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Hormonal and biochemical regulation of glucose homeostasis and insulin sensitivity in women with gestational diabetes mellitus during pregnancy

Sebastián Muñoz and Catalina SilvaDOI: <https://www.doi.org/10.33545/26174693.2025.v9.i12a.7436>**Abstract**

Gestational diabetes mellitus affects between 5% and 20% of all pregnancies worldwide, yet the hormonal interplay driving insulin resistance during pregnancy remains incompletely mapped. This research compared hormonal and biochemical profiles between women diagnosed with gestational diabetes mellitus (GDM) and normoglycemic pregnant controls at a tertiary care facility in Santiago, Chile. A total of 136 women were enrolled between their 24th and 28th gestational weeks: 64 with GDM confirmed by oral glucose tolerance testing and 72 normoglycemic controls. Fasting glucose, insulin, glycated hemoglobin (HbA1c), adiponectin, leptin, and C-peptide were measured alongside homeostatic model assessment for insulin resistance (HOMA-IR). Women with GDM showed markedly higher fasting glucose (6.8 ± 1.1 vs. 4.6 ± 0.5 mmol/L, $p < 0.001$), HOMA-IR (4.73 ± 1.82 vs. 1.89 ± 0.64 , $p < 0.001$), and leptin concentrations. Adiponectin was lower in the GDM group (6.3 ± 2.1 vs. 11.8 ± 3.2 $\mu\text{g/mL}$, $p < 0.001$). A strong positive correlation existed between fasting insulin and HOMA-IR in both groups ($r = 0.71$ GDM; $r = 0.63$ controls). Multiple regression identified adiponectin ($\beta = -0.34$), pre-pregnancy BMI ($\beta = 0.29$), and family diabetes history ($\beta = 0.21$) as independent predictors of HOMA-IR. These results highlight the role of adipokine dysregulation in GDM pathogenesis and support early metabolic screening in at-risk pregnancies.

Keywords: Gestational diabetes mellitus, insulin resistance, HOMA-IR, adiponectin, glucose homeostasis, oral glucose tolerance test, leptin, pregnancy metabolism

Introduction

Pregnancy is the most common metabolic stress test a woman will ever undergo. The progressive insulin resistance that develops across the second and third trimesters serves a physiological purpose redirecting maternal glucose to the growing fetus but in a subset of women, this adaptation tips into frank hyperglycemia [1]. Gestational diabetes mellitus (GDM) complicates roughly 14% of pregnancies globally, though reported prevalence varies widely by diagnostic criteria and population [2].

The hormonal basis for pregnancy-induced insulin resistance involves placental secretion of human placental lactogen, progesterone, cortisol, and growth hormone, all of which antagonize insulin signaling at the post-receptor level [3]. In women who maintain normoglycemia, pancreatic β -cells compensate by increasing insulin output two- to threefold. When this compensatory response falls short due to genetic susceptibility, pre-existing β -cell dysfunction, or excessive adiposity GDM emerges [4].

Beyond the classical glucose-insulin axis, adipose tissue-derived hormones (adipokines) appear to play a modulating role. Adiponectin, an insulin-sensitizing adipokine, tends to be reduced in GDM, while pro-inflammatory mediators like leptin, tumor necrosis factor- α , and interleukin-6 are elevated [5]. These adipokine shifts may amplify peripheral insulin resistance and impair glucose uptake in skeletal muscle and liver [6]. Whether adipokine changes precede or follow the onset of hyperglycemia in GDM is still debated.

In Chile, GDM prevalence has risen alongside increasing rates of maternal obesity, reaching an estimated 12.4% in urban populations [7]. Despite this, local data characterizing the combined hormonal and biochemical profile of Chilean women with GDM remain limited. This research aimed to compare fasting glucose, insulin, HbA1c, HOMA-IR, adiponectin, and leptin between GDM-affected and normoglycemic pregnant women, and to identify independent predictors of insulin resistance during pregnancy.

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Material and Methods

Material

This cross-sectional research was conducted at the Department of Obstetrics and Gynecology, Santiago Institute of Technology, Santiago, Chile, between January 2023 and August 2024. Pregnant women aged 20–40 years attending routine antenatal care between gestational weeks 24 and 28 were screened. GDM was diagnosed using a 75 g oral glucose tolerance test (OGTT) following International Association of Diabetes and Pregnancy Study Groups (IADPSG) criteria: fasting glucose ≥ 5.1 mmol/L, 1-hour ≥ 10.0 mmol/L, or 2-hour ≥ 8.5 mmol/L [8]. Women with pre-existing type 1 or type 2 diabetes, thyroid disorders, corticosteroid use, or multiple gestations were excluded. Of 198 women screened, 136 met inclusion criteria: 64 GDM and 72 controls.

Methods

Fasting venous blood was collected between 07:00 and 08:30 after a 10-hour overnight fast. Glucose was measured by the hexokinase method. Serum insulin and C-peptide were quantified by electrochemiluminescence

immunoassay. HbA1c was determined by ion-exchange high-performance liquid chromatography. Adiponectin and leptin were measured using commercial ELISA kits with intra-assay coefficients of variation below 6%. HOMA-IR was calculated as (fasting insulin [μ IU/mL] $\times$ fasting glucose [mmol/L]) / 22.5 [9]. Statistical analyses used SPSS version 28. Independent t-tests compared means between groups. Pearson correlations assessed bivariate relationships. Stepwise multiple regression identified independent predictors of HOMA-IR. Significance was set at $p < 0.05$ [10].

Ethical considerations

Ethical approval was granted by the Santiago Institute of Technology Clinical Research Ethics Board (Protocol SIT-CREB-2022/134, approved 8 November 2022). All participants provided written informed consent. Women newly diagnosed with GDM during the research were immediately referred for dietetic counselling and obstetric follow-up per institutional guidelines. All data were de-identified using numerical codes, and biological samples were destroyed following analysis.

Results

Table 1: Demographic and clinical characteristics

Parameter	GDM (n=64)	Control (n=72)	t / χ^2	p-value
Age (years)	30.8 $\pm$ 4.6	29.3 $\pm$ 4.1	2.09	0.039*
Pre-pregnancy BMI (kg/m ²)	29.4 $\pm$ 4.3	24.7 $\pm$ 3.1	7.48	<0.001*
Gestational age (weeks)	26.3 $\pm$ 1.2	25.9 $\pm$ 1.1	2.04	0.043*
Parity (median)	2	1	—	0.087
Family history DM (%)	48.4%	18.1%	13.82	<0.001*
Fasting glucose (mmol/L)	6.8 $\pm$ 1.1	4.6 $\pm$ 0.5	15.31	<0.001*
Fasting insulin (μ IU/mL)	18.2 $\pm$ 5.1	9.4 $\pm$ 2.8	12.71	<0.001*
HOMA-IR	4.73 $\pm$ 1.82	1.89 $\pm$ 0.64	12.04	<0.001*
HbA1c (%)	6.1 $\pm$ 0.7	5.1 $\pm$ 0.3	10.89	<0.001*
Adiponectin (μ g/mL)	6.3 $\pm$ 2.1	11.8 $\pm$ 3.2	12.09	<0.001*
Leptin (ng/mL)	38.7 $\pm$ 11.4	22.1 $\pm$ 7.3	10.37	<0.001*

Values as mean $\pm$ SD or percentage. * $p < 0.05$.

Women with GDM had higher pre-pregnancy BMI, fasting glucose, insulin, HOMA-IR, HbA1c, and leptin, alongside lower adiponectin compared to controls (Table 1). Family

history of diabetes was present in nearly half the GDM group versus 18.1% of controls.

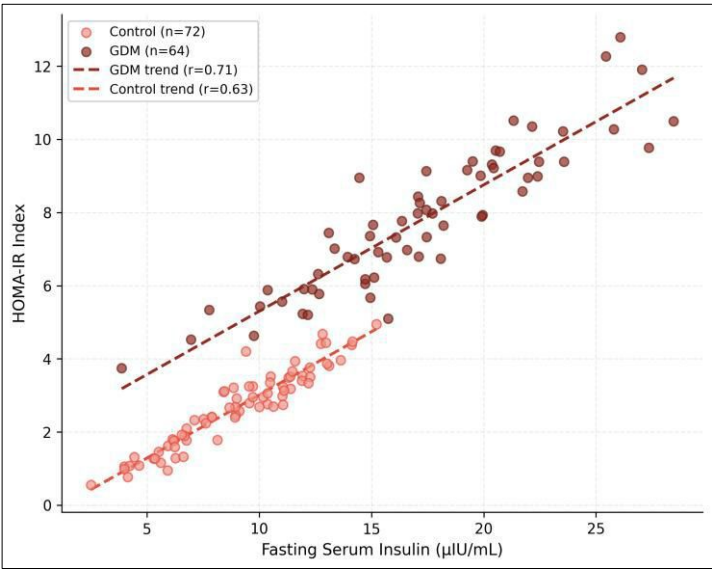


Fig 1: Scatter plot showing the correlation between fasting serum insulin and HOMA-IR in GDM and control groups. Dashed lines represent linear regression trends

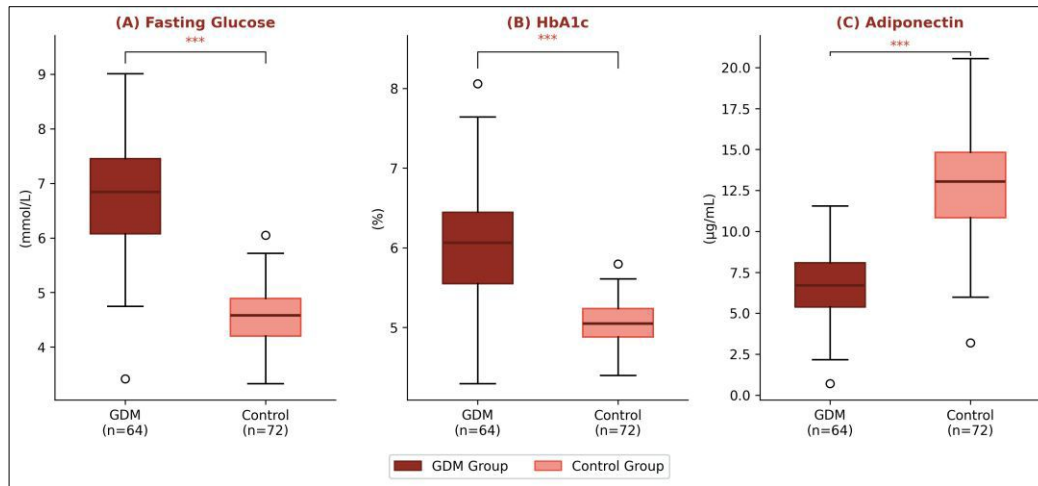


Fig 2: Box plot comparisons of (A) fasting glucose, (B) HbA1c, and (C) adiponectin concentrations between GDM and control groups. *** $p < 0.001$

Multiple regression analysis with HOMA-IR as the dependent variable identified adiponectin ($\beta = -0.34$, $p < 0.001$), pre-pregnancy BMI ($\beta = 0.29$, $p = 0.002$), and family history of diabetes ($\beta = 0.21$, $p = 0.014$) as independent predictors, collectively explaining 51.7% of

HOMA-IR variance (adjusted $R^2 = 0.517$). Leptin, despite being elevated in GDM, lost significance after adjusting for BMI. C-peptide mirrored insulin trends closely ($r = 0.89$, $p < 0.001$) but added no independent predictive value beyond fasting insulin.

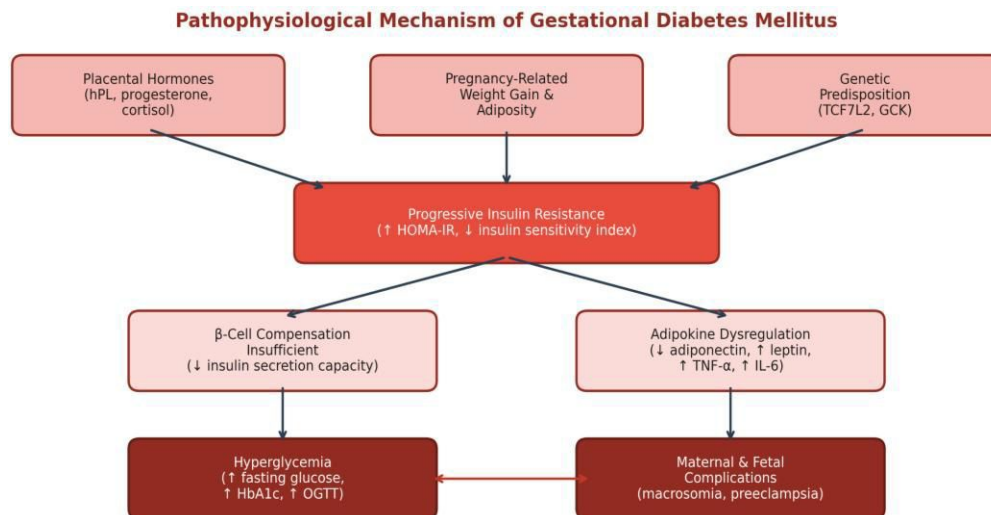


Fig 3: Schematic representation of the pathophysiological cascade in gestational diabetes mellitus, from placental hormone secretion and adiposity through insulin resistance to maternal-fetal complications

Discussion

The metabolic profile observed in this Chilean GDM cohort is broadly consistent with findings from larger international datasets. The HOMA-IR values in the GDM group (4.73 ± 1.82) exceed the threshold of 2.5 commonly used to define insulin resistance in pregnancy, and match ranges reported by Catalano *et al.* [4] in North American populations. The adiponectin deficit in GDM women (6.3 vs. 11.8 $\mu\text{g/mL}$) was particularly striking. Retnakaran *et al.* [5] proposed that low adiponectin may serve as an early biomarker for GDM risk, as reductions appear to precede clinically detectable hyperglycemia. Our regression results support this view, with adiponectin emerging as the strongest independent predictor of HOMA-IR.

The loss of leptin's predictive power after BMI adjustment suggests that elevated leptin in GDM reflects greater adipose mass rather than an independent pathogenic mechanism. This agrees with observations by Barbour *et al.* [3], who argued that leptin resistance in pregnancy primarily

mirrors the degree of maternal obesity. The high prevalence of family diabetes history (48.4%) in GDM participants points toward a genetic contribution that interacts with the metabolic demands of pregnancy [11]. The relatively high pre-pregnancy BMI in both groups (24.7 and 29.4 kg/m^2) reflects the broader trend of increasing overweight prevalence among Chilean women of reproductive age [7].

Limitations

The cross-sectional design captured metabolic profiles at a single gestational timepoint and couldn't track longitudinal changes. The sample was drawn from one urban center in Santiago, limiting generalizability to rural or indigenous Chilean populations. We didn't measure placental hormones directly, relying instead on their downstream metabolic effects. The IADPSG diagnostic criteria, while internationally accepted, may classify some women differently than older WHO thresholds, complicating cross-study comparisons.

Clinical implications

Adiponectin measurement in early pregnancy could help identify women at risk for GDM before OGTT screening at 24–28 weeks. Given that pre-pregnancy BMI and family history also predicted insulin resistance, a combined risk assessment tool incorporating these variables may improve early detection in Chilean antenatal settings.

Conclusion

This research confirmed that women with gestational diabetes mellitus in Santiago, Chile, display a distinct metabolic profile characterized by raised fasting glucose, insulin, HOMA-IR, HbA1c, and leptin alongside reduced adiponectin concentrations. Adiponectin emerged as the strongest independent predictor of insulin resistance, followed by pre-pregnancy BMI and family diabetes history. The findings support incorporating adipokine assessment into antenatal metabolic screening protocols and underscore the compound influence of genetic predisposition and maternal adiposity on GDM development. Future longitudinal research should examine whether first-trimester adiponectin levels predict subsequent GDM diagnosis and whether targeted interventions can modify the adipokine profile early enough to prevent disease onset.

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