and the presence of GDM, leptin levels, or insulin resistance. However, among GDM cases, insulin resistance models indicated a notable decrease ($p < 0.0001$) in HOMA B cell and HOMA 1 percent B cell (insulin-based) and a significant increase ($p < 0.0001$) in these same models. Additionally, C-peptide-based insulin resistance models were significantly higher ($p < 0.0001$) in GDM cases when compared to the control group.Our study did not provide evidence of a link between LEPG2548A gene alleles and GDM, leptin levels, or insulin resistance. However, C-peptide-based insulin resistance models were found to be elevated in GDM patients.

Keywords: Leptin; Gene polymorphism; Leptin gene; Insulin resistance; Gestational Diabetes

Introduction

Gestational diabetes mellitus (GDM) is characterized by varying degrees of glucose intolerance that either develops during pregnancy or is first detected during this period (Metzger et al., 2007). Globally, approximately 7% of pregnancies are affected by GDM. However, recent research by Choudhary et al. reported a higher prevalence of 9% in India (Chaudhary et al., 2017). GDM results from a decline in insulin sensitivity, leading to metabolic alterations. Leptin levels have been observed to undergo changes in GDM (McLachlan et al., 2006, Festa et al., 1999), with reports suggesting both elevations and reductions. The existing literature presents conflicting information, and definitive conclusions have yet to be established. Elevated leptin levels have been linked to insulin resistance in GDM (Laivuori et al., 2007). Given that leptin is associated with lipid metabolism, it may contribute to dyslipidemia in gestational diabetes.

Numerous studies have indicated that gene polymorphisms play a role in the development of GDM. Hofstadter and colleagues, for instance, identified a connection between the LEP G2548A polymorphism and increased leptin levels in their investigation (Hoffstedt et al., 2002). Nevertheless, no similar reports exist for the Indian population. Clinical trial findings suggest that elevated leptin levels result from the upregulation of the leptin gene due to insulin resistance and hyperinsulinemia (Laivuori et al., 2007). Leptin has been demonstrated to influence insulin sensitivity by regulating glucose metabolism, affecting insulin in muscles, and controlling hepatic gluconeogenesis (Rossetti et al., 1997). Additionally, leptin has been found to inhibit insulin secretion (Ceddia et al., 2002).

Elevated leptin levels have also been associated with an increased TG/HDL-C ratio, as indicated in a study by Lekva et al (Lekya et al., 2017). Altered leptin levels and insulin resistance may affect the lipid profiles of GDM patients. Insulin resistance is a pivotal factor in the progression of GDM, arising from a combination of reduced maternal pre-pregnancy insulin sensitivity and an inadequate response to insulin.

The objectives of this study were as follows:

1. To examine the prevalence of polymorphisms in the leptin gene (LEPG2548A) in GDM and explore their association with serum leptin levels.
2. To compare leptin levels and other biochemical parameters between GDM patients and normal pregnant women.
3. To investigate the relationship between leptin gene polymorphisms and insulin, leptin, insulin resistance, and lipid profile in gestational diabetes mellitus.

Material and Methods

Study Design and Setting

This cross-sectional investigation was conducted from July 2018 to July 2020 and took place in the Endocrinology and Molecular Genetics Wing of the Central Research Laboratory at K.S. Hegde Medical Academy, India. The study adheres to the guidelines provided by 'The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement,' and a complete STROBE checklist can be found in the Reporting guidelines. The study flow, in accordance with STROBE guidelines, is presented in Figure 1.

Study Subjects

Inclusion Criteria for Cases and Controls

The study included 100 GDM patients diagnosed according to the American Diabetes Association criteria from 2017, who were willing to participate. Additionally, 100 pregnant women with normal glucose tolerance, matched for gestational age and BMI, were recruited as a control group.

Exclusion Criteria for Cases and Controls

Excluded from the study were individuals with multiple pregnancies, pregnancies complicated by significant fetal abnormalities, known severe cardiac, renal, or hepatic diseases, as well as pregnancy-induced hypertension. To determine if a patient met the predefined criteria, a proforma was used to collect general information on demographic parameters, parity, family history of diabetes and hypertension, and past history of GDM. The NU Central Ethics Committee granted approval before the study commenced, and patients provided written informed consent.

Collection and Analysis of Blood Samples

Five milliliters of venous blood samples were obtained from the patients. Two milliliters of blood collected in a plain vial were utilized for fasting leptin, insulin, C-Peptide (assayed by ELISA), and lipid profile analysis (conducted using a fully automated chemistry analyzer). Insulin resistance models (both insulin and C-peptide based) were created using the appropriate formulae (as detailed in Table 1).

Genetic Analysis

DNA extraction and genotyping were performed using three milliliters of venous blood samples collected in EDTA (2%) vials. PCR was carried out using appropriate forward and reverse primers designed for the leptin LEP G2548A alleles. The resulting PCR products were subjected to digestion using the suitable restriction enzymes, and specific details regarding the primers and enzymes used are available in Table 2.

Regarding the sample size calculation, due to the limited literature on the association between the LEP G2548A polymorphism and the Indian population, and considering the available information from prior studies on LEP G2548A alongside a GDM prevalence of 9.0%, it was determined that a sample size of 131 patients would be necessary to achieve a study with 4% absolute precision and 95% confidence. However, due to financial constraints, the sample size was restricted to 100 individuals for both cases and controls.

For the statistical analysis, SPSS 23.0 software was employed. Hardy-Weinberg Equilibrium (HWE) was assessed among cases in relation to the LEP gene variant, and the chi-square test was used to investigate the distribution of allele frequencies among the different variants. Associations were analyzed using the Chi-square test, biochemical parameters were compared between cases and controls using the Mann-Whitney U test, and correlations were assessed using the Spearman's correlation test. To determine the likelihood of a leptin gene polymorphism contributing to GDM, odds ratios were calculated, with statistical significance defined as 'p' <0.05.

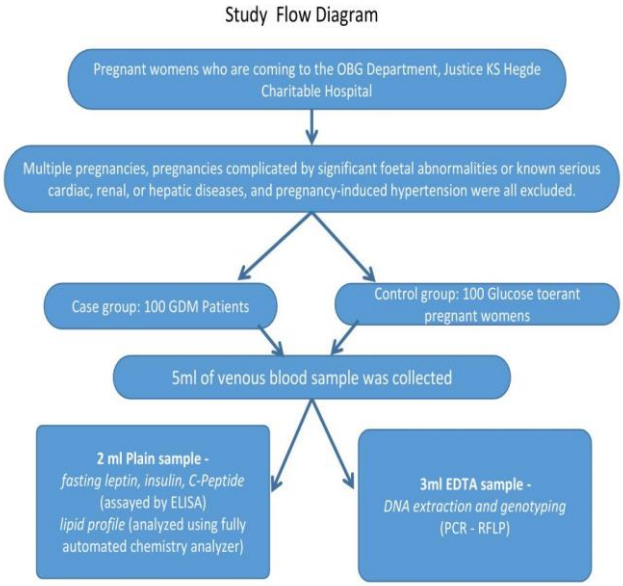

Fig 1: Study Flow Diagram

Table 1: Formulae for calculating insulin resistance models

HOMA –IR	(fasting glucose x fasting insulin)/22.5 ; insulin:µ U/L, glucose: mmol/l.
HOMA B cell	20x insulin / (Fasting blood glucose -3) ; FBS : mmol/l
HOMA 1% B cell	20x Insulin/ Fasting Plasma Glucose- 3.5 ; FBS : mmol/l
QUICKI	1/ (log G+ log I)
C-peptide insulin resistance, CIR	20/ (Glucose X C-Peptide) ; glucose and C-peptide :mmol/L

Table 2: Details of PCR-RFLP for the gene Leptin

SNP	Location of the allele (Base change)	Forward and Reverse Primers	PCR Program (35 cycles)	PCR Fragment length (Bp)	Restriction enzyme, Incubation temperature	Allele: RFLP fragment size
LEP (rs7799039)	Promoter (G>A)	F5'-TTTCCTGTAATTTT CCCGTGAG-3' R5'AAAGCAAAGACAGG CATAAAAA-3'	93°C,45', 61°C,30', 72°C,30'	242	HhaI, 37°C	Allele A:242 Allele G:181+61

Results

Patient characteristics, including age, body mass index (BMI), and gestational age, are presented in Table 4 to demonstrate the comparability of the groups. The mean age for both cases and controls was 29.62±4.3 years and 27.08 ± 3.73 years, respectively. The mean BMI for the two groups was 25.78 ± 6.84 kg/m² for cases and 25.86 ± 5.86 kg/m² for controls. The gestational age of the subjects was 25.87 ± 1.21 weeks for cases and 26.1 ± 1.54 weeks for controls.

Leptin Gene Polymorphism Pattern

Table 3 and Figure 2 display the frequencies of genotypes and alleles for LEP (rs7799039). In GDM cases, none of the genotype frequency distributions for rs7799039 variations significantly deviated from Hardy-Weinberg Equilibrium (HWE) ($p>0.05$), indicating that the alleles were in equilibrium. Association studies were conducted to investigate the connection between leptin gene polymorphism and GDM. The Chi-square statistic with Yate's correction yielded a value of 0.1694 and $p=0.68$ for the association between leptin gene polymorphism and GDM, indicating no significant association (Table 3). However, individuals with the A allele had a 1.25 times higher risk of developing GDM, as determined by the odds ratio.

No evidence of a link between LEP gene variations and leptin levels was found, with a Chi-square statistic and Yates correction yielding 0.0626 ($p=0.802$). Similarly, no significant association was observed between leptin gene polymorphisms and insulin resistance (Chi-square statistic = 0.805, $p=0.369$). However, individuals with homozygous dominant AA alleles had a 1.25-fold increased risk of developing GDM. Patients with the 'A' allele for the leptin gene had a 1.4 times higher risk of insulin resistance, according to the odds ratio.

Table 3: Hardy-Weinberg Equilibrium (HWE) for the LEP gene

Gene variant		Frequency genotypes LEP gene (rs7799039)(%)		Chi -square
		Cases	Controls	
AA	Observed	28	27	0.47 (Cases)
	Expected	29.7	24.8	
AG	Observed	53	52	
	Expected	49.6	56.2	0.654 (Control)
GG	Observed	19	34	
	Expected	20.7	31.8	
Association between GDM and LEP Gene polymorphism (Chi-square)				0.1694 p=0.68

AA: Homozygous dominant, AG: Heterozygous, GG: Homozygous Recessive

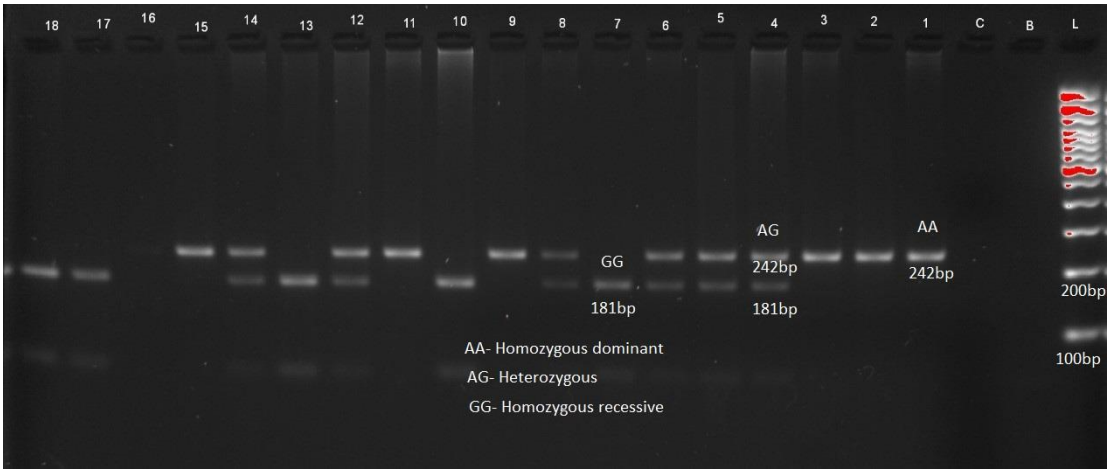

Figure 2: RFLP Pattern for the distribution of LEP gene alleles

Biochemical Parameters and Insulin Resistance

Fasting blood sugar and fasting C-peptide levels in cases were significantly higher than in controls ($p<0.0001$ and $p=0.0014$, respectively). Fasting serum insulin and leptin levels in GDM patients were insignificantly low ($p=0.6968$ and $p=0.213$, respectively). Lipid profile measurements, including TG, TC, HDL, LDL, and VLDL, showed no significant differences (with respective p values) between cases and controls, as presented in Table 4. Comparison of insulin resistance models revealed significantly lower insulin-based IR models (HOMA B cell and HOMA 1% B cell) ($p<0.0001$) as well as significantly higher C-peptide-based IR models (HOMA B cell C, HOMA 1% B cell C) ($p<0.0001$) in cases compared to controls (Table 4).

Additionally, C-peptide-based insulin resistance models (HOMA IR -C and CIR) were significantly higher ($p<0.0001$) in cases than in controls (Table 4). There was no significant difference between patients and controls in insulin-based HOMA IR and QUICKI, as shown in Table 4.

Biochemical Parameters and Insulin Resistance with Leptin Gene Polymorphism

When comparing biochemical markers among subjects with different leptin genotypes (AA, AG, and GG), insulin, C-peptide, leptin, TG, TC, HDL, LDL, and VLDL levels did not differ significantly (Table 5). Similarly, different insulin resistance models, both insulin and C-peptide-based, including HOMA IR, HOMA B cell, HOMA 1% B cell, QUICKI, HOMA IRC, HOMA B cell - C, HOMA 1% B cell - C, and CIR, did not significantly vary among various leptin genotypes (Table 6).

Table 4: Depicting metabolic parameters in cases and controls

Parameter	GDM	Control	p value	Spearman's Correlation	
				r value	p value
Mean age(yrs)	29.62±4.3	27.08 ±3.73			
BMI ($kg/m^{2)}$	25.78 ±6.84	25.86±5.86			
Gestational age(wk)	25.87± 1.21	26.1±1.54			
FBS (mmol/L)	7.49±1.87	4.95±1.32	<0.0001*		
Fasting Insulin µIU/L	5.46±11.95	7.13±6.74	0.6968	-0.606	0.0005*
C-peptide(nmol/L)	2.17±1.71	1.57±1.55	0.0014	-0.203	0.29
Leptin(ng/ml)	57.33±23.96	63.11±25.46	0.213	-	-
TG(mmol/L)	2.68±1.1	2.79±0.83	0.069	-	-
TC (mmol/L)	5.75±1.29	5.99±1.19	0.12	-	-
HDL (mmol/Ll)	1.33±0.31	1.41±0.32	0.73	-	-
LDL (mmol/L)	3.85±1.3	4±1.16	0.255	-	-
VLDL (mg/dl)	1.23±0.51	1.26±0.35	0.06	-	-
HOMA IR	2.94±4.64	1.63±2.09	0.604	-0.4856	0.0065*
HOMA B cell	35.78±50.55	75.73±90.89	<0.0001*	-0.4262	0.0211*
HOMA 1% B cell	42.62±63.75	114.03±156.99	<0.0001*	-0.4274	0.02*
QUICKI	2.39±3.46	8.89±9.8	0.466	0.501	0.0056*
HOMA IRC	0.7±0.62	0.36±0.38	<0.0001*	-0.214	0.27
HOMA B cell-C	11.03±10.07	17.31±17.25	0.0045*	-0.030	0.876
HOMA 1% B cell-C	13.58±13.16	24.65±44.5	0.0002*	-0.034	0.859
CIR	3.13±5.07	11.47±31.17	<0.0001*	-0.214	0.265

*p value significant

Table 5: Depicting metabolic parameters in cases with different genotypes of leptin gene

	AA	AG	GG	p-value
FBS (mmol/L)	7.76 ± 1.70	7.71 ± 1.70	6.39 ± 2.36	0.030*
Insulin (µIU/L)	10.16 ± 14.76	9.11 ± 12.05	4.17 ± 4.74	0.343
C-peptide (nmol/L)	1.91 ± 1.26	2.53 ± 1.94	1.58 ± 1.42	0.091
Leptin (ng/mL)	56.3 (14.34-102.6)	56.8 (7.7-98.03)	69.4 (2.7-92.88)	0.579
Triglyceride (mmol/L)	2.32 (1.1-4.65)	2.5 (0.99-6.21)	2.32 (1.77-2.88)	0.618
Cholesterol (mmol/L)	5.97 (2.9-8.07)	5.69 (3.1-9.78)	5.61 (4.01-8.28)	0.659
HDL (mmol/L)	1.69 (0.75-2.02)	1.32 (0.78-2.04)	1.27 (0.72-1.71)	0.098
LDL (mmol/L)	3.92 (1.66-5.87)	3.55 (1.22-7.76)	4.32 (2.04-6.15)	0.157
VLDL (mmol/L)	1.05 (0.49-2.12)	1.14 (0.47-3)	1.06 (0.8-1.53)	0.121

Table 6: Comparison of IR models in different genotypes of Leptin gene

	AA	AG	GG	p-value
HOMA-IR	3.57 ± 1.14	3.25 ± 0.95	1.15 ± 0.34	0.402
Glucose/Insulin	10.7 ± 1.91	19.8 ± 2.27	31.8 ± 2.95	0.674
HOMA -B Cell	35.4 ± 15.27	35.3 ± 15.89	37.7 ± 17.05	0.946
HOMA 1% - B Cell	39.4 ± 16.4	40.8 ± 19.2	53.5 ± 18.7	0.912
QUICKI	1.023 ± 0.97	4.87 ± 0.96	4.98 ± 0.91	0.992
HOMA IR C	0.58 ± 0.38	0.85 ± 0.67	0.44 ± 0.37	0.074
HOMA B Cell C	10.17 ± 5.36	10.98 ± 6.94	12.42 ± 9.15	0.322
HOMA 1% B Cell C	12.6 ± 5.97	13.04 ± 9.99	16.57 ± 3.08	0.17
CIR	3.12 ± 1.34	3.56± 1.78	4.14 ± 1.89	0.07

Discussion

The prevalence of A alleles was found to be higher than G alleles for the LEP G2548A polymorphism (Table 3), consistent with the pattern seen in a Taiwanese study by Wang et al. (Wang et al., 2006). However, in many populations, research has shown that the G allele is more common than the A allele (Vasku et al., 2006;Boumaiza et al., 2012;Le Stunff et al., 2000). Limited studies have explored the association between the LEP G2548A polymorphism and GDM. In a Czech study with a smaller sample size, Vasku et al. found that GDM patients with AA and AG genotypes had a significantly higher risk of GDM than those with the GG genotype (Vasku et al., 2006). However, the current study found no association between the LEP G2548A polymorphism and GDM (Table 3).

This study also found no association between polymorphisms in the leptin gene and its expression in the blood. Previous reports have suggested that the LEP G2548A polymorphism significantly influences leptin gene expression (Furusawa et al., 2011; Suriyaprom et al., 2007)), which contrasts with findings from an Egyptian study by Abdel (Abdel et al., 2011) . According to Vasku et al., individuals with the mutant variant (AA) and heterozygous (AG) alleles had a significantly higher risk of gestational diabetes mellitus due to the higher transcriptional activity of the LEP gene (Vasku et al., 2006). This study supports the idea that leptin plays a role in the etiopathogenesis of GDM.

Pawlik et al., Sahin et al., Mammès et al., and Hoffstedt et al. have all reported an association between the LEP rs2167270 A allele and increased leptin expression and enhanced transcriptional activity (Pawlik et al., 2016; Sahin et al.,2013;Mammes et al., 2000). When leptin levels were evaluated among GDM patients with different genotypes, patients with the AA allele had the highest serum leptin levels, though the differences were minor. During pregnancy, maternal serum leptin levels rise two to three times over non-pregnant levels, peaking at 28 weeks of pregnancy (Schubring et al.,1998). However, there is inconsistent data on maternal leptin levels in GDM, with studies reporting higher leptin levels, lower leptin levels, or no significant variations when compared to controls (Simmons et al.,2002;Mokhtari et al.,2011;Fruscalzo et al.,2015;Noureldeen et al., 2014). In a study by Noureldeen et al., no significant changes in leptin concentrations were found in the second trimester of GDM patients, while decreased leptin levels were observed in the third trimester (Noureldeen et al., 2014). Qiu and colleagues found that each 10ng/ml increase in leptin levels during the early trimesters of pregnancy was associated with a 20% higher risk of GDM (Qiu et al., 2004). Serum leptin concentrations and placental leptin expression were significantly higher in GDM compared to healthy pregnant women(Endo et al., 2006; Ozcimen et al., 2008). Therefore, mutations in the leptin and its receptor genes may influence the expression of their proteins. In a case-control study, Kautzky-Willer et al. found that leptin levels were higher in GDM women than in the control group in the third trimester (Kautzky-Willer et al.,2001).

Research by Vitoratus et al. and Qiu et al. also identified an association between the leptin gene and its expression(Vitoratus et al.,2001 and Qiu et al.,2004). Blood leptin levels are linked to glucose tolerance during pregnancy, as suggested by the researchers maternal third-trimester leptin concentrations were significantly lower in GDM cases(Liu et al.,2003; Festa et al.,1999). Elevated maternal leptin concentration may enhance the mobilization of maternal stored adiposity, supporting trans-placental lipid substrate transfer (Hauguel et al.,2006). There is substantial evidence indicating that the placenta is the primary source of plasma leptin (Bi et al.,1997). Compared to adipose tissue, the human placental promoter region may be regulated differently, and the fetus may contribute to the mother's leptin load from the early second trimester (Christou et al.,2002). This is supported by a positive correlation between umbilical cord plasma leptin levels and the birth weight of babies (Gross et al.,1998).

Increased leptin concentrations have been observed in the majority of studies involving GDM (Ategbo et al.,2006;Chen et al.,2010). Furthermore, hyperleptinemia in early pregnancy appears to predict an increased risk of developing GDM later in pregnancy, regardless of maternal adiposity. In our study, no significant difference was observed in serum insulin levels between GDM cases and controls, but C-peptide was significantly higher ($p=0.0014$) among cases (Table 4). When comparing cases with different genotypes of the leptin gene (AA, AG, and GG), insulin and C-peptide concentrations did not significantly differ ($p=0.343$ and $p=0.091$, respectively).

Polymorphisms in the leptin gene may lead to altered expression of their proteins. However, in the present study, no significant difference was observed in serum insulin levels between cases and controls, but C-peptide was significantly higher ($p=0.0014$) among cases (Table 4). There was no significant difference in C-peptide levels among various genotypes.

Insulin Resistance and Leptin Polymorphism

Comparison of insulin resistance models revealed significantly lower insulin-based IR models (HOMA B cell and HOMA 1% B cell) ($p<0.0001$) as well as significantly higher C-peptide-based IR models (HOMA B cell C, HOMA 1% B cell C) ($p<0.0001$) in cases compared to controls (Table 4). Additionally, C-peptide-based insulin resistance models (HOMA IR -C and CIR) were significantly higher ($p<0.0001$) in cases than in controls (Table 4). Leptin is known to suppress insulin production through glucagon-like peptide 1, cAMP, and protein kinase C (Lam et al.,2004; Lee et al.,2003). Insulin secretion typically increases as pregnancy progresses,

peaking in the third trimester (Catalano et al.,2002), while insulin sensitivity decreases by approximately 70% (Sivan et al.,2002) . Beta cells in the pancreas compensate for increased insulin resistance during normal pregnancy to maintain blood glucose control (Catalano et al.,1992). Reduced early-phase insulin production has been associated with decreased beta cell activity in women with GDM (Xiang et al.,1999). Furthermore, when insulin secretion was adjusted for insulin resistance, women with GDM showed significantly worse beta-cell function than normal pregnant women . Ryan et al. found greater insulin resistance in women with GDM compared to healthy pregnant controls (Ryanet al.,1985). Moreover, women with GDM had higher endogenous glucose production compared to healthy pregnant controls . Leptin has a direct impact on pancreatic-cell gene expression, leading to reduced insulin secretion (Seufert et al.,1999; Seufert et al.,2004). Leptin also influences beta-cell proliferation, apoptosis, and growth (Morroqui et al.,2012). Plasma leptin levels were found to have positive and negative associations with HOMA-IR and QUICKI, respectively. Some studies supported these associations, while others contradicted them(Yilmaz et al.,2010).

Lipid Parameters and Leptin Gene Polymorphism

No significant differences were observed in lipid profile markers, including TG, TC, HDL, LDL, and VLDL levels, between patients and controls in our study (Figure 2). Fasting blood sugar and leptin showed a significant negative correlation in correlation studies. In GDM patients, a significant positive correlation was found between leptin and TG, TC, and VLDL levels. Among insulin-resistant GDM patients, a significant negative correlation was observed between leptin levels and insulin, insulin-based IR models, HOMA IR, HOMA B cell, HOMA 1% B cell, and QUICKI (Table 4).

Pregnancy-related dyslipidemia is a well-known phenomenon. HDL cholesterol increases at 12 weeks of pregnancy in response to estrogen and remains elevated throughout pregnancy (Halstead et al.,1993). Women with GDM have higher blood triacylglycerol concentrations than normal pregnant women, but lower LDL-cholesterol values (Koukkou et al.,1996). In a study by Nawal et al., total cholesterol, HDL cholesterol, and apolipoprotein levels did not significantly differ between GDM patients and control subjects (Murtadha et al.,2002).

Limitations & Generalizability The study's small sample size was a limitation. The study could be conducted in a larger population, along with the measurement of leptin resistance.

Conclusion

According to our study findings, there is no association between the LEPG2548A allele and gestational diabetes, leptin levels, or insulin resistance. In GDM patients, C-peptide-based insulin resistance were raised. The findings could lead to a cycle in which a leptin gene polymorphism affects leptin levels, which then affects insulin secretion and resistance, contributing to pregnancy induced dyslipidemia and gestational diabetes.

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Competing interests: None

Data availability Figshare. A Cross-sectional Study on The Association of Leptin Gene Polymorphism And Metabolic Parameters in Gestational Diabetes Mellitus. DOI: https://doi.org/10.6084/m9.figshare.20321739.v1

This project contains the following underlying data:

- Leptin CONTROL and CASE Dataset
- Study flow diagram

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