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Echocardiography

Does Gestational Diabetes History Increase Epicardial Fat and Carotid Intima Media Thickness?

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Background: Gestational diabetes mellitus (GDM) is defined as glucose intolerance that has begun during pregnancy. Recent studies have proven that development of atherosclerosis may be established in this population even without presence of type 2 diabetes. For assessment of atherosclerosis, epicardial fat thickness (EFT) is recently being used as a surrogate marker. In this study, we aimed to prove that women with GDM history are more inclined to have higher EFT levels than women without GDM history. Methods: Sixty-two patients with previous GDM and 33 age- and sex-matched controls were allocated. Epicardial fat thicknesses of the subjects were measured with transthorasic echocardiography and carotid intima media thickness (c-IMT) was measured with ultrasound. Insulin resistance (IR) of each subject was assessed with Homeostasis model of assessment—insulin resistance (HOMA-IR). Results: Carotid IMT and EFT were significantly higher in previous GDM group than controls. Serum gamma-glutamyl transferase (GGT), uric acid, and high-sensitivity C-reactive protein (hs-CRP) levels were also found significantly higher in the patients with previous GDM as compared to the controls. We observed that carotid IMT (β = 310, P = 0.003), total cholesterol (β = 315, P = 0.002), BMI (β = 308, P = 0.002), HbA1c (β = 227, P = 0.018), and HOMA-IR (β = 184, P = 0.049) were independently correlated with EFT. Conclusions: Although the number of patients included in this study is limited, high EFT results may indicate presence of atherosclerosis in women with previous GDM. (Echocardiography 2014;31:1182–1187)

Key words: atherosclerosis, echocardiography, epicardial fat, gestational diabetes

Gestational diabetes mellitus (GDM) is defined as glucose intolerance that has begun during pregnancy.[1] Approximately 1 in every 10 pregnancies is affected.[2] Although dysglycemia often improves with birth, patients with GDM are at lifelong, increased type 2 diabetes development risk.[3] Insulin resistance (IR) is the major cause of GDM and is also associated with cardiovascular diseases.[2] Chronic inflammation due to IR results with atherosclerosis and makes the mother a future candidate for cardiovascular diseases.[4] Recent studies have proven that development of atherosclerosis may be present even if the patient does not have type 2 diabetes.[5,6]

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Carotid intima media thickness (c-IMT) is a surrogate marker for atherosclerosis and found to be related with IR.[7] Another marker, epicardial fat thickness (EFT) is recently used for assessment of atherosclerosis, even in selected populations.[8] This novel method reflects the metabolic effects of IR on epicardial adipose tissue which has both pro-inflammatory and anti-inflammatory activities.[9] Measurement of EFT is practical, inexpensive, and efficient. Validation studies have shown correlation between EFT and c-IMT levels,[10] announcing EFT as a useful and noninvasive method to predict cardiometabolic disorders. EFT is also found to be related to IR and arterial stiffness.[11]

In our study, EFT and c-IMT were measured in women with a history of GDM and healthy controls along with other metabolic parameters. To our knowledge, there is no study investigating EFT in GDM population. We aimed to prove that women

with GDM history are more inclined to have higher EFT levels compared to women without GDM history.

Methods:

Study protocol was approved by Selcuk University Medical Faculty Ethics Committee and an informed written consent was received from each subject. Sixty-two patients with previous GDM and 33 age- and sex-matched controls were allocated from endocrinology and obstetric and gynecology outpatient clinics between 2012 and 2013. Eligible subjects were women aged between 20 and 50 years and had GDM. Exclusion criteria included presence of a valvular or congenital heart disease; cardiac rhythm other than sinus; previous myocardial infarction; hypo- or hyperthyroidism; chronic obstructive pulmonary disease or cor-ulmonale; systemic diseases (etc. hemolologic, hepatic, and renal diseases) or any disease that could impair coronary flow reserve; hypertrophic cardiomyopathy; family history of coronary artery disease; excessive alcohol consumption (>120 g/day); previous lipid metabolism disorders; history of dyslipidemia; smoking; and diabetes mellitus. Diabetes was diagnosed with these criteria: fasting plasma glucose (FPG) level measured on 3 separate days in a week found to be >126 mg/dL or impaired oral glucose tolerance test (FPG <126 mg/dL but 2 hour plasma glucose after a 75 g oral glucose challenge >140 mg/dL).

Subjects were excluded from the study if they had ST segment or T-wave changes specific for myocardial ischemia, Q-waves, and incidental left bundle branch block on ECG. The controls were women with pregnancy history those had no sign of gestational complication. Waist circumference (cm), body mass index (BMI) (kg/m^2), systolic blood pressure (BP) (mmHg), diastolic BP (mmHg), heart rate (beats/min), total cholesterol (mg/dL), high-density lipoprotein (HDL) cholesterol (mg/dL), low-density lipoprotein (LDL) cholesterol (mg/dL), triglyceride (mg/dL), γ-glutamyl transferase (IU/L), uric acid (mg/dL), high sensitive- C-reactive protein (CRP) (mg/L), fasting glucose (mg/dL), fasting insulin (μU/mL), HbA1c levels were measured. LDL was calculated using Friedelwald's Formula.[12] Blood glucose was measured by routine laboratory techniques. Plasma concentration of fasting insulin was measured using immunoturbidimetric method. The homeostasis model assessment index for insulin resistance (HOMA-IR) was calculated with the formula: fasting serum insulin (microunits/mL) $\times$ (FPG) (micromoles/L)/22.5, which has been found to be correlated with glucose clamp measurement in nondiabetic, diabetic, and hypertensive populations.[13] The coefficients of variation were <5% for every measurement.

Echocardiographic Examination:

Each subject was examined using an Acuson Sequoia C256 Echocardiography System equipped with a 3V2c broadband transducer with second harmonic capability (Acuson, Mountain View, CA, USA). Complete transthorasic M-mode, two-dimensional, and subsequent standard and pulsed tissue Doppler echocardiographic examinations were performed on each subject in the lateral decubitus position. Images were digitally stored and reviewed by a single cardiologist blinded to the patients' information to avoid interreader variability. The left ventricular ejection fraction and the left ventricular (LV) and left atrial (LA) diameters were measured on M-mode traces recorded in the parasternal long-axis view according to established standards.[14] Left ventricular mass (LVM) was calculated by using the Devereux Formula.[15] The EFT is identified as the relatively echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium; its thickness is measured perpendicularly on the free wall of the right ventricle at end-systole in 3 cardiac cycles and measured perpendicularly from the free wall of the right ventricle at end-diastole. The maximum EFT was measured from the point on the free wall of the right ventricle along the mid-line of the ultrasound beam perpendicular to the aortic annulus as a landmark.[16]

Carotid Intima Media Thickness Measurement:

A high-resolution 7.5 MHz linear array ultrasound transducer (attached to a Hitachi EUB 6500, Osaka, Japan) was used to measure c-IMT. It was measured from the far wall of the right carotid artery within 10 mm proximal to the bifurcation on two-dimensional ultrasound images. Three points were measured on 1 scan, which was synchronized with the R-wave peaks on the ECG to avoid possible errors resulting from variable arterial compliance. Mean c-IMT was calculated from 6 measurements on 2 scans.[17] To test the coefficient of repeatability of the EFT and c-IMT measurement, measurements were repeated 2 days later in 10 control subjects. Intra-observer intraclass correlation coefficient for EFT was 0.910, and 0.951 for c-IMT.

Statistical Analyses:

All analyses were conducted using SPSS 9.0 (SPSS for Windows 9.0, Chicago, IL, USA). Data were expressed as mean $\pm$ standard deviation. The 2 groups were compared using the Student's *t*-test for multiple comparisons. Chi-square statistics were used to assess differences between categorical variables. Pearson's correlation analysis was

used to test univariate relations. Prediction of independent variables was obtained by a stepwise, multivariate linear regression model including potential confounders. A P-value of <0.05 was considered significant.

Results:

Clinical Characteristics of the Study Population:

Clinical and demographic features and among the study population are presented in Table I. Mean postpartum duration of both groups were approximately 6 years. Age, postpartum duration, waist circumference, BMI, systolic and diastolic BP, heart rate, lipid profiles, fasting glucose and insulin levels, HbA1c ratio, HOMA-IR, insulin levels, and fasting glucose levels were similar between the groups. However, serum γ-glutamyl transferase, uric acid, and hs-CRP levels were significantly higher in patients with previous GDM compared to the controls.

Analyses of the Echocardiographic Measurements:

Intraventricular septum (IVS) thickness, LV posterior wall (PW) thickness, left ventricular diastolic diameter (LVDD), left ventricular systolic diameter (LVSD), LV ejection fraction (EF), left atrium diameter, and left ventricular mass index (LVMI) were similar between the previous GDM and control groups (Table II). Mitral E-wave was alike in both groups. However, mitral A-wave max, mitral E-wave deceleration time (DT) and isovolumetric relaxation time (IVRT) were significantly different between the 2 groups. Lateral Em was slightly, and lateral Am and lateral Em/Am ratio were significantly dissimilar between the groups. Carotid IMT and EFT were also significantly higher in previous GDM group than control group (Table III).

Relationship of EFT and Various Study Variables:

Epicardial fat thickness significantly and positively correlated with HbA1c ratio ($r = 243$, $P = 0.027$), hs-CRP level ($r = 433$, <0.001), HOMA-IR ($r = 385$, <0.001), total cholesterol ($r = 316$, $P = 0.002$), LDL cholesterol ($r = 318$, $P = 0.002$), waist circumference ($r = 235$, $P = 0.015$), c-IMT ($r = 531$, $P < 0.001$), and BMI ($r = 310$, $P = 0.002$). However, EFT was significantly and negatively correlated with lateral Em/Am ratio ($r = -217$, $P = 0.038$).

In stepwise multivariate linear regression analysis, when EFT was taken as the dependent variable; age, waist circumference, BMI, systolic and diastolic BP, HbA1c, hs-CRP, HOMA-IR, total and LDL cholesterol, lateral Em/Am ratio, and c-IMT were included as independent variables, we observed that c-IMT ($\beta = 310$, $P = 0.003$), total cholesterol ($\beta = 315$, $P = 0.002$), BMI ($\beta = 308$, $P = 0.002$), HbA1c ($\beta = 227$, $P = 0.018$), and HOMA-IR ($\beta = 184$, $P = 0.049$) were independently correlated with EFT.

TABLE I

Demographic and Biochemical Characteristics in Patients with GDM History and the Control Subjects

	Previous GDM (n = 62)	Healthy Controls (n = 33)	P-Value
Age (years)	33.7 ± 5.7	32.8 ± 4.9	0.39
Waist circumference (cm)	85.0 ± 5.9	84.4 ± 4.9	0.56
Body mass Index (kg/m^2)	26.9 ± 3.9	26.1 ± 2.7	0.26
Systolic BP (mmHg)	119.1 ± 9.3	115.8 ± 12.7	0.20
Diastolic BP (mmHg)	75.2 ± 4.9	73.7 ± 8.0	0.96
Heart rate (beats/min)	73.0 ± 3.5	72.7 ± 4.6	0.79
Total cholesterol (mg/dL)	188.7 ± 27.1	181.8 ± 32.1	0.30
HDL cholesterol (mg/dL)	45.9 ± 9.4	45.7 ± 10.6	0.93
LDL cholesterol (mg/dL)	118.1 ± 23.9	111.0 ± 30.3	0.26
Triglyceride (mg/dL)	130.7 ± 44.5	125.4 ± 58.4	0.65
GGT (IU/L)	22.7 ± 8.5	17.7 ± 5.1	0.013
Uric acid (mg/dL)	4.86 ± 1.36	4.17 ± 1.40	0.003
Hs-CRP (mg/L)	3.29 ± 2.06	2.23 ± 2.35	0.05
Fasting glucose (mg/dL)	92.3 ± 6.9	92.9 ± 4.5	0.64
Fasting insulin (μU/mL)	11.6 ± 6.1	10.3 ± 4.1	0.65
HbA1c (ratio)	5.11 ± 0.41	5.02 ± 0.26	0.22
HOMA-IR	2.80 ± 1.52	2.38 ± 1.02	0.34

BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; GGT = gamma-glutamyl transferase; hsCRP = high-sensitivity C-reactive protein; HOMA-IR = homeostasis model assessment index for insulin resistance; GDM = gestational diabetes mellitus.

TABLE II

Echocardiographic Findings and Standard and Tissue Doppler Parameters of the Left Ventricle

	Previous GDM (n = 62)	Healthy Controls (n = 33)	P-Value
IVS thickness (cm)	0.85 ± 0.13	0.89 ± 0.10	0.16
PW thickness (cm)	0.83 ± 0.12	0.84 ± 0.09	0.40
LVDD (cm)	4.54 ± 0.41	4.46 ± 0.33	0.31
LVSD (cm)	2.93 ± 0.72	2.81 ± 0.23	0.33
LAD (cm)	3.14 ± 0.33	3.07 ± 0.34	0.36
EF (%)	68.4 ± 4.0	67.1 ± 4.2	0.32
LVMI (g/m^2)	74.4 ± 14.5	75.5 ± 13.7	0.13
Mitral E-wave max (cm/sec)	83.7 ± 11.8	84.6 ± 8.1	0.63
Mitral A-wave max (cm/sec)	73.3 ± 12.5	62.1 ± 8.2	<0.001
Mitral E-wave-DT (ms)	195.9 ± 29.6	184.3 ± 23.0	0.04
IVRT (ms)	104.3 ± 11.6	97.1 ± 14.2	0.01
Lateral Em (cm/sec)	14.0 ± 2.7	13.0 ± 3.0	0.10
Lateral Am (cm/sec)	11.7 ± 1.9	9.6 ± 1.3	<0.001
Lateral Em/Am ratio	1.22 ± 0.23	1.35 ± 0.19	0.006
IMT (cm)	0.50 ± 0.06	0.46 ± 0.05	0.001
EFT (mm)	5.39 ± 1.35	4.32 ± 1.09	<0.001

IVS = interventricular septum; PW = posterior wall; LVDD = left ventricular diastolic diameter; LVSD = left ventricular systolic diameter; EF = ejection fraction; LVMI = left ventricular mass index; LAD = left atrium diameter; Em = early peak velocity; Am = atrial peak velocity; IMT = intima media thickness; EFT = epicardial fat thickness; IVRT = isovolumetric relaxation time; GDM = gestational diabetes mellitus; DT = deceleration time.

TABLE III

Correlation Analysis between EFT and Various Parameters

	R Value	P-Value
HbA1c ratio	0.243	0.027
Hs-CRP (mg/L)	0.433	<0.001
HOMA-IR	0.385	<0.001
Waist circumference (cm)	0.235	0.015
IMT (mm)	0.531	<0.001
BMI (kg/m^2)	0.310	0.002
Total cholesterol (mg/dL)	0.316	0.002
Triglyceride (mg/dL)	0.120	0.258
HDL cholesterol (mg/dL)	0.041	0.700
LDL cholesterol (mg/dL)	0.318	0.002
Lateral Em/Am ratio	-0.217	0.038
Systolic BP (mmHg)	0.162	0.14
Diastolic BP (mmHg)	0.079	0.47
Age (years)	0.068	0.52

BP = blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; HOMA-IR = homeostasis model assessment index for insulin resistance; IMT = intima media thickness; EFT = epicardial fat thickness; BMI = body mass index.

Discussion:

In this study, women with GDM history were found to have higher EFT levels than control subjects. This is the first study to assess atherosclerotic process in patients with GDM history using EFT. Another novel result of this study is the finding of LV diastolic dysfunction in GDM group compared to controls.

Difference between EFT values of women with GDM and healthy controls may be attributed to IR. Epicardial adipose tissue has metabolic effects and it is also affected from metabolic disorders. There are several studies with increased EFT results in patients with IR.[15,18] Most of these studies have investigated metabolic syndrome and its association with EFT. IR is a contributing factor to pathophysiological mechanism of GDM and increased EFT levels in patients with GDM can be a result of this contribution.

Previous researches have shown relation between BMI and EFT. As reported by Nakazato et al.,[19] weight loss reduces epicardial fat; therefore, it is possible to relate excess weight gain of the mother in GDM with increased EFT results. In our study, EFT values were also correlated with BMI.

Although we have not aimed to assess inflammation parameters, we found a relationship between hs-CRP levels and EFT in our study results. Inflammation in study population may be caused by induction of reactive oxygen species due to increased blood glucose concentration. Hyperglycemia is known to provoke oxidative stress and cause high levels of free radicals.[20] In our study, biochemical parameters like GGT and uric acid, related to oxidative stress, were found higher in subjects with GDM than control subjects.

With free radicals, high blood glucose levels damage cardiovascular tissues and as a result

inflammatory mediators are activated. In a cross-sectional study, 25 women with gestational diabetes history were compared with women without GDM, 1 year after their delivery and CRP and interleukin-6 levels were found higher in patients with GDM compared to normal women.[21] In Framingham study, CRP has been found linked to metabolic syndrome [22] and other studies have proven association between CRP and metabolic disorders such as obesity or hyperlipidemia.[23,24]

In recent years, inflammation has found to be linked to atherosclerosis. For assessment of atherosclerosis, new surrogate markers have been developed including c-IMT. In our study, EFT levels were also positively correlated with c-IMT levels. This relationship has been found in various studies investigating diseases that are manifestations of IR.[25] Cetin et al.[26] reported the same correlation in patients with type 2 diabetes and Colak et al.[27] found that patients with nonalcoholic fatty liver disease have high EFT and c-IMT levels independent of metabolic syndrome. These results may indicate an association between EFT and atherosclerosis.

To our knowledge, there are no long-term data revealing the rate of mortality and morbidity due to cardiovascular diseases related to high EFT levels. New studies with longer follow-up duration and larger sample size are needed to confirm the effect of high EFT levels on cardiovascular diseases.

Another novel result of our study is the finding of LV diastolic dysfunction in patients with GDM history compared to controls. This can be associated with previously discussed myocardial damage due to hyperglycemia. There are animal models supporting this postulation independent of other risk factors.[28] In one study by Park et al.,[29] after adjusting for other risk factors EFT has been found significantly associated with LV diastolic dysfunction even after adjusting for other risk factors in patients with metabolic syndrome.

Epicardial fat thickness is a recently proposed surrogate marker to evaluate atherosclerosis. In our study, our main aim was to show a relation between EFT and GDM, because if there is a possibility of foreseeing atherosclerotic process in this population, it can be useful to follow-up and if needed manage these patients with regular echocardiographic imaging. As stated before EFT measurement is easy, noninvasive, and practically can be done in every office where an echocardiographic imaging is present. It is radiation free and contrast agent is not needed for the procedure, all indicating that if validated EFT can be used in every age group and population including pregnant women without safety concerns. Women with GDM history are at lifelong risk of atherosclerosis and with an accessible method like this; early identification of patients who are prone to atherosclerosis can help creating preventive measures for this population.

There are several limitations in this study. First, it was an observational study with limited number of subjects; second, although number of cases were adequate for power analysis, because some of the risk factors were excluded, results cannot be generalized to the whole population. We also have not analyzed inflammation associated markers except hs-CRP.

Study results suggest, women with GDM history may have atherosclerosis risk even without development of type 2 diabetes. With more prospective studies validating EFT levels and investigating mortality risk and EFT levels, women with GDM may benefit from a noninvasive, easy to access, and to perform method for early manifestations of atherosclerosis.

References

1. Wendland EM, Torloni MR, Falavigna M, et al: Gestational diabetes and pregnancy outcomes–a systematic review of the World Health Organization (WHO) and the International Association of Diabetes in Pregnancy Study Groups (IADPSG) diagnostic criteria. *BMC Pregnancy Childbirth* 2012;31:23.
2. American Diabetes Association: Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2006;29(Suppl 1): S43–S48.
3. Cheung NW, Byth K: Population health significance of gestational diabetes. *Diabetes Care* 2003;26:2005–2009.
4. Shah BR, Retnakaran R, Booth GL: Increased risk of cardiovascular disease in young women following gestational diabetes mellitus. *Diabetes Care* 2008;31:1668–1669.
5. Bo S, Valpreda S, Menato G, et al: Should we consider gestational diabetes a vascular risk factor? *Atherosclerosis* 2007;194:e72–e79.
6. Tarim E, Yigit F, Kilicdag E, et al: Early onset of subclinical atherosclerosis in women with gestational diabetes mellitus. *Ultrasound Obstet Gynecol* 2006;27:177–182.
7. Marini MA, Succurro E, Castaldo E, et al: Cardiometabolic risk profiles and carotid atherosclerosis in individuals with prediabetes identified by fasting glucose, postchallenge glucose, and hemoglobin A1c criteria. *Diabetes Care* 2012;35:1144–1149.
8. Altun B, Tasolar H, Eren N, et al: Epicardial adipose tissue thickness in hemodialysis patients. *Echocardiography* 2013 Dec 24 [Epub ahead of print].
9. Tok D, Kadife I, Turak O, et al: Increased epicardial fat thickness is associated with low grade systemic inflammation in metabolic syndrome. *Turk Kardiyol Dern Ars* 2012;40:690–695.
10. Iacobellis G, Pellicelli AM, Sharma AM, et al: Relation of subepicardial adipose tissue to carotid intima-media thickness in patients with human immunodeficiency virus. *Am J Cardiol* 2007;99:1470–1472.
11. Park HE, Choi SY, Kim HS, et al: Epicardial fat reflects arterial stiffness: assessment using 256-slice multidetector coronary computed tomography and cardioankle vascular index. *J Atheroscler Thromb* 2012;19:570–576.
12. Friedewald WT, Levy RI, Fredrickson DS: Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972;18:499–502.
13. Caliskan M, Pamuk BO, Gullu H, et al: Effect of family history of type-2 diabetes on coronary flow reserve and it's

relationship with insulin resistance: An observational study. *Anadolu Kardiyol Derg* 2012;13:48–56.
14. Caliskan M, Erdogan D, Gullu H, et al: Impaired coronary microvascular and left ventricular diastolic functions in patients with ankylosing spondylitis. *Atherosclerosis* 2008;196:306–312.
15. Roman MJ, Okin PM, Kizer JR, et al: Relations of central and brachial blood pressure to left ventricular hypertrophy and geometry:The Strong Heart Study. *J Hypertens* 2010;28:384–388.
16. Iacobellis G, Ribaudo MC, Assael F, et al: Echocardiographic epicardial adipose tissue is related to anthropometric and clinical parameters of metabolic syndrome: A new indicator of cardiovascular risk. *J Clin Endocrinol Metab* 2003;88:5163–5168.
17. Maritim AC, Sanders RA, Watkins JB: Diabetes, oxidative stress, and antioxidants: A review. *J Biochem Mol Toxicol* 2003;17:24–38.
18. Aydin H, Toprak A, Deyneli O, et al: Epicardial fat tissue thickness correlates with endothelial dysfunction and other cardiovascular risk factors in patients with metabolic syndrome. *Metab Syndr Relat Disord* 2010;8: 229–234.
19. Nakazato R, Rajani R, Cheng VY, et al: Weight change modulates epicardial fat burden: A 4-year serial study with non-contrast computed tomography. *Atherosclerosis* 2012;220:139–144.
20. Paneni F, Beckman JA, Creager MA, et al: Diabetes and vascular disease: Pathophysiology, clinical consequences, and medical therapy: Part I. *Eur Heart J* 2013;34: 2436–2443.
21. Heitritter SM, Solomon CG, Mitchell GF, et al: Subclinical inflammation and vascular dysfunction in women with previous gestational diabetes mellitus. *J Clin Endocrinol Metab* 2005;90:3983–3988.
22. Rutter MK, Meigs JB, Sullivan LM, et al: C-reactive protein, the metabolic syndrome, and prediction of cardiovascular events in the Framingham Offspring Study. *Circulation* 2004;110:380–385.
23. Ukkola O, Kesäniemi YA: Leptin and high-sensitivity C-reactive protein and their interaction in the metabolic syndrome in middle-aged subjects. *Metabolism* 2007;56:1221–1227.
24. Mendall MA, Patel P, Ballam L, et al: C-reactive protein and its relation to cardiovascular risk factors: A population based cross sectional study. *BMJ* 1996;312: 1061–1065.
25. Sengul C, Cevik C, Ozveren O, et al: Echocardiographic epicardial fat thickness is associated with carotid intima-media thickness in patients with metabolic syndrome. *Echocardiography* 2011;2011:853–858.
26. Cetin M, Cakici M, Polat M, et al: Relation of epicardial fat thickness with carotid intima-media thickness in patients with type 2 diabetes mellitus *Int J Endocrinol* 2013;2013:769175.
27. Colak Y, Karabay CY, Tuncer I, et al: Relation of epicardial adipose tissue and carotid intima-media thickness in patients with nonalcoholic fatty liver disease. *Eur J Gastroenterol Hepatol* 2012;24:613–618.
28. Marsh SA, Dell'italia LJ, Chatham JC: Interaction of diet and diabetes on cardiovascular function in rats. *Am J Physiol Heart Circ Physiol.*2009;296:H282–H292.
29. Park HE, Choi SY, Kim M: Association of epicardial fat with left ventricular diastolic function in subjects with metabolic syndrome: Assessment using 2-dimensional echocardiography. *BMC Cardiovasc Disord* 2014;14:3.