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Evaluating Serum Endosialin (CD248) Levels as a Diagnostic Marker in Gestational Diabetes: A Case-Control Study

Tevfik Berk Bildaci,[1] Can Ata,[1] Ufuk Atlihan,[2] Huseyin Aytug Avsar,[3] Secuk Erkilinc[1]

[1]*Obygynecology Department, Izmir Democracy University Buca Seyfi Demirsoy Training and Research Hospital, Faculty of Medicine, Izmir, Turkey*
[2]*Obgynecology Department, Private Izmir Karataş Hospital, Izmir, Turkey*
[3]*Obgynecology Department, Tinaztepe University Galen Hospital, Faculty of Medicine, Izmir, Turkey*

Abstract

Objectives. Gestational diabetes mellitus (GDM), a pregnancy-induced hyperglycemia, affects approximately 17% of pregnancies globally. Its pathophysiology remains unclear, with inflammation and vascular remodeling playing key roles. CD248, a glycoprotein linked to inflammation and vascular remodeling, has been implicated in various conditions, but its role in GDM is uncertain.

Methodology. A prospective case-control study was conducted with 169 pregnant women aged 18 to 49 at a tertiary hospital. Serum CD248 levels were assessed at 24 to 28 weeks of gestation prior to the oral glucose tolerance test (OGTT). Statistical analyses evaluated the association between CD248 levels, BMI and GDM status.

Results. Of the participants, 32 (18.9%) were diagnosed with GDM. CD248 levels were lower in GDM patients (8.15 ± 10.16 ng/mL) than in controls (11.42 ± 15.44 ng/mL), but the difference was not statistically significant (p = 0.084). Although CD248 levels did not correlate with OGTT values, it was positively associated with BMI (p <0.001).

Conclusion. Unlike earlier findings associating elevated CD248 levels with early pregnancy GDM risk, this study found no significant relationship during later gestational stages. These results highlight a potentially complex and context-dependent role for CD248 in GDM pathophysiology.

Key words: CD248, Endosialin, Gestational Diabetes Mellitus, Inflammation, OGTT

INTRODUCTION

Gestational diabetes mellitus (GDM) is typically defined as hyperglycemia first identified during pregnancy, with blood glucose levels that are below the diagnostic thresholds for overt diabetes, whether during or outside of pregnancy. Based on the 2010 screening and diagnostic criteria established by the International Association of Diabetes and Pregnancy Study Groups (IADPSG), the global prevalence of GDM is estimated to be 17%.[1] Increased maternal glucose concentration shows a linear correlation with perinatal complications in early (before 20 weeks) and late pregnancy (24 to 28 weeks). It is also linked to long-term cardiometabolic risks for both mother and offspring.[2-4] The pathophysiology of GDM remains incompletely understood, but it is characterized by a pancreatic β-cell defect that fails to compensate for pregnancy-induced insulin resistance. This defect is influenced by factors such as genetic predisposition, epigenetic changes, placental hormones, adipokines, oxidative stress and inflammatory cytokines. Notably, GDM has been linked to chronic, low-grade inflammation and angiogenesis, suggesting parallels with other conditions like cancer and atherosclerosis, where inflammation plays a central role.[5-7] Vasculogenesis and angiogenesis are the two sequential processes involved in blood vessel formation during vascular development. In women with GDM, angiogenesis has been reported to be higher compared to those with type 1 diabetes mellitus and healthy controls.[8]

CD248, also referred to as endosialin or tumor endothelial marker 1, is a type I transmembrane glycoprotein that was initially identified on the blood vessels of various human tumors and subsequently recognized as an abnormally expressed marker of tumor endothelial cells, contributing to the reorganization of tumor blood vessels. In addition, CD248 is expressed in mesenchymal-derived cells, including pericytes, fibroblasts, vascular smooth muscle cells and osteoblasts.[9,10] CD248 plays a critical role in vascular and extracellular remodeling, partly by promoting a pronounced

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Corresponding author: Tevfik Berk Bildaci, MD
Buca Seyfi Demirsoy Eğitim ve Araştırma Hastanesi Kozağaç Mah. Özmen Cad. No:147 Buca, 35390, Izmir, Turkey
E-mail: berkbildaci@gmail.com
ORCiD: https://orcid.org/ 0000-0002-6432-6777

hypoxic response.[11] It is significantly upregulated in the context of tumor growth, inflammation and injury-induced fibrosis in various organs, such as the liver and kidney.[12,13] Global inactivation of the CD248 gene in mice reduces disease severity in various models of human diseases, including inflammatory arthritis and atherosclerosis. This reduction is characterized by decreased tissue infiltration of pro-inflammatory leukocytes and reduced circulating levels of cytokines and chemokines, such as IL-1β, CCL2 and CCL5. Moreover, the absence of CD248 has been found to alleviate inflammation and fibrosis in models of both acute and chronic liver injury, as well as renal fibrosis.[14] Elevated CD248 in early pregnancy was shown to predict development of GDM later on.[15]

We hypothesize that chronic low-grade inflammation and placental neovasculogenesis, may result in elevated levels of CD248, which could serve as a biomarker for identifying patients at increased risk of developing GDM. We aim is to explore alternative diagnostic methods for GDM aside from oral glucose tolerance test which is the current gold standard.

METHODOLOGY

This prospective case-control study was conducted at Izmir Democracy University Buca Seyfi Demirsoy Research and Training Hospital from May to October 2024.

Patients aged 18 to 49 years, with no previous history of diabetes or systemic diseases, were included in the study. Exclusion criteria included multi-gestational pregnancies, alcohol consumption and the use of any medication other than those recommended by local health authorities for pregnancy supplementation, specifically 1200 IU of vitamin D and 30 mg of iron. Blood samples were collected from participants between the 24th and 28th week of pregnancy, just before the OGTT was done. The samples were collected between 8:30 AM and 10:00 AM on the day of the procedure while patients were in a fasting state. Blood samples were immediately stored at 4°C and left to clot for 4 to 6 hours. Following the clotting process, serum samples were centrifuged at 2000G for 10 minutes within a temperature range of 2 to 8°C. The resulting supernatant was portioned into 1 ml aliquots, transferred into cryotubes, and promptly frozen at -40°C for subsequent analysis. This freezing method and the selected temperature, which was not -80°C, were chosen as the only feasible option given the limited resources of our hospital. Before analysis, the samples were brought to room temperature (25°C) for thawing. Notably, the researcher responsible for the laboratory procedures was unaware of the patients' gestational diabetes status.

GDM was confirmed with a 75g OGTT. The diagnosis of GDM was made if any of the following conditions were met: fasting glucose levels of 92 mg/dL (5.1 mmol/L) or higher, 1-hour glucose levels of 180 mg/dL (10.0 mmol/L) or higher, or 2-hour glucose levels of 153 mg/dL (8.5 mmol/L) or higher. Initially, patients with GDM were treated with dietary therapy whenever feasible. If dietary measures failed to meet the target glucose levels (fasting ≤95 mg/dL, 1 hour postprandial ≤140 mg/dL, 2 hours postprandial ≤120 mg/dL), insulin therapy was started with guidance from an endocrinologist.

The analysis was done using enzyme-linked immunosorbent assay (ELISA) kits specifically designed for CD248 (Ref: DZE201128848-LOT 202409, Shanghai Sunred Biological Technology Co.). To ensure precision and reliability in the measurements, the inter-assay and intra-assay coefficients of variation (CV) for CD248 were both determined to be less than 10%.

Ethics and statistical analysis

A total of 169 patients voluntarily agreed to participate in the study after providing informed consent. Ethical approval for the research was obtained from the Buca Seyfi Demirsoy Training and Research Hospital Ethics Committee under reference number 2024/275. Statistical analyses were conducted using the Statistical Package for Social Sciences (SPSS) version 23.0 (IBM Co., Chicago, IL). Kolmogorov-Smirnov analysis was used to assess data distribution. The independent sample t-test was applied for normally distributed data, while the Mann-Whitney U test was used for non-normally distributed data. Chi-square tests, Pearson correlation tests and linear regression analyses were also conducted as appropriate. A p-value of <0.05 was considered statistically significant.

RESULTS

Since a double-blinded method was used for patient selection, where neither the patients nor the researchers knew the OGTT results before sample collection, the groups were not matched in numbers. Thirty-two out of 169 patients who completed glucose testing were diagnosed with GDM. A post hoc analysis yielded a power of 0.81, with a significance level set at 0.05 and an effect size of 0.5. The incidence of GDM was 18.9%. The mean age of patients with GDM was 28.53 ± 6.05 years, while those without GDM was 28.74 ± 5.12 years (p = 0.204). Additional patient characteristics are detailed in Table 1.

It was determined that CD248 data does not follow a normal distribution (p = 0.000). Neither log nor square root transformation resulted in a normally distributed CD248 dataset; therefore, further analyses were conducted using non-parametric tests. The mean CD248 level was 8.15 ± 10.16 ng/mL in patients with GDM and 11.42 ± 15.44 ng/mL in patients without GDM. When comparing CD248 levels between the GDM and non-GDM groups, no significant difference was observed between the two groups (p = 0.084). A significant correlation was observed between BMI and hour-to-hour glucose values on the OGTT, while CD248 levels showed no correlation with glucose values on the OGTT. Further details are provided in Table 2.

Table 1. Characteristics of patients and comparison based on GDM status

		Patients with GDM (n = 32)	Control group (n = 137)	Significance (*p*)
Age		28.53 ± 6.05	28.74 ± 5.12	0.844
Gravida		2.47 ± 1.59	2.45 ± 1.55	0.958
Parity		1.00 ± 1.02	1.18 ± 1.28	0.454
Mean Gestational Week		25.94 ± 1.34	25.72 ± 1.59	0.464
Body Mass Index (BMI)		30.23 ± 5.80	27.44 ± 4.47	**0.003**
Smoking	Present	4 (2.4%)	28 (16.6%)	0.172
	Absent	30 (17.8%)	107 (63.3%)	

Student's T-test and Chi-square test were used where appropriate. Significant values are presented in bold.

Table 2. Correlations between CD248 levels, BMI and glucose levels on OGTT

		Fasting glucose	1-hour glucose	2-hour glucose
CD248	Correlation (r)	-0.091	-0.050	-0.064
	Significance (p)	0.242	0.515	0.408
BMI	Correlation (r)	0.320	0.281	0.104
	Significance (p)	**0.000**	**0.000**	0.179

Pearson correlation analysis performed. Significant values are presented in bold.

None of the variables—age, gravidity, parity, BMI, gestational week and smoking status—had a significant confounding effect on the relationship between GDM status and CD248 levels (p = 0.444, 0.589, 0.354, 0.721, 0.211, and 0.437, respectively).

DISCUSSION

This study evaluated the diagnostic potential of plasma CD248 levels in a cohort of 169 pregnant patients undergoing an OGTT. However, plasma CD248 levels did not exhibit a significant association with GDM status.

In a previous study, Wei et al., reported that elevated CD248 levels in early pregnancy were associated with an increased likelihood of developing GDM during gestational ages characterized by peak insulin resistance, with a reported range of 5–10 ng/mL for all patients, regardless of GDM status.[15] In contrast, our study found that CD248 levels did not vary significantly in patients at 24 to 28 weeks gestational age and, notably, were lower in patients with GDM than those without. As the first study to evaluate CD248 levels specifically during the 24th–28th week of gestation, we propose that the previously observed elevation in early pregnancy may reflect increased placental inflammation and angiogenesis, which does not appear to continue alongside the rising insulin resistance later in pregnancy.

In murine models, CD248 knockout has been linked to enhanced insulin sensitivity, suggesting that CD248 may impede insulin signaling pathways.[16] Conversely, our study observed that elevated serum CD248 levels in pregnant women correlated with improved insulin sensitivity. This discrepancy may be attributed to the complex and context-dependent roles of CD248 in humans, particularly during pregnancy, where it might interact with other physiological factors influencing insulin sensitivity.

BMI is widely recognized as a key factor influencing glucose metabolism and insulin resistance, particularly in the context of GDM. Our findings highlight the relationship between BMI and glucose levels at different time points during OGTT, and its association with CD248 levels. This suggests that higher BMI may contribute to impaired glucose regulation, especially in the early phases of the test. This aligns with existing evidence linking increased adiposity to reduced insulin sensitivity, often resulting in elevated postprandial glucose levels. Additionally, CD248 is known to play a role in adipose tissue physiology, further supporting its potential involvement in metabolic regulation. For instance, a study by Zhang et al. demonstrated that CD248 is abundantly expressed in mature white adipocytes and significantly correlates with BMI, suggesting its involvement in adipocyte function and obesity-related processes.[17] Additionally, Patrick et al. reported that CD248 influences lipid metabolism in adipose tissue, further supporting its association with BMI and metabolic regulation.[18] These studies corroborate our observations, underscoring the relevance of CD248 in adipose tissue dynamics and its potential impact on metabolic health.

CONCLUSION

This study is the first to investigate CD248 levels during the 24th–28th week of gestation and their association with GDM status. While our findings did not reveal a significant relationship between elevated CD248 levels and the development of GDM, they contribute valuable insights to a field with limited existing research. The lack of association highlights the need for further studies with larger, well-matched cohorts and optimal sample handling to better understand the role of CD248 in pregnancy-related metabolic changes. These results underscore the complexity of GDM pathophysiology and the potential for alternative biomarkers to improve diagnosis and management.

Limitations

A limitation of our study is the unequal distribution of case and control subject numbers, which was implemented to ensure researcher blinding; however, our findings on serum CD248 levels are consistent with previous literature. Additionally, preserving serum samples under optimal conditions, such as storage at -80°C, could yield more precise measurements and further validate the results.

Conflict of Interest Statement
The authors declare no conflicts of interest.

Statement of Authorship
All authors certified fulfillment of ICMJE authorship criteria.

CRediT Author Statement
TBB: Conceptualization, Investigation, Resources, Data Curation, Writing – original draft preparation; **CA:** Validation, Investigation, Data Curation; **UA:** Software, Formal analysis; **HAA:** Formal analysis, Project administration; SE: Methodology, Writing – review and editing, Supervision.

Data Availability Statement
Data are available from the corresponding author upon reasonable request.

Author Disclosure
The authors declared no conflict of interest.

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