Experimental
&
Clinical Article

Investigation of Serum Cartonectin Concentrations in Pregnant Women with Gestational Diabetes Mellitus; a Prospective Non-Interventional Cohort Study

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ABSTRACT

OBJECTIVE: To investigate serum cartonectin concentrations in pregnant women diagnosed with Gestational Diabetes Mellitus (GDM).

STUDY DESIGN: This prospective non-interventional cohort study was conducted on 176 pregnant women. The study group consisted of 88 pregnant women diagnosed with GDM, and the control group consisted of 88 pregnant women with normal 75-g OGTT results. First, the study and control groups, and then the subgroups were compared in terms of serum cartonectin concentrations.

RESULTS: The study and control groups were similar in terms of BMI and gestational age at blood sampling (p=0.599, p=0.854). The study and control groups were similar in terms of median serum cartonectin concentrations (6.28 ng/ml and 7.13 ng/ml, respectively, p=0.165). In the subgroup analysis, the normal weight control group, overweight control group, normal weight study group, and overweight study group were compared in terms of serum cartonectin concentrations. The lowest median cartonectin concentration was detected in the overweight study group, followed by the overweight control group, normal weight study group, and normal weight control group (5.8 ng/ml, 6.5 ng/ml, 6.9 ng/ml, and 8.2 ng/ml, respectively, p=0.235).

CONCLUSION: Serum cartonectin concentrations were found to be similar in the GDM and control groups. However, the number of participants in this study is limited to draw a definitive conclusion. Many studies with larger series are needed to reveal whether serum cartonectin is involved in the pathophysiology of GDM.

Keywords: Cartonectin, Gestational diabetes mellitus, Oral glucose tolerance test, Pregnancy

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Introduction

Gestational diabetes Mellitus (GDM) traditionally refers to abnormal glucose tolerance that begins or is first detected during pregnancy (1). Normal pregnancy is associated with marked changes in glucose metabolism (2). Animal studies have shown a 3- to 4-fold increase in β-cell mass during pregnancy, mediated by hypertrophy, hyperplasia, and decreased apoptosis (3). This may explain a 200% to 250% increase in insulin secretion relative to baseline to maintain euglycemia during pregnancy (4-6).

There is a progressive increase in insulin resistance during pregnancy due to the circulation of placenta-associated hormones such as growth hormone, corticotropin-releasing hormone, human placental lactogen, prolactin, estrogen, and progesterone (1). In addition, excess weight gained in early pregnancy and increased fat tissue contribute to insulin resistance in the later stages of pregnancy (7). It has also been shown that changes in the expression of some genes may affect the development of GDM (8). As a result, GDM occurs in some pregnant women with a possible genetic and epigenetic background, the effect of placental hormones, and the contribution of nutrition (1).

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Recently, cartonectin also known as C1q/TNF-related protein 3 (CTRP3), cartducin, or collagenous repeat-containing sequence of the 26-kDa protein (CORS-26) was reported to be a novel adipokine with a glucose-lowering effect by suppressing hepatic gluconeogenesis (9). There are 15 different protein products (CTRP 1-15) in the CTRP family, which includes also cartonectin, and these are highly conserved throughout vertebrate evolution (10).

Cartonectin is expressed mainly in adipose tissue, but also in the kidney, testis, uterus, and bone (10). Cartonectin has been shown not only to be involved in carbohydrate metabolism but also to play a role in the immune system and cardiovascular functions (11,12). However, among all the pathophysiological events, the most researched one has been the relationship of cartonectin with glucose metabolism (10).

In a study published by Peterson et al. in 2010, the role of cartonectin in glucose metabolism was evaluated in detail (9). They showed that serum cartonectin concentrations are inversely correlated with leptin levels, cartonectin increases with fasting and decreases in diet-induced obese mice with high leptin levels. Administration of recombinant cartonectin reduced glucose levels in normal and insulin-resistant leptin-deficient obese mice without changing insulin or adiponectin levels. The glucose-lowering effect in mice was linked to the activation of the Akt signaling pathway in the liver and suppression of hepatic gluconeogenic gene expression. As in mice, recombinant human cartonectin has also been shown to reduce glucose output in hepatocytes by suppressing gluconeogenic enzyme expression (9).

In 2014, Ban et al. published their study investigating the serum cartonectin concentrations of newly diagnosed Type 2 Diabetes Mellitus (T2DM) patients (13). Serum cartonectin concentrations were found to be significantly lower in patients with T2DM than in controls. In addition, serum cartonectin showed a significantly negative correlation with glucose and CRP and a significant positive correlation with leptin. They suggested that serum cartonectin may serve as a new biomarker for early diagnosis of T2DM (13).

In light of the information provided above, we aimed to evaluate circulating cartonectin concentrations in pregnant women with GDM as well as age- and BMI-matched control subjects. Accordingly, we hypothesize that serum cartonectin concentration will be lower in the GDM group than in the control group.

Material and method

This prospective non-interventional cohort study was conducted with 176 pregnant women aged between 18 and 39 years who applied to the Umraniye Training and Research Hospital, Department of Obstetrics and Gynecology between May 2023 and July 2023. While the study group consisted of 88 pregnant women diagnosed with GDM, the control group consisted of 88 healthy pregnant women with normal 75-g oral glucose tolerance test (OGTT) results. The study and control groups were matched in terms of age, body mass index (BMI), and gestational week at blood sampling. Participants' age, BMI, obstetric histories, laboratory and ultrasound findings, and perinatal outcomes were recorded.

Smokers, multiple pregnancies, and those who conceive with the in vitro fertilization method were not included in the study. Those with any pregestational disease or a history of GDM in previous pregnancies were not included in the study. Those who developed any pregnancy-related disease other than GDM in the study group and those who developed any pregnancy-related disease in the control group were not included in the study.

75 g OGTT was applied to all participants between 24 and 28 weeks of gestation. OGTT results were evaluated according to the criteria recommended by the IADPSG. Accordingly, GDM was diagnosed when a single threshold value was met or exceeded; fasting value, 92 mg/dL; 1-hour value, 180 mg/dL; 2-hour value, 153 mg/dL (14).

Considering the relationship between cartonectin and BMI, we divided the study and control groups into two subgroups according to the participants' BMI. Those with a BMI below 25 kg/m^2 were classified as normal weight, and those with a BMI of 25 kg/m^2 and above were classified as overweight. First, the study group and the control group, and then the four subgroups were compared in terms of serum cartonectin concentrations.

To investigate cartonectin concentrations, blood samples were taken from the participants' antecubital vein into laboratory tubes using a 20-gauge catheter after an 8-hour fast in the morning. The blood samples taken were kept at room temperature for 1 hour and then centrifuged at 2000 rpm for 10 minutes. After centrifugation, the remaining serum in the upper part of the biochemistry tube was transferred to the Eppendorf tube and stored at -80 degrees. Cartonectin concentrations were studied with the Human Cartonectin/CTRP3/COR-26 ELISA Kit (Sunredbio, Room212, MeiLan Building, No.6497 HuTai Road, Baoshan District, Shanghai, China. Catalog No: 201-12-6501) using the enzyme-linked immunosorbent assay method. The cartonectin kits used in the study were run on the Diagnostic Automation Inc. Device (Model: ELX800DA, 23961 Craftsman Rd, Suite D/E Calabasas, CA 91302, USA) with Kc Junior software. For the Human Cartonectin ELISA Kit used in the study, a measurement value of 0.2 ng/mL - 50 ng/ml and a sensitivity of 0.179 ng/mL was determined.

Istanbul Umraniye Training and Research Hospital Local Ethics Committee approved this study (Ethics Committee Approval Number: B.10.1.TKH.4.34.H.GP.0.01/132, Date: 25/04/2023). The study protocol was maintained by the

Declaration of Helsinki. Informed and written consent was obtained from all participants.

Statistical analysis

Power analysis of the study was performed using the G*Power (v3.1.9) program to determine sample sizes. The power of the study is expressed as 1-β (β=Type II error probability) and has 80% power. Assuming that the effect size (d=0.5) will be observed according to the effect size coefficients determined by Cohen, it was determined that the required number of participants should be 128 (64 for the study group and 64 for the control group). Considering that there would be dropouts during the study, 88 participants were included in each group. Since there was no dropout, the study was conducted on 176 participants, 88 in the study group and 88 in the control group.

Statistical analysis was performed with the Statistical Package for the Social Sciences (SPSS) version 25.0. The Kolmogorov-Smirnov test was used to determine whether the data were distributed normally or not. Descriptive statistical methods (mean, standard deviation, median, Min, Max, frequency, rate) were used while evaluating the study data. An Independent t-test was used for the comparison of two groups showing parametric distribution, and the Mann-Whitney U test was used for the comparison of two groups showing non-parametric distribution. One Way ANOVA test was used for the comparison of more than two groups showing parametric distribution, and the Kruskal Wallis test was used for the comparison of more than two groups showing non-parametric distribution. Correlation analysis was used to determine the relationship between numerical data. The chi-square test was used in the analysis of categorical data. Statistical significance was accepted at $p<0.05$ for all values.

Results

In this study, 88 pregnant women with GDM and 88 pregnant women with normal 75-g OGTT results were compared in terms of serum cartonectin concentrations.

Both groups were similar in terms of age, pre-pregnancy BMI, BMI at blood sampling, gestational week at blood sampling, gravida, and parity ($p>0.05$, for all) (Table I).

Fasting, 1st hour and 2nd-hour glucose levels in the OGTT and HbA1c level were significantly higher in the study group than in the control group ($p<0.001$, for each). The median serum cartonectin concentration was found to be 6.28 ng/ml in the study group, while it was determined as 7.13 ng/ml in the control group ($p=0.165$) (Table II).

Table I: *Demographic characteristics of control and study groups*

		Control group (n=88)	Study group (n=88)	
		Median (Min-Max)	Median (Min-Max)	p
Age (years)		28 (18-39)	30 (18-39)	0.097*
Pre-pregnancy BMI (kg/m^2)		23.3 (17.3-26.3)	23.6 (18.2-29.5)	0.482*
BMI at blood sampling (kg/m^2)		25.1 (19.4-29.7)	25 (19.3-29.9)	0.599*
Gestational week at blood sampling		26 (24-28)	25 (24-28)	0.854*
Gravida		2 (1-8)	2 (1-7)	0.748*
		n (%)	n (%)	
Parity	Nulliparous	49 (55.7)	57 (64.8)	0.218***
	Multiparous	39 (44.3)	31 (35.2)	

** Mann-Whitney U Test; ** Independent-T test; ***Chi-Square test; BMI: Body mass index*

Table II: *Comparison of control and study groups in terms of laboratory findings*

	Control group (n=88)	Study group (n=88)	
	Mean ± SD Median (Min-Max)	Mean ± SD Median (Min-Max)	p
75 g OGTT fasting blood glucose level (mg/dL)	82 (69-92)	90 (70-138)	<0.001*
75 g OGTT 1st-hour blood glucose level (mg/dL)	119 (79-177)	180.5 (97-284)	<0.001*
75 g OGTT 2nd-hour blood glucose level (mg/dL)	102 (47-142)	158 (72-255)	<0.001*
HbA1c (%)	4.8±0.2	5.1±0.3	<0.001**
Serum cartonectin (ng/mL)	7.13 (0.88-50)	6.28 (2.44-50)	0.165*

** Mann-Whitney U test; ** Independent T-test; ***Chi-Square test; OGTT: Oral glucose tolerance test*

The study and the control groups were divided into two subgroups according to the BMI of the participants; normal weight control group, overweight control group, normal weight study group, and overweight study group. Gestational week at blood sampling and the serum cartonectin concentrations were similar in these four groups (p=0.803 and p=0.235, respectively). The lowest median cartonectin concentration was detected in the overweight study group, followed by the overweight control group, normal weight study group, and normal weight control group (5.8 ng/ml, 6.5 ng/ml, 6.9 ng/ml, and 8.2 ng/ml, respectively) (Table III).

Seventy-three pregnant women in the study group followed a diet for blood glucose regulation until delivery. The remaining 15 pregnant women had to receive insulin treatment.

Spearman correlation analysis was performed to evaluate the relationship between GDM-related parameters and cartonectin. There was a significant negative relationship detected between serum cartonectin and maternal age (r=-0.340, p<0.001), gravida (r=-0.270, p<0.001), and 75-g OGTT 1st-hour blood glucose level (r=-0.175, p=0.020). No significant relationship was found between serum cartonectin and pre-pregnancy BMI, BMI at blood sampling, 75-g OGTT fasting blood glucose level, 75-g OGTT 2nd-hour blood glucose level, and HbA1c level (Table IV).

Discussion

In this study, serum cartonectin concentrations were investigated in pregnant women with and without GDM. Unlike our hypothesis at the beginning of the study, we found serum cartonectin concentrations to be similar in the group with and without GDM.

Increasing evidence suggests that, in addition to the known classical pathways in the pathophysiology, adipokines also contribute to the development of T2DM (15,16). Similarly, after it was determined that cartonectin is an adipokine that suppresses gluconeogenesis in hepatocytes, many studies evaluating the relationship between cartonectin and T2DM have been reported. Following conflicting results reported in publications, a meta-analysis of studies evaluating serum cartonectin concentrations in patients with T2DM was published in 2020. According to this meta-analysis, which included 12

Table III: *Comparison of the control group with normal weight, control group with overweight, study group with normal weight, and study group with overweight in terms of serum cartonectin concentrations*

	Control group Normal weight1 (n=44)	Control group Overweight2 (n=44)	Study group normal weight3 (n=44)	Study group Overweight4 (n=44)	p	Post Hoc
	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)	Median (Min-Max)		
BMI at blood sampling (kg/m²)	23.3 (19.4-24.9)	27.8 (25.3-29.7)	23.8 (19.3-24.9)	27.5 (25.2-29.9)	0.000	2>1 (<0.001) 2>3 (<0.001) 4>1 (<0.001) 4>3 (<0.001)
Gestational week at blood sampling	26 (24-28)	26 (24-28)	27 (24-28)	26 (24-28)	0.803	
Serum cartonectin (ng/mL)	8.2 (1.20-50)	6.5 (0.88-50)	6.9 (3.43-40.09)	5.8 (2.44-50)	0.235	

Kruskal Wallis Test; BMI: Body mass index

Table IV: *Correlation between serum cartonectin concentrations and GDM-related parameters*

	r	p
Age (Years)	-0.340	<0.001
Pre-pregnancy BMI (kg/m²)	-0.120	0.113
BMI at blood sampling (kg/m²)	-0.082	0.280
Gravida (n)	-0.270	<0.001
75 g OGTT fasting blood glucose level (mg/dL)	-0.112	0.137
75 g OGTT 1st-hour blood glucose level (mg/dL)	-0.175	0.020
75 g OGTT 2nd-hour blood glucose level (mg/dL)	-0.125	0,098
HbA1c (%)	-0.131	0.083

Spearman Correlation; BMI: Body mass index; OGTT: Oral glucose tolerance test

studies, circulating cartonectin concentrations were negatively associated with T2DM status (17).

In another review published in 2019, it was stated that the hypoglycemic effect of cartonectin may not only suppress hepatic gluconeogenesis but also have a hypoglycemic effect in different pathways. Some of those; improving beta cell function, inducing Akt/PKB signaling pathways leading to more insulin sensitivity, increasing Glut4 and protein kinase mRNA expression, modulating other adipokines, and correction of serum lipid profile (18).

Few studies evaluating the relationship between serum carotectin and GDM have also been reported in the literature. In this context, the first study was published by Li et al. in 2017 (19). In this study, serum cartonectin concentration in the GDM group was found to be significantly lower than in the group with normal glucose tolerance (NGT). In the subgroup analysis performed according to BMI, the lowest serum cartonectin concentration was detected in the overweight GDM group. This was followed by the normal-weight GDM group, the overweight NGT group, and the normal-weight NGT group, respectively. Also, a significant and negative relationship was detected between cartonectin and pre-pregnancy BMI, fasting plasma glucose, 75 g OGTT 1st hour plasma glucose, 75 g OGTT 2nd hour plasma glucose, and homeostasis model assessment of insulin resistance (HOMA-IR) levels, while no relationship was found between gestational age, parity, and BMI increase during pregnancy (19). In another study by Xia et al., serum cartonectin concentration in the GDM group was determined to be lower than in the control group. Pearson's correlation analysis showed that serum cartonectin was negatively correlated with fasting plasma glucose, fasting insulin, and HOMA-IR (20). In a study published by Fadaei et al. in 2023, it was determined that serum cartonectin concentration was lower in the GDM group than in the control group. A significant relationship was shown between serum cartonectin concentrations and HOMA-IR, BMI, and triglyceride levels in the GDM group (21). Unlike these studies, we found serum cartonectin concentrations to be similar in the study and control groups. While we could only show a significant negative relationship between serum cartonectin and age, gravida, and 75 g OGTT 1st-hour glucose level, we could not show a significant relationship between serum cartonectin and BMI before pregnancy or at the time of blood sampling.

In 2020, another study evaluating serum cartonectin concentration in GDM was published by Geca et al (22). In this study, the mean serum cartonectin concentration was found to be significantly higher in the GDM group than in the non-GDM control group. They divided the GDM group into two groups, the group that only dieted and the group that used insulin for blood glucose regulation, and compared them with the control group. The highest median serum cartonectin concentration was detected in the GDM group using insulin, followed by the GDM group that only dieted and the control group. (22). Unlike this study, we found serum cartonectin concentrations to be similar in the study group and the control group.

This single-center study has some limitations. The small number of participants and the fact that the serum cartonectin concentrations of the participants were evaluated only once are important limitations. Not knowing the changes in serum cartonectin concentrations throughout normal pregnancies and not evaluating the changes in serum cartonectin concentrations after blood glucose regulation in pregnant women with GDM are also important limiting factors.

In conclusion, in this study, serum cartonectin concentrations were found to be similar in the group with and without GDM. It has been clearly shown in the literature that low serum cartonectin concentrations are associated with T2DM. However, the number of participants in this study is limited to state a similar relationship in GDM. Additionally, conflicting results have been reported in previous studies. Therefore, we think that more studies with large series are needed to reveal the relationship between serum cartonectin concentrations and GDM.

Declarations

Ethics approval and consent to participate: All participants signed informed written consent before being enrolled in the study. The study was reviewed and approved by the ethics committee of Istanbul Umraniye Training and Research Hospital Local Ethics Committee (EEthics Committee Approval Number: B.10.1.TKH.4.34.H.GP.0.01/132, Date: 25/04/2023). All procedures were performed according to the Declaration of Helsinki.

Availability of data and materials: The data supporting this study is available through the corresponding author upon reasonable request.

Competing interests: The authors declare that they have no competing interests.

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Authors' contributions: Onur Gebes is responsible for software, validation, formal analysis, and investigation. Ibrahim Kale is responsible for conceptualization, methodology, and writing the original draft. Tuba Beser Gebes is responsible for data curation, funding acquisition, and resources. Murat Muhcu is responsible for reviewing and editing, visualization, supervision, and project administration.

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