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Tip 2 diyabetli hastalarda epikart yağ yastıkçığı ile endotel fonksiyon bozukluğunun ilişkisi

The relationship between epicardial adipose pad and endothelial dysfunction in patients with type 2 diabetes mellitus

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ÖZET

Amaç: Epikart yağ dokusu (EYD) kalp damar hastalığı riski ile ilişkilidir. Bu çalışmanın amacı tip 2 diabetes mellituslu (DM) hastalarda EYD kalınlığı ile endotel işlevlerinin ilişkisini araştırmaktır.

Çalışma planı: Tip 2 DM'li hastalar brakiyal arter akım aracılı dilatasyon (AAD) değerlerine göre iki gruba ayrıldı. Endotel fonksiyon bozukluğu (EFB) grubu <%7 AAD oranı <%0,7 olan 46 hastadan EFB olmayan grup ise AAD oranı >%7 olan 46 hastadan oluştu. EYD kalınlığı sağ ventrikül serbest duvarından parasternal kısa ve uzun eksen görüntülerinden ölçülerek ortalama değerleri alındı. Hastaların demografk, antropomet-rik ve laboratuvar verileri kaydedildi.

Bulgular: EYD ortalama çapları EFB grubunda 8,0±1,8 cm iken EFB olmayan grupta 6,6±1,2 cm olarak saptandı (p<0,001). HbA1C düzeyleri EFB grubunda EFB olmayan gruba göre anlamlı olarak yüksek bulundu (sırasıyla, 8,55 [7,30-9,80], 7,45 [6,50-9,30], p=0,042). Brakiyal arter AAD değişim oranı ile EYD ortalama çapı arasında istatistiksel olarak anlamlı negatif bir ilişki vardı (r=-0,437, p<0,001). Brakiyal arter AAD değişim oranı, DM süresi ve HbA1c ile zayıf negatif ilişkili bulundu (sırasıyla, r=-0,216, p=0,038, r=-0,266, p=0,010). EYD, beden kütle indeksi ve bel çevresi ile de kuvvetli pozitif bir ilişki içindeydi (sırasıyla, r=0,405, p<0,001, r=0,515, p<0,001). Nötrofl sayısı EFB olan grupta EFB olmayan gruba göre daha yüksekti. Çok değişkenli lojistik regresyon analizinde EYD kalınlığı ve HbA1c (sırasıyla, odds oranı [OO]: 1,887, %95 GA [1,298-2,743], OO: 1.485 %95 GA [1,054-2,093]) EFB'nin bağımsız belirteçleri olarak saptandı.

Sonuç: Epikart yağ dokusu kalınlığı tip 2 DM'li hastalarda EFB'yi öngörmektedir.

ABSTRACT

Objectives: Epicardial adipose tissue (EAT) has been shown to be related to cardiovascular risk. The aim of the present study was to investigate the relationship betvveen EAT and endothelial function in patients with type 2 diabetes mellitus (DM).

Study design: Type 2 DM patients were divided into two groups according to their brachial flow-mediated dilatation (FMD) values. The endothelial dysfunction (ED) group consisted of 46 patients with FMD change of <7%, while 46 patients with FMD change of >7% were accepted as the non-ED group. EAT thickness was measured on the right ventricular free wall from the transthoracic echocardiographic parasternal long- and short-axis views. The patients' demographic, anthropometric and laboratory fndings were recorded.

Results: The mean diameter of EAT was 8.0±1.8 cm in the ED and 6.6±1.2 cm in the non-ED groups (p<0.001). HbA1c levels were signifcantly higher in the ED group than non-ED group (8.55 [7.30-9.80], 7.45 [6.50-9.30], respectively; p=0.042). There was a negative correlation betvveen FMD values and EAT (r=-0.437, p<0.001). FMD values vvere weakly and negatively correlated vvith duration of DM and HbA1c levels (r=-0.216, p=0.038; r=-0.266, p=0.010, respectively). EAT thickness was strongly correlated vvith body mass index (BMI) and waist length (r=0.405, p<0.001; r=0.515, p<0.001, respectively). The neutrophil count was signifcantly higher in the ED group than in the non-ED group. In multivariate logistic regression analysis, HbAlc levels and EAT thickness were found as predictors of ED in type 2 DM (odds ratio (OR): 1.887, 95% confdence interval (Cl): 1.298-2.743, p=0.001; OR: 1.485, 95% Cl: 1.054-2.093).

Conclusion: EAT thickness predicts ED in patients vvith type 2 DM.

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Diabetes mellitus (DM) is a chronic disease with currently increasing incidence. World Health Organization predicts that nearly 360 million diabetic patients will be living in 2030 in the entire world.[1]Mortality rates due to cardiovascular diseases in diabetic patients have been reported to be three times more frequent than nondiabetics.[2] Epidemiological studies have shown the correlation between glycemic control, and cardiovascular mortality.[3] Diabetes which is considered to be equivalent to coronary artery disease, is known to cause vascular diseases as a result of complications of minor, and major vessels which contribute to increases in mortality rates. Dysfunction of the vascular endothelium occurring in diabetic patients is believed to be the most important cause of complications developing in minor, and major vessels.[4]8090

Endothelium regulates vascular tonus, and permeability, ensures equilibrium between coagulation, and fibrosis, preserves integrity of subendothelial matrix, leukocytic flow, and proliferation of vascular smooth muscles.[4] When endothelial functions deteriorate, endothelium synthetizes vasoactive adhesion molecules, cytokines, and growth factors, and release them into the circulation. During this process, macrophages adhere to the endothelium, move towards the arterial wall, and play an important role in the formation of the atherosclerotic plaque. This phenomenon is considered as the onset of atherosclerotic process.[5] Any direct method of measuring endothelial function is not available. In the evaluation of endothelial dysfunction (ED) various methods including measurements of brachial artery flow-mediated dilation (FMD), levels of plasminogen activator inhibitor-1 activity, serum adhesion molecules, and von Willebrand factor have been used.

Adipose tissue is a very complex endocrine organ which produces a wide range of molecules, and exerts regional, and systemic effects which all stimulated interest in investigations related to adipose tissue. [67] Epicardial adipose tissue (EAT) is an active endocrine organ producing many bioactive molecules which might effect cardiac functions so as to maintain paracrine control.

In this study we aimed to investigate the correlation between epicardial tissue thickness, and endothelial dysfunction detected using brachial artery FMD measurements.

PATIENTS AND METHOD

A total of 92 patients with type 2 diabetes were included in the study. Enlightened consent forms were obtained from all patients. The study was designed in compliance with Helsinki Declaration of The World Medical Association, and approval of the local ethics committee was obtained for the study protocol. As diagnostic criteria, Fasting blood glucose levels of ≥ 126 mg/dL, and use of antidiabetic drugs and/or insulin were considered as diagnostic criteria for DM.DM Patients with any known previous diagnosis of heart disease, acute/chronic renal failure, an acute or chronic infection, acute or chronic hepatobiliary, hematological, autoimmune, chronic inflammatory, and malignant disease were excluded from the study. A total of 47 patients with a FMD change of < 7 % in measurements performed before, and after application of cuff pressure on brachial artery were included in the ED group, while those with a > 7 % difference between these measurements constituted non-ED group. Age, gender, body mass index (BMI) , waist circumference of the patients, and duration of DM were recorded.

Measurement of the epicardial adipose tissue

Epicardial adipose tissue was measured using Vivid 3 (General Electric Medical Systems, Horten, Norway) brand echocardiograph. From the transthoracic long,- and short- axis parasternal views EAT thickness were measured using 2-D, and M-mode echocardiographic techniques while the patient was lying on his/her left side. Parasternal short-, and long- axis views were evaluated, and recorded during 10 or more cardiac cycles. Echocardiograms were evaluated by a cardiologist blinded to the patients' demographic, and clinical information. Patients with poor quality echocardiographic images were not included in the study. On the right ventricular free wall, measurements of EAT were made synchronously with systolic movements of both ventricles. Average of three long-, and short-axis maximum measurements were performed from 1 /3 basal section of ventricles to determine EAT thickness. EAT is seen as a non-echoeic or intense hyperechogenic areas. The rationale of measuring EAT from the right ventricle is that EAT of the right ventricle is extremely thick, and also with appropriate orientations of light projections from all angles the most accurate EAT measurements from parasternal long-, and short-axis views can be obtained. If present, hypertrophy of the right ventricular trabeculae, and moderator band do not effect epicardial adipose tissue measurements

Biochemical analysis

Venous blood samples were obtained from the patients after an 8 hour -overnight fasting period. Fasting blood glucose levels were measured using glucosidase method (Konelab-60I). Triglyceride, total cholesterol, low-, and high-density lipoprotein cholesterol levels were measured using automated bioanalyzer (Roche Diagnostic, Indianapolis, USA). Hemoglobin, erythrocyte distribution width, neutrophils, lymphocyte, platelets, mean platelet volume, white blood cell counts were estimated using Sysmex K-1000 device (Block. Scientifc, Bohemia, NY, USA).

Flow-mediated dilation method

Technique was performed on the left brachial artery by a 7.5 MHz sector linear array transducer, using colour-Doppler ultrasonograph device of Vivid 3 Echocardiography device (General Electric Medical Systems, Horten, Norway). Firstly, baseline anteroposterior diameter of the longitudinally visualized brachial artery segment 4-5 cm proximal to the elbow was measured on intimal-luminal interface concurrently with end-diastolic ECG recordings. Then cuff of the sphyngomanometer placed around the forearm was inflated up to at least 50 mm Hg above systolic blood pressure, and left at that level for 5 minutes. Then the cuff was deflated to induce reactive hyperemia along the brachial artery. Longitudinal image of the artery was recorded 30 seconds before, and 2 minutes after deflation of the cuff. Measurement of AP diameter of the brachial artery was repeated one minute later.

Statistical Analysis

Normality of distribution of data was investigated using Kolmogorov-Smirnov/Shapiro-Wilk tests. Descriptive statistics was summarized as mean ± standard deviation or median (percentiles) based on the distribution pattern of the numerical data. Categorical data were summarized as numbers, and percentages. For correlation analysis of categorical data as cross tabulation statistics, Pearson *chi*-square test, and likelihood ratio test were used. For intergroup comparisons as for numerical variables, based on the distribution of data parametric independent samples *t*-test, and nonparametric Mann-Whitney U-test were used. As correlation coefficients of numerical variables Pearson, and Spearman correlation coefficients were used. $P< 0.05$ was considered as the level of significance.

Table 1. Basic characteristics of the study groups

	EAT group (n=46)	Non-EAT group (n=46)	*p*
Age (year)	55±8	54±8	0.689
Female (%)	51	49	0.815
Duration of type 2 DM (mos)	50	43	0.168
Hypertension (%)	51	49	0.797
Smoking (%)	59	41	0.328
Fasting blood glucose (mg/dL)	195 (141-242)	162 (131-253)	0.519
Creatinine (mg/dL)	0.80 (0.7-1.0)	0.85 (0.8-1.0)	0.447
Triglyceride(mg/dL)	208±115	182±83	0.231
Total cholesterol (mg/dL)	205±51	199±45	0.555
LDL-C (mg/dL)	124±37	117±39	0.387
HDL-C (mg/dL)	41.0 (34.00-47.25)	41.5 (36.00-48.25)	0.590
$HbA1_C$ (%)	8.5 (7.30-9.80)	7.4 (6.50-9.30)	0.042
C-reactive protein (mg/L)	4.4 (1.875-7.225)	3.0 (1.875-6.175)	0.244
Body mass index (kg/m^2)	32±6	31±4	0.177

Continuous variables with normal distribution were expressed as mean ± standard deviation, and variables with non-normal distribution as median (percentiles) ED: Endothelial dysfunction; DM: Diabetes mellitus, LDL-C: low-density lipoprotein cholesterol; HDL-C: High-density lipoprotein cholesterol, $p<0.05$ statistically significant .

Using predetermined possible factors, in the prediction of ED, for the determination of independent markers logistic regression analysis was used. Hosmer-Lemeshow test of goodness of fit was used to decide how our model fitted the data. Among the predetermined markers for the inclusion in the logistic regression, $p \leq 0.25$ rule was used to select those which differed between groups For statistical analysis, demo version of SPSS 17.0 program was employed.

RESULTS

Mean FMD changes were 11.43 % (9.18-17.95) in the non-ED, and 2.44 % (0.00-4.24) in the ED groups ($p<0.001$). Significant intergroup differences were not detected as for mean age, gender, serum creatinine, fasting blood sugar, lipid profile, CRP, BMI, duration of diabetes, smoking, and history of hypertension (Table 1). EAT long-axis diameter was 8.5±1.8 cm in the ED, and 7.2±1.3 cm in the non-ED groups ($p<0.001$).

EAT short-axis diameter was 7.4±1.8 cm in the ED, and 6.0±1.2 cm in non-ED groups ($p<0.001$). Mean EAT diameters were 8.0±1.8 in the ED, and 6.6±1.2 cm in non-ED groups ($p<0.001$).

$HbA1_C$ levels were significantly higher in the ED group relative to non-ED group (8.55 [7.30-9.80], 7.45 [6.50-9.30], respectively: $p=0.042$). A negative correlation existed between percent change in brachial artery FMD, and mean EAT diameter ($r=-0.437$, $p<0.001$). A weak correlation was found between the percent change in brachial artery FMD, duration of diabetes, and HbA1c levels ($r=-0.216$, $p=0.038$, $r=-0.266$; $p=0.010$, respectively). A strongly positive correlation existed between EAT thickness, BMI, and waist circumference ($r=0.405$, $p<0.001$, $r=0.515$, respectively $p<0.001$). Hematological parameters of all patients are summarized in Table 2. Neutrophil counts were higher in the ED group when compared with the non-ED group. All other hematological parameters were comparable between groups.

Table 2. Hematological parameters of all patients

	EAT group (n=46)	Non-EAT group (n=46)	*p*
Neutrophil counts (/μL)	4380 (3560-5625)	3900 (3295-4615)	0.046
Lymphocyte counts (/μL)	2270 (1797-2762)	2255 (1810-2600)	0.628
Platelet count s(/μL)	278000±67983	270000±66034	0.604
Neutrophil/lymphocyte ratio	2.0 (1.62-2.51)	1.8 (1.39-2.23)	0.082
Platelet /lymphocyte ratio	112 (92.57-146.15)	129 (99.69-151.11)	0.301
Erythrocyte distribution width (%)	16 (14.50-16.40)	15 (14.37-16.62)	0.972
Mean platelet volume (fL)	9.1 (8.55-9.62)	9.1 (8.30-9.90)	0.751
White blood cell counts (/μL)	7939±2186	7171±1534	0.054
Hemoglobin (g/dL)	13.3±1.5	13.4±1.5	0.568

ED: Endothelial dysfunction. $p<0.05$ level of statistical significance

Table 3. Logistic regression analysis of the data used in the determination of endothelial dysfunction

Risk factor	OR (95 % CI)	*p*
HbA1c	1.485 (1.054-2.093)	0.024
Epicardial fat tissue	1.887 (1.298-2.743)	0.001
Body mass index	1.033 (0.922-1.157)	0.580
Neutrophil/lymphocyte ratio	1.441 (0.780-2.661)	0.244
Duration of diabetes mellitus	0.998 (0.991-1.006)	0.642
Triglyceride	1.000 (.0994-1.005)	0.872
C-reactive protein	0.983 (0.884-1.093)	0.749

In the multivariate logistic regression analysis EAT thickness (OR: 1.887, 95% CI [1,298-2,743]) and HbA1c levels (OR: 1.485, 95 % CI [1.054-2.093]) were detected as independent markers of ED (Table 3).

DISCUSSION

The present study has demonstrated that EAT thickness is an independent marker demonstrating ED in type 2 diabetics, and consequently contributed new information to the literature. Increased EAT thickness in type 2 DM patients with ED relative to diabetics without ED is a newly introduced information as far as we know. Our study has for the first time demonstrated that mean EAT thickness is an independent marker in the prediction of ED. EAT diameters examined using transthoracic echocardiograph can give an idea about the presence of ED (if any) . This finding of ours has added valuable, and novel information to available literature data.

In normal adult individuals, epicardial fat pad is a visceral adipose tissue which surrounds heart, including right ventricular free wall, and left ventricular apex, atrioventricular, interventricular areas, common coronary arteries, and atria [8] Iacobellis et al .[9] indicated that EAT thickness measured from right ventricular free wall is associated with visceral adipose tissue thickness, and therefore increase in EAT thickness can be a risk factor for coronary artery disease. In a study performed on white hypercholesterolemic rabbits, despite the presence of atherosclerotic lesions on intraepicardial segments of the left descending artery (LDA), such lesions were not detected within intramyocardial segments of LDA.[10] In a study performed by Eroğlu et al. [11] EAT thickness was measured in 140 hypertensive patients, and 60 control subjects, and in a significantly higher number of hypertensive patients increased EAT thickness was detected in, and a positive correlation was observed between EAT thickness, diastolic, and systolic blood pressure measurements. In the light of all these studies, EAT was suggested as a potential marker for coronary heart diseases.

Epicardial fat tissue has different functions when compared with other bodily visceral adipose tissue sources, and it induces release of many cytokines termed as adipokines. EAT also provides 50-70 % of the myocardial energy, uptake, and release of free fatty acids which it uses through beta oxidative processes..[12]

In a study on 153 patients without a history of heart attack, congestive heart failure, and cardiomyopathy, EAT thickness of the patients who underwent coronary angiography with the indication of chest pain, was measured using coronary angiography, and EAT thickness was detected as 1. 76±1.36 mm in mildly stenotic coronary arteries, 3.39±1.64 mm in a single vessel stenosis, and 4.12±2.03 mm in multvessel coronary artery disease ($p<0.001$), and increased EAT thickness was observed in line with the severity of coronary artery disease.[13]

Eroğlu et al.[11] found increased EAT thickness in 140 hypertensive patients when compared with those normotensive control subjects, and suggested EAT thickness as an independent marker of the diagnosis of hypertension. Although hypertension is known as an etiological factor for ED, in their study endothelial functions of the patients, and differences (if any) in EAT thickness of the patients with or without ED were not analyzed, In our study, patients with DM which is another major cause of ED were considered as groups with or without ED, and increased EAT thickness was found in diabetic patients with ED. Discrimination of hypertensive patients as those with or without ED will be a rational approach.

Type 2 DM patients are known to be under the risk of coronary heart diseases. Wang et al .[14] compared 49 type 2 DM patients, and 78 non-diabetic control subjects, and using multi-detector coronary tomographs measured epicardial fat tissue volume, applied Gensini scoring system, graded coronary calcification, and reported significantly increased epicardial fat tissue volume in type 2 DM patients relative to the control group.

With recent investigations, EAT thickness is not only an indicator of cardiometabolic risk, but it is also becoming a therapeutic target .[15] Assuming that visceral adipose tissue decreases, and its cardiometabolic levels changes favourably with losing weight in obese patients, therefore with aerobic exercise, low-calorie diet, use of surgical alternatives, and of some drugs cardiometabolic status of the patients can be improved.

Indeed, using low-calorie diet for 12 weeks, Kim et al.[16] reported decreases in echocardiographically measured EAT diameters (≈17 %), BMI (9 %), and abdominal diameter (11 %) in obese patients. With their dietary therapy, more rapid, and increased amounts of decrease especially in EAT diameters were observed. In another study, similar outcomes have been demonstrated in obese patients.[17] As reported in many studies, significant decreases in EAT levels could be obtained with aerobic exercise.[18] Starting from this study, in obese type 2 DM patients, weight loss achieved by appropriately low-calorie diet, and exercise programs can be presumably lead to rapid, and significant reduction in EAT thickness. Consequently, the development of ED can be delayed or ED can be improved. Besides, development of the most challenging micro-, and macrovascular complications of type 2 DM can be retarded.

In our study, type 2 DM patients with or without ED were compared, and using FMD method EAT diameters were found to be significantly higher in the ED group. With this study, we have demonstrated that in the demonstration of ED which is a predictor of micro-, and macrovascular complications, EAT can be an important parametre.

Limitations of the study

As a limitation of this study we didn't analyze serum nitrate levels in addition to FMD method.

Conflict of interest: None declared

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Anahtar sözcükler: Akım aracılı dilatasyon; diabetes mellitus, tip 2; endotelyal disfonksiyon; epikart; vücut ağırlığı; yağ doku.

Key words: Flow- mediated dilatation; diabetes mellitus, type 2; endothelial dysfunction; epicardium; body vveight; adipose tissue.