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Endothelium-Dependent Hemostatic Factors in Women with Previous Gestational

Gestasyonel Diyabet Öyküsü Olan Hastalarda Endotel Bağımlı Hemostatik Faktörler

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Abstract

Purpose: Women with previous gestational diabetes mellitus (pGDM) are at increased risk for developing type 2 diabetes and cardiovascular disorders. The aim of this study was to investigate the levels of endothelium-dependent hemostatic factors in women with pGDM.
Material and Method: Eighty women with pGDM and 40 healthy women with no history of pGDM were included. The levels of glucose, insulin, c-peptide, lipids, C-reactive protein (CRP), and endothelium-dependent hemostatic factors, including plasminogen activator inhibitor-1 (PAI-1), von Willebrand factor, fibrinogen, tissue factor (TF), tissue plasminogen activator, and total tissue factor pathway inhibitor (TFPI), were measured.
Results: Women with pGDM had higher levels of CRP (p<0.001), fibrinogen (p=0.001), PAI-1 (p<0.001), TF (p=0.035), and total TFPI (p=0.009) compared to controls. Circulating levels of CRP and PAI-1 were significantly elevated in women with pGDM even after adjustment of body mass index (BMI) (CRP; p=0.022, and PAI-1; p=0.039). PAI-1 levels were positively correlated with BMI (r=0.374, p<0.001), waist-hip ratio (r=0.251, p=0.006), low density lipoprotein -cholesterol (r=0.246, p=0.007), triglyceride (r=0.296, p=0.001), fasting glucose (r=0.339, p<0.001), 2-h. plasma glucose (r=0.247, p=0.007), fasting insulin (r=0.334, p<0.001) and insulin resistance index (r=0.36, p<0.001), and negatively correlated with high-density lipoproteins-cholesterol (r=-0.420, p<0.001) and quantitative insulin sensitivity check index (r=-0.323, p<0.001).
Discussion: Our study shows that women with pGDM exhibit altered levels of endothelium-dependent hemostatic factors which seem to be associated with cardiovascular risk factors.
Keywords: Previous gestational diabetes, endothelium-dependent hemostatic factors, cardiovascular risk factors

Öz

Amaç: Gestasyonel diyabet (GDM) öyküsü olan kadınlar yaşamlarının ilerleyen dönemlerinde artmış tip 2 diyabet, kardiyovasküler hastalık riski altındadır. Bu çalışmanın amacı, öyküsünde GDM olan kadınlarda endotel fonksiyonların göstergesi olan endotel bağımlı hemostatik föktörleri değerlendirmektir.
Gereç ve Yöntem: Çalışmaya seksen GDM öyküsü olan kadın ve gebeliklerinde GDM taraması normal 40 sağlıklı kadın katılmıştır. Tüm kadınların plazma glukoz, insülin, c-peptid, lipid düzeyleri, C-reaktif protein (CRP) ve endotel bağımlı hemostatik faktörler PAI-1, von Willebrand faktörü, doku faktörü (TF), plazminojen aktivatörü, doku faktörü yolu inhibitörü (TFPI) düzeyleri değerlendirildi.
Bulgular: GDM öyküsü olan kadınlarda CRP (p<0,001), fibrinogen (p=0,001), PAI-1 (p<0,001), TF (p=0,035), ve toplam TFPI (p=0,009) kontrol grubuna göre daha yüksek saptandı. Vücut kitle indeksine (VKİ) göre düzeltildiğinde de CRP ve PAI-1 GDM öyküsü olan kadınlarda yüksek bulundu (CRP: p=0,022, ve PAI-1; p=0,039). PAI-1 seviyeleri VKİ (r=0,374, p<0,001), bel/kalça oranı (r=0,251, p=0,006), düşük yoğunluklu yağ proteini-kolesterol (r=0,246, p=0,007), trigliserid (r=0,296, p=0,001), açlık glukozu (r=0,339, p<0,001), 2. saat plazma glukozu (r=0,247, p=0,007), açlık insülin (r=0,334, p<0,001) ve insülin direnci indeksi (r=0,36, p<0,001) ile pozitif ve yüksek yoğunluklu lipoproteinler-kolesterol (r=-0,420, p<0,001) ve kantitatif insülin duyarlılığı kontrol indeksi (r=-0,323, p<0,001) ile negatif kolere olduğu saptandı.
Tartışma: Çalışmamız GDM öyküsü olan kadınlardaki artmış endotel bağımlı hemostatik faktörler kardiyovasküler risk faktörleri ile ilişkili olabileceğini göstermektedir.
Anahtar kelimeler: Gestasyonel diyabet öyküsü, endotel bağımlı hemostatik föktörler, kardiyovasküler risk faktörleri

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Introduction

Previous gestational diabetes mellitus (pGDM) is associated with an increased risk for developing type 2 diabetes mellitus (DM). Previous studies have shown that women with pGDM feature cardiovascular risk markers, such as obesity, insulin resistance, subclinical inflammation, and endothelial dysfunction (1,2).

Endothelial dysfunction is a key event in the development of atherosclerosis. Researchers have studied markers of endothelial function to determine the particular risk of developing atherosclerosis in selected populations (3,4,5,6). The levels of these markers are found to be associated with early stage of atherosclerosis which was considered by non-invasive assessments, such as ultrasonography of the carotid artery, namely by measuring carotid intima media thickness, and ankle-arm index in apparently healthy people with certain cardiovascular risk factors (7,8,9). It has been shown in previous studies that fibrinolytic malfunction leads to atherosclerosis in patients with insulin-resistance. Once the coagulation system gets activated, tissue factor and factor FVIIa generate thrombin. The next step is the conversion of fibrinogen to fibrin. This is followed by adaptive mechanisms, such as plasmin-mediated fibrinolysis that is triggered by the activation of plasminogen to plasmin which is catalyzed by tissue-type plasminogen activator (t-PA). Fibrinolysis, in turn, solubilizes the fibrin structures that one can call clot lysis. This process ends up with the formation of fibrin degradation products. There are some inhibitors of this fibrinolytic process. Plasminogen activator inhibitor-1 (PAI-1) is the most significant inhibitor of this system that works by reducing the activity of fibrinolysis mainly by putting an inhibitory signal on t-PA. As a result, thrombosis is promoted by decreased fibrinolytic activity which is maintained by the suppressed activation of plasminogen caused by elevated levels of PAI-1 (10).

Previous studies have suggested that insulin resistance modulates circulating levels of the coagulation factors. It has been also shown that the levels of these markers are correlated with inflammation, as determined by the sensitive inflammatory marker C-reactive protein (CRP) (11).

In this study, we aimed to investigate the levels of endothelium-dependent hemostatic factors total tissue factor pathway inhibitor (TFPI), tissue factor (TF), von Willebrand factor (vWF), t-PA, and PAI–1 as well as the parameters of endothelial function and inflammation CRP in women with pGDM.

Materials and Methods

Ninety patients with pGDM and 40 age-matched controls were enrolled. Gestational diabetes mellitus (GDM) was diagnosed according to the modified Carpenter and Coustan criteria (12). Healthy controls were selected from hospital staff without any known diseases. Controls had a 1-hour glucose value of less than 140 mg/dL after a 50-g glucose challenge test during their pregnancy, and were defined as having normal glucose tolerance. Women with DM, thyroid dysfunction, severe chronic kidney disease or liver disease and those on chronic medication known to influence carbohydrate metabolism or hemostasis were excluded. Among 90 women with pGDM, 10 were excluded as they were diagnosed with type 2 DM after a 75-g oral glucose tolerance test (OGTT). The study was approved by the institutional Ethics Committee of Dokuz Eylül University. All subjects gave written informed consent.

All subjects were evaluated after 10 hours fasting. Weight, height, and waist circumference were measured. Height was recorded to the nearest 0.5 cm, and weight was measured to the nearest 0.1 kg. Body mass index (BMI) was calculated as weight/height^2 (kg/m^2). Girth measurements were estimated as the average of duplicate measures. Waist circumference (WC) was measured from the mid-level between the iliac crest and the lowest rib, and the hip circumference at the trochanter major level to the nearest 0.5 cm. Foot-to-foot body fat analyzer (TBF-300, Tanita Body Composition Analyzer, Germany) was used for bioelectrical impedance analysis. Total body water (TBW), fat-free mass, fat mass (FM) and fat percentage (%) were recorded. Blood was drawn between 8:00 am and 9:00 am at fasting. Blood samples were transferred into tubes containing fluoride for plasma glucose assay, buffered citrate for hemostatic markers, and tubes suitable for serum separation. Samples were centrifuged for a minimum 10 min at 3.000 g. Aliquots were frozen at -80 °C until the time of assay.

Glucose was measured by the hexokinase method (Hitachi, Tokyo, Japan). Lipids were measured by enzymatic reactions (Hitachi, Tokyo, Japan). Insulin and C-peptide were measured by a chemiluminescent immunoassay (Immulite 1000, DPC, USA). The quantitative insulin-sensitivity check index (QUICKI) (13) and homeostasis model assessment for insulin resistance (HOMA-IR) (14) were calculated as defined previously. CRP was measured by an immunoturbidimetric assay (Cobas Integra 400-Roche Diagnostics CH-4070 Basel, Switzerland). Fibrinogen and D-dimer were measured using the Clauss method (Dade Behring Diagnostics; Behring Fibrintimer, IL, US). PAI-1, TF, vWF, tPA and TFPI were measured using ELISA (American Diagnostica Inc., Stanford, CT, US).

The sample size was calculated prior to study using the Power and Precision software (version 2, 2000, Biostat, Englewood, NJ, US). Data are presented as means ± standard deviation. The Kolmogorov-Smirnov test was used for assessment of variable distribution. Continuous variables were compared by the independent t-test. Chi-square test was used for comparison of categorical variables. Correlation analysis was conducted by using Spearman's correlation coefficient. To avoid confounding factors, such as the effect of BMI on studied parameters, partial correlation analysis was performed. Statistical significance was defined as a two-sided p value of <0.05. The statistical analysis was performed by Statistical Package of Social Science (SPSS), version 15.0.

Results

The characteristics of subjects are presented in Table 1. Women with pGDM and healthy controls did not differ in means of age, postpartum duration and smoking habits. As expected, BMI, waist-hip ratio (WHR), body fat percentage and FM were higher in women with pGDM. Twenty-three (28.7%) women in the pGDM

group had impaired glucose tolerance (IGT) and twelve (15%) women in the pGDM group had hypertension. Fifty-five (68.8%) women with pGDM had a family history of DM.

Women with pGDM had higher fasting glucose, postprandial glucose, total cholesterol, LDL-cholesterol and triglyceride levels than controls. Fasting insulin and C-peptide levels and HOMA-IR scores were higher in the pGDM group. Women with pGDM had decreased HDL-cholesterol (p=0.03) and QUICKI score (Table 1).

Compared to control group, women with pGDM had higher levels of CRP, fibrinogen, PAI-1, TF, and TFPI (Table 2). After adjusting BMI, CRP (p=0.022) and PAI-1 (p=0.039) remained higher in women with pGDM. PAI-1 levels were correlated with BMI (r=0.374, p<0.001), WHR (r=0.251, p=0.006), LDL-cholesterol (r=0.246, p=0.007), triglyceride (r=0.296, p=0.001), HDL-cholesterol (r=-0.42, p<0.001), fasting glucose (r=0.339, p<0.001), 2-h. plasma glucose (r=0.247, p=0.007), insulin (r=0.334, p<0.001), HOMA-IR (r=0.36, p<0.001), QUICKI (r=-0.323, p<0.001), CRP (r=0.272, p=0.004), and TF (r=0.235, p=0.011) in the whole group.

Discussion

Increased levels of endothelium-dependent hemostatic factors may be associated with increased cardiovascular risk in women with pGDM (15,16,17,18). Increased levels of CRP, a marker of subclinical inflammation, have been reported in pregnancy complicated by GDM and also in women with pGDM (19,20,21,22).

Table 1. Clinical characteristics and metabolic parameters of women with previous gestational diabetes mellitus and healthy controls

Parameter	pGDM (n=80)	Control (n=40)	p
Age (year)	36±6	34±4	0.106
Years postpartum	3.2±4.6	4.3±3.6	0.170
BMI (kg/m^2)	28.3±6.5	22.7±2.6	<0.001
WHR	0.86±0.07	0.78±0.05	<0.001
Fat %	34.7±8.5	26.9±6.4	<0.001
Fat mass	26.3±12.0	16.5±5.6	<0.001
Smoking (packet/year)	0.9±2.2	1.2±2.5	0.543
Fasting glucose (mg/dL)	89.3±11.5	78.1±9.2	<0.001
2-hour plasma glucose (mg/dL)	115.9±30.6	82.6±14.8	<0.001
Insulin (µU/mL)	13.7±11.9	7.0±3.9	<0.001
HOMA-IR	3.1±2.6	1.3±0.8	<0.001
QUICKI	0.3±0.030	0.4±0.04	<0.001
Total cholesterol (mg/dL)	188.7±40.1	169.3±27.9	0.003
LDL cholesterol (mg/dL)	105.1±31.2	90.1±23.7	0.008
HDL cholesterol (mg/dL)	58.8±17.1	66.1±17.2	0.030
Triglycerides (mg/dL)	128.2±113.7	79.9±29.5	0.001

pGDM: Previous gestational diabetes mellitus, BMI: Body mass index, WHR: Waist-hip ratio, HOMA-IR: Homeostasis model assessment for insulin resistance, QUICKI: Quantitative insulin-sensitivity check index, LDL: Low density lipoprotein, HDL: High density lipoprotein, Data are presented as mean ± standard deviation

Exalted plasma PAI-1 level is the key feature of insulin resistance (23,24). There are numerous studies reporting elevated levels of PAI-1 in type 2 DM (25) as well as in non-diabetic overweight and obese individuals (26,27) and those with metabolic syndrome (28). Plasma concentration of PAI-1 has previously been used as a surrogate marker of endothelial damage (5,29). As previously shown, increased levels of PAI-1 in women with pGDM could result from tissue cytokine disturbances. Increased amounts of intraabdominal adipose tissue contribute directly to the pathogenesis of subclinical inflammation, insulin resistance and endothelial dysfunction (30).

Women with pGDM had insulin resistance, obesity, dyslipidemia and elevated plasma levels of endothelium-dependent hemostatic factors compared to healthy controls. A significant number of women with pGDM displayed classical features of metabolic syndrome. In the present study, we studied a group of women with pGDM, a population known to be at increased risk of developing type 2 DM (31,32).

Our data showed that levels of TFPI (another marker of endothelial disturbance) were elevated in the pGDM group. To the best of our knowledge, this is the first study showing that TFPI is increased in women with pGDM. TFPI is a vascular anticoagulant that can cause an inhibition in the tissue factor associated steps of coagulation. TFPI is mainly synthesized in the endothelial cells, but the mechanisms by which TFPI is bound to and released from the endothelial cells have not been entirely elucidated (33). It has been shown that elevated TFPI is associated with endothelial dysfunction in diabetic patients with coronary heart disease, and speculated to be an indicator of subclinical atherosclerosis (6,18,34). In a previous study, Sakkinen et al. (35) have reported that plasma TFPI activity positively correlated with subclinical atherosclerosis in people with no known disorder. Sakata et al. (8) showed that TFPI levels were associated with carotid intima media thickness, an indicator of endothelial dysfunction.

In pGDM women without any traditional cardiovascular risk factors (such as obesity, hyperlipidemia, hypertension and

Table 2. The comparison of endothelium dependent hemostatic factors and inflammatory markers in women with previous gestational diabetes mellitus and healthy controls

Parameter	pGDM (n=80)	Control (n=40)	p
CRP	3.6±3.5	1.2±1.1	<0.001
Fibrinogen	4.1±1.1	3.4±0.7	0.001
D-dimer	218.4±103.8	213.5±89.7	0.803
PAI-1	43.1±19.5	28.5±13.8	<0.001
vWF	100.4±36.3	96.7±35.6	0.596
TF	123.7±88.4	91.4±50.5	0.035
t-PA	5.8±4.5	6.4±5.8	0.554
Total TFPI	49.0±26.8	39.9±9.9	0.009

pGDM: Previous gestational diabetes mellitus, CRP: C-reactive protein, PAI-1: Plasminogen activator inhibitor type 1, vWF: von Willebrand factor, TF: Tissue factor, t-PA: Tissue plasminogen activator, TFPI: Tissue factor pathway inhibitor, Data are presented as mean ± standard deviation

impaired glucose tolerance), we found higher levels of CRP, fibrinogen, PAI-1 and TF. Our data suggests that a low-grade inflammation state and endothelial dysfunction could be present independently of other cardiovascular risk factors in women with previous GDM. This finding is in line with a study by Di Cianni et al. (20), where they found higher CRP values in pGDM women without metabolic syndrome. Our findings may be partly explained by the presence of central obesity in women with pGDM. We should note that WHR was different between the subgroup of women with pGDM, who had no traditional cardiovascular risk factor, and healthy controls. Pannacciulli et al. (36) reported that total adiposity, central fat, and insulin resistance were the main determinants of plasma PAI-1 concentrations in the presence of normal glucose tolerance, as we observed in the present study. As previously shown, increased PAI-1 expression in subjects with pGDM could result from tissue cytokine disturbances, such as elevated transforming growth factor beta-1 (TGF-β1) expression (37). TGF-β1 has been shown to be expressed in the adipose tissue, where it up-regulates the production of PAI-1 (38). Visceral adiposity is associated with insulin resistance, and it is one of the main factors contributing to the development of atherosclerosis.

Our study had several limitations. First, we did not exclude women who were at lactation period. It is not known if lactation has any effect on the levels of endothelium-dependent hemostatic factors. Second, insulin resistance was assessed by HOMA-IR in our study. No insulin clamp study was performed. Third, central obesity was evaluated by waist circumference and WHR. No imaging studies were performed.

Conclusion

Women with pGDM had increased levels of endothelium-dependent hemostatic factors which may contribute to increased cardiovascular risk. Women with pGDM had higher levels of CRP, fibrinogen, PAI-1, and TF. Our data showed that levels of TFPI (another marker of endothelial disturbance) were elevated in women with pGDM. PAI-1 levels were positively correlated with BMI, WHR, LDL-cholesterol, triglyceride, fasting glucose, 2-hour plasma glucose, fasting insulin and HOMA-IR, and negatively correlated with HD-cholesterol and QUICKI index. Even in pGDM women without any traditional cardiovascular risk factors (such as obesity, hyperlipidemia, hypertension and impaired glucose tolerance), levels of CRP, fibrinogen, PAI-1 and TF were elevated. Our data suggest that a low-grade inflammation state and endothelial dysfunction could be present independently of other cardiovascular risk factors in women with pGDM.

Ethics

Ethics Committee Approval: The study was approved by the institutional Ethics Committee of Dokuz Eylül University, Informed Consent: It was taken.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: Tevfik Demir, Barış Akıncı, Serkan Yener, Leyla Argun, Mehmet Ali Özcan, Sevinç Eraslan, Concept: Tevfik Demir, Barış Akıncı, Serkan Yener, Design: Tevfik Demir, Sevinç Eraslan, Data Collection or Processing: Tevfik Demir, Barış Akıncı, Serkan Yener, Leyla Argun, Analysis or Interpretation: Tevfik Demir, Barış Akıncı, Serkan Yener, Leyla Argun, Literature Search: Tevfik Demir, Writing: Tevfik Demir.

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