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Epicardial fat thickness in patients with gestational diabetes mellitus and its association with N-terminal pro-brain natriuretic peptide

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Abstract. – OBJECTIVE: The female population with gestational diabetes mellitus (GDM) has a postpartum profile with increased cardiovascular (CV) risk factors and heightened prospective CV risk. Epicardial fat tissue was reported to be related to cardiometabolic diseases as metabolically active adipose tissue and natriuretic peptides (NPs) have been shown to have metabolic effects. This study's aim was to determine the relationship between epicardial fat thickness (EFT) and NPs in the female population diagnosed with GDM.

PATIENTS AND METHODS: The study involved 161 pregnant women: 96 with GDM, and 65 healthy controls. GDM was diagnosed following the American Diabetes Association (2013) norms for diagnosing diabetes. All patients underwent echocardiography to measure EFT. N-terminal pro-brain natriuretic peptide (NT-proBNP) and other parameters were quantified in blood samples. The Independent Samples t-test, Pearson's correlation test, and a multivariable logistic regression analysis (LRA) were performed for statistical evaluation. A *p*-value <0.05 was considered statistically significant.

RESULTS: Fasting (91.46±14.29 mg/dl *vs.* 82.18±8.21 mg/dl) (*p*<0.001), first-hour (202.30± 21.60 mg/dl *vs.* 161.57±16.21 mg/dl) (*p*<0.001), and second-hour (176.95±20.43 mg/dl *vs.* 130.93±16.95 mg/dl) glucose levels (*p*<0.001), fasting insulin level (14.54±3.50 mUL/mL *vs.* 11.51±2.04 mUL/mL; *p*<0.001), and Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) value (3.28±0.99 *vs.* 2.31±0.45; *p*<0.0001) in GDM Group were significantly higher than Control Group. The GDM Group also had significantly increased EFT values compared to the Control Group (4.74±0.65 mm *vs.* 3.77±0.66 mm; *p*<0.0001), whereas NT-proBNP levels of diabetic women were considerably lower compared to controls (21.59±19.86 pg/ml *vs.* 39.74±33.96 pg/ml; *p*<0.0001). In addition, EFT thickness and the NT-proBNP level were determined to be significantly negatively correlated (r=-32, *p*<0.0001).

CONCLUSIONS: EFT evaluation might play a prognostic role in detecting cardiometabolic risk associated with potential disorders such as GDM. This study showed a potential interplay between epicardial adipose tissue and NPs secreted by cardiomyocytes and practical effects on fat metabolism in GDM subjects.

Key Words:
Gestational diabetes mellitus, Epicardial fat thickness, N-terminal pro-brain natriuretic peptide.

Introduction

Gestational diabetes mellitus (GDM) is described as impaired glucose tolerance in pregnancy, naturally improving after delivery or by the end of the postpartum period. GDM's prevalence is approximately 4% in all pregnancies. Mothers who have GDM encounter an elevated risk of pregnancy-related complications and a higher risk for various medical conditions much later than its termination. For example, GDM considerably elevates a mother's risk for Type-2 diabetes mellitus (DM) and cardiovascular (CV) disorders in the puerperium[1].

The epicardial adipose tissue (EAT) is the fatty tissue encircling the coronary arteries and is basically visceral fat deposition between the pericardium and myocardium[2]. Contemporary evidence has implied that EAT might energetically contribute to the pathogenesis of athero-thrombotic disorders in coronary arteries[3,4]. Known to have a shared embryologic origination with intraabdominal fat tissue, EAT is physiologically active[5,6]. A study conducted in Turkey by Nar et al[7] reported significantly higher EAT measurements in patients with GDM, suggesting a strong correlation between EAT and postprandial glucose levels.

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Natriuretic peptides (NPs) secreted from the cardiac ventricle as a reaction against hemodynamic changes, especially in systolic heart failure conditions, are used as solitary or combined with other biomarkers[8-10]. These peptides are also determined to exert various metabolic effects, as their increased amounts are related to preventing insulin resistance (IR). Conversely, their low levels are associated with IR, diabetes mellitus (DM), and high low-density lipoprotein cholesterol levels[11-13]. Several recent studies[14,15] have reported that the N-terminal pro-brain natriuretic peptide (NT-proBNP) level was significantly lower in GDM cases than in controls.

Our working hypothesis was that EAT, an index for heart adiposis measured with echocardiography, is associated with NT-proBNP level in circulation and other metabolic parameters in the presence of GDM. The study was conducted to investigate the hypothesis' validity.

Patients and Methods

This prospective cross-sectional study comprised 96 non-obese pregnant women with GDM, aged between 22 years and 44 years, as the GDM group, together with 65 pregnant women with no GDM, aged between 19 years and 38 years, as the Control group, who presented to the Outpatient Clinic of Endocrinology and Metabolism Department at the Aydin State Hospital in Turkey from September 2012 to March 2013. The study fully complied with ethical rules mentioned in the Declaration of Helsinki announced by the World Medical Association and revised in 2013. The Ethics Committee of Ege University Medical Faculty approved the study's protocol (Protocol #13-2/9). Then, the study protocol was explained to every subject before the study, and written informed consent was obtained from participants prior to enrollment.

Information related to maternal age, parity, gestational age, height, pre-pregnancy body weight, reproductive medical history, and pre-pregnancy BMI was obtained from medical records. Standard methods were used for measuring maternal height and weight.

Inclusion criteria consisted of the following: GDM diagnosed in the gestation's second or third trimester, following the National Diabetes Data Group's standards, no history of pre-pregnancy diabetes, no family history implying monogenic diabetes, a body mass index (BMI)<40 kg/m^2, and no accompanying chronic, acute, or infectious systemic disorder. In addition, GDM was diagnosed following the American Diabetes Association (2013) norms for diagnosing diabetes[16]. Plasma glucose levels were measured while fasting, and one and two hours later to perform a 75-gr oral glucose tolerance test (OGTT). These measurements were made at 24 to 28 weeks of pregnancy in women with no previous diagnosis of overt diabetes. A diagnosis of GDM was made founded on only a single blood glucose level over the determined cut-off values (fasting: ≥92 mg/dl [5.1 mmol/l], one hour: ≥180 mg/dl [10.0 mmol/l], two hours: ≥153 mg/dl [8.5 mmol/l]). The control group involved pregnant women with similar clinical features, such as gestational age, except that a normal OGTT result was obtained between 24 and 26 weeks.

On the other hand, self-reporting was used to identify smoking status; active smokers and those with pre-pregnancy smoking history were excluded.

All patients underwent echocardiography to measure EFT. Fasting, first-hour, and second-hour blood glucose levels, Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) values, and N-terminal pro-brain natriuretic peptide (NT-proBNP) levels were quantified in blood samples.

Blood Collection/Measurements

For biochemical analysis, venous samples were obtained at the time of participation in the study. First, the blood was centrifuged and distributed into aliquots. Then, they were maintained at 4°C until measured. NT-proBNP's plasma level was assessed with electrochemiluminescence immunoassay (ECLIA) with a Roche Elecsys 2010 and commercial kits (Roche Diagnostics, Mannheim, Germany).

The insulin sensitivity index was determined from the OGTT result using the Homeostatic Model Assessment for Insulin Resistance (HOMA-IR) equation. HOMA is obtained by multiplying the fasting plasma glucose (FPG) and the fasting plasma insulin (FPI) and then dividing the product by the constant of 22.5 [HOMA= (FPG x FPI)/22.5][17]. Results for HOMA index <3 were regarded as normal, while results ≥3 suggested grave insulin resistance.

Managing GDM has been based on a protocol suggested by the American Diabetes Associa-

tion[16], meaning the initiation of medical nutrition treatment with a sanative goal as a capillary glucose level below 95 mg/dL for fasting and below 140 mg/dL for the one-hour postprandial timepoint. If these goals were not reached after repetitive measurements, a treatment with Neutral Protamine Hagedorn (NPH) insulin or regular insulin was started.

Echocardiographic Investigation

2-D Doppler echocardiography was performed in all cases. Echocardiography was made with an iE33 cardiac ultrasound system (Philips Healthcare, Best, The Netherlands) and 2.5-MHz to 5-MHz probes. The cases' examinations proceeded while they were placed in the left lateral decubitus position after a rest of five minutes, as advised by the American Society of Echocardiography. Echocardiographically, EAT is typically described as the comparably echo-free space between the myocardium's outer border and the pericardium's visceral level. Through three cardiac cycles, its broadness was quantified vertically on the right ventricle's free wall during end-systole. Since EAT undergoes compression during the diastole, its broadness is optimally assessed during end-systole; the ultrasound beam is orientated perpendicularly at an area on the right ventricle's free wall, getting help from the aortic annulus as an anatomic landmark. The mean value of 3 cardiac cycles obtained from every echocardiographic standpoint was calculated[18].

Statistical Analysis

Continuous data were presented as mean±SD. The Independent Samples *t*-test analyzed and compared the differences between the two groups. In addition, associations among variables were assessed with Pearson's correlation test.

Then, a multivariable logistic regression analysis (LRA) was performed to identify independent predictors of GDM and the variables' contributions to the thickness of EAT using the forward selection method and starting with the univariable evaluation.

Furthermore, the helpfulness of EFT in predicting the presence of GDM was analyzed thoroughly using receiver operating characteristics (ROC) curve analysis. The sensitivity and specificity values were presented when a significant cut-off value was observed. A p-value <0.05 was considered statistically significant.

Results

The average maternal age of diabetic women (31.96±4.71 years) was significantly higher compared to controls (28.84±4.26 years, $p<0.001$). The two groups were similar regarding blood pressure. Lipid profiles of both groups (TC, HDL-C, LDL-C, and TG levels) were also similar. On the other hand, those with GDM had a significantly higher BMI than the controls [(GDM Group - 27.56±4.65) *vs.* (Controls - 21.80±2.26); $p<0.0001$]. Fasting ($p<0.0001$), first-, second-, and third-hour glucose levels ($p<0.0001$), fasting insulin level ($p<0.0001$), and HOMA-IR ($p<0.0001$) were significantly elevated in diabetic women compared to controls. The epicardial fat thickness (EFT) of females who were diagnosed with GDM was significantly increased when compared to those without GDM [(GDM Group - 4.74±0.65 mm) *vs.* (Controls - 3.77±0.66); $p>0.001$]. In addition, the serum NT-proBNP concentration of the group with GDM was significantly lower than that of Controls [(GDM Group - 21.59±19.86 pg/ml) *vs.* (Controls - 39.74±33.96 pg/ml); $p<0.001$] (Table I).

Correlations

Positive significant correlations were present between EFT and age (r=24, $p<0.002$), 1-hour (r=46, $p<0.0001$), 2-hour (r=47, $p<0.0001$), 3-hour (r=17, $p<0.01$) glucose levels, fasting insulin level (r=21, $p<0.006$), and HOMA-IR (r=24, $p<0.002$). EFT was also correlated with BMI (r=30, $p<0.0001$). A significant negative correlation was present between EFT and the NT-proBNP level (r=-32, $p<0.0001$).

The results of the multivariable LRA revealed that 1-hour glucose, 2-hour glucose, HOMA-IR, and EFT variables were involved significantly in the model constructed. It was determined that a 1-unit increase in 1-hour glucose value increased the risk of GDM by 1.05 times (i.e., increased it by 5%) [OR (95% CI) = 1.05 (1.002, 1.1), $p=0.042$], a 1-unit increase in 2-hour glucose value increased the risk of GDM by 1.119 times (i.e., increased by 11.9%) [OR (95% CI) = 1.119 (1.051, 1.191), $p<0.001$], whereas a 1-unit increase in the HOMA-IR value increased the risk of GDM 6.648 times (i.e., 554.8%) [OR (95% CI) = 6.648 (1.377, 32,089), $p=0.018$], and a 1-unit increase in the EFT value increased the risk of GDM 9.323 times (i.e., increased by 832.3%) [OR (95% CI) = 9.323 (2.561, 33,943), $p=0.001$] (Table II).

Table I. Distribution of demographic characteristics and variable measurements in the study groups (Mean ± SD).

	GDM (n = 96)	Controls (n = 65)	p
Age (years)	31.96 ± 4.71	28.84 ± 4.26	< 0.001*
BMI (kg/m^2)	27.56 ± 4.65	21.80 ± 2.26	< 0.001*
Blood Pressure (mmHg)	116.06 ± 11.34	116.53 ± 9.25	0.791
OGTT-Blood Glucose (mg/dl)			
Fasting	91.46 ± 14.29	82.18 ± 8.21	< 0.001*
1-hour	202.30 ± 21.60	161.57 ± 16.21	< 0.001*
2-hour	176.95 ± 20.43	130.93 ± 16.95	< 0.001*
3-hour	112.40 ± 34.22	89.68 ± 18.07	< 0.001*
Fasting Insulin (mUL/mL)	14.54 ± 3.50	11.51 ± 2.04	< 0.001*
HOMA-IR	3.28 ± 0.99	2.31 ± 0.45	< 0.001*
EFT (mm)	4.74 ± 0.65	3.77 ± 0.66	< 0.001*
NT-proBNP (pg/ml)	21.59 ± 19.86	39.74 ± 33.96	< 0.001*

*$p < 0.05$ (Independent samples *t*-test); GDM: Gestational diabetes mellitus; BMI: Body mass index; OGTT: Oral glucose tolerance test; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; EFT: Epicardial fat thickness; NT-proBNP: N-terminal pro-brain natriuretic peptide.

Table II. The results of multivariable logistic regression analysis performed to identify independent predictors of GDM and the variables' contributions to EFT.

	Univariable analysis		Multivariable analysis	
	OR (95% CI)	p	OR (95% CI)	p
Age (years)	1.166 (1.08, 1.259)	< 0.001*	-	-
BMI (kg/m^2)	1.787 (1.491, 2.142)	< 0.001*	-	-
Blood pressure (mmHg)	0.996 (0.963, 1.029)	0.801	-	-
OGTT-Blood Glucose (mg/dl)				
Fasting	1.098 (1.056, 1.142)	< 0.001*	-	-
1-hour	1.143 (1.097, 1.19)	< 0.001*	1.05 (1.002, 1.1)	0.042*
2-hour	1.161 (1.108, 1.217)	< 0.001*	1.119 (1.051, 1.191)	< 0.001*
3-hour	1.03 (1.017, 1.044)	< 0.001*	-	-
Fasting insulin (mUL/mL)	1.453 (1.262, 1.673)	< 0.001*	-	-
HOMA-IR	6.836 (3.544, 13.185)	< 0.001*	6.648 (1.377, 32.089)	0.018*
EFT (mm)	16.458 (6.487, 41.753)	< 0.001*	9.323 (2.561, 33.943)	0.001*
NT-proBNP (pg/ml)	0.974 (0.961, 0.988)	< 0.001*	-	-

*$p < 0.05$ (Multivariable logistic regression analysis by the forward elimination method); GDM: Gestational diabetes mellitus; BMI: Body mass index; OGTT: Oral glucose tolerance test; HOMA-IR: Homeostatic Model Assessment for Insulin Resistance; EFT: Epicardial fat thickness; NT-proBNP: N-terminal pro-brain natriuretic peptide; OR: Odds Ratio; CI: Confidence Interval.

In the ROC curve analysis, a cut-off value of 4.05 mm for EFT was determined for GDM prediction with a sensitivity of 88% and a specificity of 73% (ROC AUC: 0.89; 95% CI: 0.798-0.916; $p<0.001$) (Figure 1).

Discussion

To our knowledge, this study was the first to determine NT-proBNP levels and EFT simultaneously at around 26 weeks of gestation. In addition, for the first time, both parameters were shown to be negatively associated with GDM. Previously, NT-proBNP level was reported to be significantly lower in insulin-dependent GDM cases, and EFT was shown to be more in pregnant women previously diagnosed with GDM than healthy pregnants[7,15,19].

Recent studies[7,19-23] determined that EFT increased in Types 1 and 2 DM and GDM cases, in whom metabolic syndrome and central obesity correlated with even more enhanced EAT. The study population with GDM had increased EFT compared to the healthy control subjects. This result might be the consequence of insulin

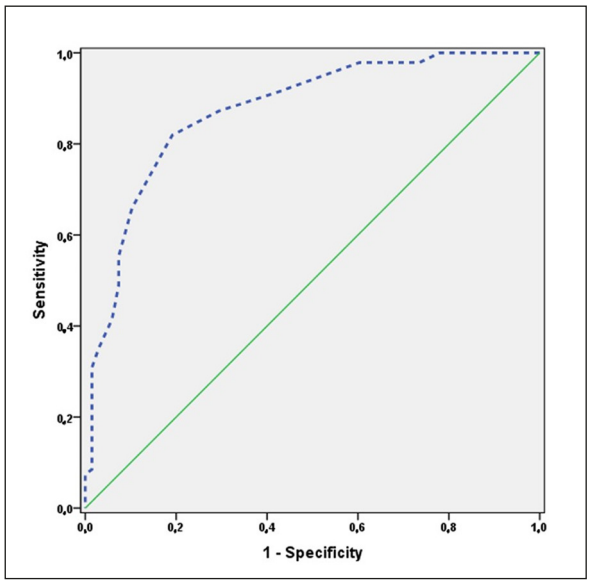

Figure 1. The Receiver Operated Characteristics (ROC) curve analysis results. The cut-off value for prediction of GDM: 4.05 mm [Sensitivity: 88%; Specificity: 73% (ROC AUC: 0.89; 95% CI: 0.798-0.916; $p < 0.001$)].

resistance, which the HOMA-IR index indicated. Our observations are consistent with previous reports[7,24,25] on childhood obesity and GDM patients.

NPs have been reported[11,12,26] to have novel physiological functions and various metabolic effects. For example, a connection between the NP system and plasma glucose and insulin levels has been observed in several studies[11,12,26]. In addition, low NP values were reported to be connected with IR and Type-2 DM, and elevated NP levels appear to protect against IR[11,12]. A study[26] on women's health indicated that persons with an NT-proBNP level close to the normal range's upper limit have a significantly lower diabetes prevalence. The cause of the relatively low NP levels of obesity is uncertain; various pathophysiological processes have been suggested[27-29], such as decreased cardiac production and release and enhanced peripheral breakdown. Our results support the hypothesis that pregnant women, even those with GDM having a higher prevalence of subclinical CV disease and left ventricular dysfunction which would increase NP levels, have low values compared with healthy controls[14,27-29]. Women's NP levels were lower than non-diabetic individuals in only a few studies[14,15].

Glucose metabolism participates in atherosclerosis's progression, and its association with EAT has been newly introduced to the medical literature. FPG and EAT, assessed with echocardiography and CT, have been reported to be strongly correlated[30]; thus, EAT appears to participate in the development of IR. Furthermore, Iacobellis et al[31] reported that EFT's cut-off point was 9.5 mm when IR was considered individually, and EFT's top values were determined in cases with exceptionally high amounts of intra-abdominal fat and IR. Our study's optimal cut-off point of 4.05 mm gave high sensitivity and specificity to discriminate the cases with GDM. A recently published study by Versteylen et al[32] has reported that EAT volume and coronary artery disease progression were correlated in patients with and without DM. Our results have confirmed the results of past studies[30-32].

Furthermore, we have also shown a relationship between the NP level and epicardial adiposity for the first time. Diabetic subjects with a decreased level of NP had increased EFT compared to healthy individuals. The effects of NP on lipid distribution were observed[33] in depots of body fat tissue irrespective of the inherent clinical state. The major lipolytic effect is minor in the gluteofemoral and abdominal subcutaneous fat regions and maximum in visceral adipose tissues[34]. In addition, since epicardial fat is suggested to be the actual cardiac visceral fat depository and originates from visceral fat, our results confirmed the effect of NPs on body fat distribution in patients with GDM. Fat accretion in the vicinity of abdominal visceral organs and the heart was related to the progression of clinical features in DM and multiple CV risk factors[35-39]. The interaction between epicardial fat and NP levels may be bidirectional. It has been considered that increased body mass causes decreased NP levels; however, weight loss has been reported to increase NP levels[40-44]. Past studies[30,45-47] have shown that EFT is related to BMI and visceral obesity, i.e., waist circumference, BMI, and visceral fat. The development of epicardial adiposity may be due to the lack of an inhibitory effect regarding NP-mediated lipolysis. The maintenance of visceral fat may result in detrimental obesity and metabolic disorders. It has been reported[11,48] that obese individuals with no cardiac failure might be susceptible to a relative NP scarcity, probably due to the ectopic fatty tissue's lipotoxic/cytokine effect on heart tissue, causing flawed NP production and secretion. Epicardial fat tissue was also reported as a resource for various bioactive molecules and is considered to interoperate locally with the coronary arterial system and myocardium through

paracrine and vasocrine releases. When pathologically increased in amount and with the addition of various concurrent metabolic or hemodynamic conditions, it acts as a proinflammatory organ with adverse lipotoxic and prothrombic effects[6]. A comprehensive study[49] showed that a GDM history seemed to act as an independent risk factor for premature atherosclerosis in females who had never been diagnosed with Type-2 DM or metabolic syndrome, irrespective of obesity before pregnancy. Increased EFT is another finding of subclinical atherosclerosis in GDM patients and might represent a potential marker of this condition[50].

Limitations

Evaluating epicardial adipose tissue is an encouraging method in clinical and investigative practice. Echocardiographic assessment is an affordable and practical process to measure EFT. However, it has various limitations, i.e., it cannot measure total EAT volume, and its utilization in obese individuals is limited[51]. On the other hand, several methods to measure the epicardial adipose tissue's volume have been reported, with CT scanning being the most precise; however, they are costly, complicated, and cumbersome, limiting their utilization routinely in diagnostic algorithms[52].

Conclusions

Our observations support the potential interplay between EAT and NPs secreted by cardiomyocytes and their practical effects on fat metabolism in GDM subjects. Our findings also provide evidence that an easy-to-perform EFT measurement might have a predictive role in detecting the initiation of cardiometabolic diseases.

Conflict of Interest

The authors declare that they have no conflict of interests.

Ethics Approval

The approval of the Ethics Committee of Ege University, Faculty of Medicine, was obtained with Protocol #13-2/9 when the study's project was submitted to Ege University, Faculty of Medicine, Scientific Research Projects Committee.

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Informed Consent

The study protocol was explained to every subject before the study. In addition, written informed consent was obtained from participants prior to enrollment.

Availability of Data and Materials

Data are available upon request from the corresponding author.

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