ORIGINAL ARTICLE

Epicardial adipose tissue volume predicts long term major adverse cardiovascular events in patients with Type 2 diabetes

Epikardiyal yağ dokusu hacmi tip 2 diyabetik hastalarda uzun dönem major istenmeyen kardiyovasküler olayları predikte eder

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ABSTRACT

Objective: Epicardial adipose tissue (EAT) is a metabolically active visceral fat depot that plays an important role in coronary atherosclerosis. In this study, our aim was to investigate the relationship between long-term major adverse cardiovascular events (MACEs) and EAT volume detected by coronary computed tomography angiography (CCTA) in patients with Type 2 diabetes mellitus (T2-DM) without previous coronary events.

Methods: A total of 127 patients with diabetes who underwent CCTA between 2012 and 2014 were enrolled retrospectively. The study population was divided into 2 groups according to whether they experienced or did not experience MACE, which was defined as cardiac death, non-fatal myocardial infarction or unstable angina requiring hospitalization, coronary revascularizations (percutaneous coronary intervention or coronary artery bypass grafting surgery), heart failure, peripheral arterial disease, or ischemic stroke. In both groups, EAT volumes were measured by CCTA.

Results: During 60±7 months follow-up period, 22 participants experienced MACEs. Data were evaluated with univariate and multivariate analyses and receiver operating characteristic (ROC) analysis. Age, male sex, coronary artery disease, hemoglobin A1c, glucose, creatinine, C- reactive protein, and cholesterol levels were found to be associated with MACE. EAT volume (odds ratio [OR]: 1.027; 95% confidence interval [CI]: 1.010-1.044, p=0.002) and low-density lipoprotein (OR: 1.015; 95% CI: 1.000-1.030, p=0.050) were found to be independent predictors for MACE. ROC analysis indicated that EAT volumes >123.2 mL had a 72.7% sensitivity and a 77.1% specificity for predicting long-term MACE in patients with T2-DM (area under the curve: 0.820; 95% CI: 0.733–0.908).

Conclusion: EAT volume is an independent predictor of long-term MACE in patients with T2-DM without previous coronary events. EAT volume may be used additionally in risk stratification for MACE besides the well-known vascular risk factors in patients with T2-DM.

ÖZET

Amaç: Epikardiyal yağ dokusu (EYD) koroner aterosklerozda önemli rol oynayan metabolik olarak aktif viseral yağ deposudur. Çalışmamızda amacımız koroner olay geçirmemiş tip 2 diyabetik (T2-DM) hastalarda uzun dönem majör istenmeyen kardiyovasküler olay (MİKO) ile koroner bilgisayarlı tomografi anjiyografi (KBTA) ile ölçülen EYD hacim ilişkisini değerlendirmektir.

Yöntemler: 2012-2014 yılları arasında KBTA yapılmış toplam 127 diyabetik hasta retrospektif olarak çalışmaya dahil edildi. Hastalar MİKO varlığına göre iki gruba ayrıldı. MİKO kardiyak ölüm, hastane yatışı gerektiren ölümcül olmayan miyokart enfarktüsü ya da kararsız angina, koroner revaskülarizasyon (perkütan koroner girişim, koroner arter baypas greftleme cerrahisi), kalp yetersizliği, periferik arter hastalığı, iskemik inme olarak tanımlandı. İki grubun EYD hacmi KBTA ile ölçüldü.

Bulgular: 60±7 aylık takip süresinde 22 MİKO tespit edildi. Tek ve çok değişkenli analizler ve alıcı işlem karakteristiği (ROC) analizi ile veriler değerlendirildi. Yaş, erkek cinsiyet, koroner arter hastalığı, hemoglobin A1c, glukoz, kreatinin, C-reaktif protein (CRP) ve kolesterol kan düzeyleri MİKO ile ilişkili bulundu. EYD hacmi (OR: 1.027; %95 GA: 1.010-1.044, p: 0.002) ve düşük dansiteli (yoğunluklu) lipoprotein (OR: 1.015; 95% CI: 1.000-1.030, p: 0.050) MİKO için bağımsız öngördürücü olarak bulundu. ROC analiz sonucuna göre 123.2 mL üzerinde EYD hacmi, %72.7 duyarlılık ve %77.1 özgüllük ile T2-DM hastalarında uzun dönem MİKO'yu öngördürür (Eğri altındaki alan: 0.820; %95 CI: 0.733–0.908).

Sonuç: EYD hacmi, öncesinde koroner olay geçirmemiş T2-DM hastalarda uzun dönem MİKO'yu bağımsız olarak öngördürebilmektedir. EYD hacmi T2-DM hastalarda iyi bilinen vasküler risk faktörleri yanı sıra risk sınıflamasında ek olarak kullanılabilir.

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Type 2 diabetes mellitus (T2-DM) is a well-known risk factor for cardiovascular diseases. New methods have been investigated to predict the progression of coronary artery disease (CAD) in patients with T2-DM. Epicardial adipose tissue (EAT) is a specialized visceral adipose tissue between the visceral pericardium and myocardium,[1] and it has been linked to CAD risk factors and subclinical atherosclerosis and manifest CAD through a paracrine or endocrine mechanism by exerting inflammatory mediators.[2] EAT has also been associated with fatal and nonfatal coronary events in the general population, regardless of the presence of classical risk factors.[3] The aim of this study was to investigate whether EAT volume assessed by coronary computed tomography (CT) angiography (CCTA) can predict the long-term major cardiovascular adverse events (MACEs) in patients with T2-DM without previous coronary events. To the best of our knowledge, our study is the first to evaluate the relationship between EAT volume and long-term MACE in patients with T2-DM without previous CAD.

METHODS

Patient selection

Our study was designed as a single-center retrospective cohort study. A total of 253 consecutive patients with T2-DM who underwent CCTA between 2012 and 2014 were scanned. CCTA indications were atypical chest pain, 15%–50% pretest probability ratio according to Bayesian approach, inconclusive stress test results, search for CAD before noncoronary cardiac surgery, and suspected coronary anomalies. Previous diagnosis of CAD, previous coronary revascularization procedures, heart failure, valvular heart disease, aortic aneurysms, peripheral arterial atherosclerosis, ischemic stroke, Type 1 DM, renal dysfunction, hepatitis B or C infection, other known liver diseases, hemolytic disorders, acute/chronic inflammatory conditions, neoplastic diseases, missing laboratory parameters and follow-up data, and poor quality CCTA were the exclusion criteria. After the exclusion of these patients, 127 patients with T2-DM without previous CAD were included. The study protocol was approved by the Ethics Committee of University of Health Sciences İstanbul Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital (Approval Date: October 30, 2018; Approval Number: 2018-52). This study was performed in accordance with the requirements of the Declaration of Helsinki.

Abbreviations:

3D	*3-dimensional*
AUC	*Area under the curve*
BMI	*Body mass index*
CABG	*Coronary artery bypass grafting*
CAD	*Coronary artery disease*
CCTA	*Coronary computed tomography angiography*
CI	*Confidence interval*
CRP	*C-reactive protein*
CT	*Computed tomography*
DM	*Diabetes mellitus*
EAT	*Epicardial adipose tissue*
LDL	*Low-density lipoprotein*
MACE	*Major cardiovascular adverse event*
MI	*Myocardial infarction*
MSCT	*Multislice computed tomography*
OR	*Odds ratio*
PCI	*Percutaneous coronary intervention*
ROC	*Receiver operator characteristic*
T2-DM	*Type 2 diabetes mellitus*

CCTA

A Dual-source CT system (Definition Flash; Siemens Medical Solution, Forchheim, Germany) with 280 ms of rotation time, 2×128 slices, a pitch of 3.4, and a 60% R-R interval was used. The tube current for the protocol was set at 180–300 mAs, and 0.6-mm slice collimation was used. Nonionic contrast reagent (400 mgI/mL Iomeron; Bracco, Milan, Italy) was administered at a rate of 5 mL/s (80–100 mL total) through an 18-G needle positioned in the antecubital vein using a dual-head power injector. Images were obtained during a single 6-second interval in which the patients held their breath using the bolus-tracking technique.

Image analysis

A 3-dimensional (3D) workstation (Syngo.via; Siemens Healthineers, Erlangen, Germany) was used to analyze the scans, blinded to the clinical data of the patients; a consensus diagnosis was achieved using CCTA. The characteristics of the stenosis and the number of coronary plaques/segments based on the modified American Heart Association classification were analyzed.[4] Plaques were defined as 1-mm^2 structures within or adjacent to a vessel lumen that could be clearly distinguished from the lumen and the surrounding pericardial tissue. Plaque burden was calculated as the sum of the atherosclerotic segments (1 point for each) in the coronary arteries, which were divided into 15 segments.[5] CAD was defined as the presence of plaque or any degree of stenosis. The adipose tissue between the surface of the myocardium and visceral pericardium was defined as EAT. EAT was quantified by manually tracing the pericardium on 10–18 axial CCTA sections. Volumetric software

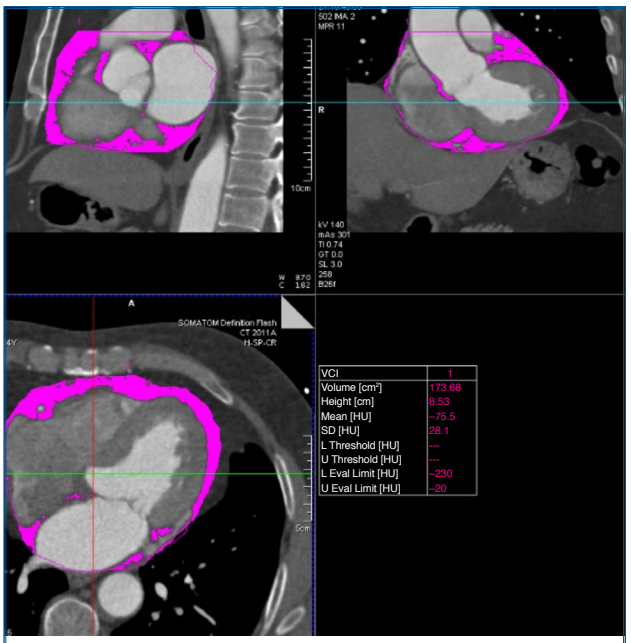

Figure 1. Computed tomography slice showing how the total epicardial adipose tissue volume was measured in sagittal, coronal, and axial views. The table shows the numeric values.

(Syngo.via; Siemens Healthineers, Forchheim, Germany) was used to perform manual quantification of EAT. To obtain total EAT volume starting from the right pulmonary artery middle level to cardiac apex, by using 0.75 mm thickness of axial sections, external cardiac borders were drawn manually for every 16 sections (Fig. 1).

The number of slices had to be traced manually, ranging from 5 to 9 in each patient. The computer software then automatically interpolated and traced the epicardium in all the slices interposed between the manually traced slices. EAT was semiautomatically reconstructed by the software into a 3D region of interest, which was controlled visually and adjusted manually if deemed necessary. Within this region of interest delineated by the pericardium, contiguous 3D voxels between limits of –250 HU and –30 HU were defined as fat voxels. This resulted in a measurement of left atrioventricular groove EAT in cubic centimeters (cm^3).

Patient follow-up and MACEs

The mean follow-up duration was 60±7 months. The primary endpoint of the study was the long-term presence of MACE. MACE was defined as cardiac death, nonfatal myocardial infarction (MI) or unstable angina requiring hospitalization, coronary revascularizations (percutaneous coronary intervention [PCI] or coronary artery bypass grafting [CABG]), heart failure, peripheral arterial disease, or ischemic stroke. Demographic information, cardiovascular risk factors (age, sex, family history, smoking habits, hyperlipidemia, and hypertension), CCTA reports, and MACE presence were obtained after a systematic review of the patients' hospital records retrospectively. Missing variables were obtained by telephone interviews with the patients and/or their relatives, and survival data were obtained from the electronic hospital system or National Population Registry. Then, the study population was divided into 2 groups according to whether they experienced or did not experience MACE.

Statistical analysis

Statistical Package for the Social Sciences, version 24.0 (IBM Corp.; Armonk, NY, USA) was used for data analysis. The normal distribution of continuous variables was checked using the visual (histograms and probability curves) and analytical methods (Kolmogorov–Smirnov's and Shapiro–Wilk tests). Normally distributed numerical variables are presented as mean±standard deviation, non-normally distributed numerical variables are presented as median (minimum–maximum value), and categorical variables are presented as percentages (%). Independent sample t-test was used for normally distributed continuous variables, and Mann–Whitney U test was used for continuous variables not showing normal distribution. Chi-square test or Fisher exact test was used to compare categorical variables. Logistic regression analysis was performed to determine the independent predictors of MACE in patients with T2-DM. For univariate analysis, $p<0.25$[6,7] was accepted as statistically significant, and for multivariate analysis, $p<0.05$ was accepted as statistically significant. Receiver operator characteristic (ROC) curve analysis was conducted to determine the cut-off value; the significant prediction was accepted when the area under the ROC curve was >0.5. According to the cut-off value, Kaplan–Meier survival analysis was performed.

Using the group sample numbers of 105 for the participants who did not experience MACE and 22 for those who experienced MACE, a margin of error of 5%, and the effect size obtained from data in Hajsadeghi et al.'s [8] study, the power of the study

according to the analysis made with G*Power 3.1.9.2 program was found to be 99.9%.

RESULTS

During 60±7 months follow-up period, 22 patients (mean age: 57.05±7.59 years; 59.1% male) experienced MACE consisting of 1 cardiac death, 6 cases of PCI, 3 cases of CABG, 3 cases of peripheral arterial disease, 2 cases of heart failure, 1 case of ischemic stroke, 4 cases of both CABG and peripheral arterial disease, and 2 cases of both PCI and heart failure. A total of 105 patients were event free (mean age: 54.14±.51 years; 39% male). The baseline demographics and the clinical and laboratory characteristics of the study participants are summarized in Table 1. There were no significant differences in age, sex, prevalence of hypertension, DM regulation, and smoking status across the study groups (p>0.05).

Biochemical parameters showed that plasma creatinine (0.8 vs. 0.6 mg/dL, p=0.001) and C-reactive protein (CRP) (1.97±0.85 vs. 1.44±0.69 mg/L, p=0.002) levels were significantly higher in the participants who developed MACE. Total cholesterol (215.4±56.8 vs. 184.2±41.3 mg/dL, p=0.003), low-density lipoprotein (LDL) (133.2±46.3 vs. 108.6±36.8 mg/dL, p=0.007), and triglyceride (188.5 vs. 150 mg/dL, p=0.012) levels were also significantly higher in the participants who developed MACE, whereas and high-density lipoprotein (40±9.3 vs. 45.3±9.4 mg/dL, p=0.017) levels were significantly lower in the participants who developed MACE than in those who did not. There was no statistically significant difference between the groups in terms of uric acid levels (p=0.660).

After evaluation of CCTA images, EAT volumes (159.5±51.2 vs. 106.9±34.2 mL, p<0.001) were found significantly higher among the participants who developed MACE than among those who did not. The number of patients with CAD detected by CCTA (20 vs. 58, p=0.002) was significantly higher among the participants who developed MACE.

In a univariate regression analysis (Table 2), age, male sex, CAD, hemoglobin A1c, glucose, CRP, cholesterol levels, creatinine, and EAT volumes were found to be significantly associated with MACE. According to the multivariate regression analysis (Table 2), EAT volume (odds ratio [OR]: 1.027; 95% confidence interval [CI]: 1.010–1.044, p=0.001) was an independent predictor of MACE, adjusting for other risk factors in patients with T2-DM. In addition, LDL (OR: 1.015; 95% CI: 1.000–1.030, p=0.050) was found to be an independent predictor of MACE.

Table 1. Baseline demographic, clinical, and laboratory characteristics of the study groups

Characteristics	MACE (+) (n=22)	MACE (-) (n=105)	*p*
Age (year)	57.05±7.59	54.14±8.51	0.141
Sex (male), n (%)	13 (59.1)	41 (39)	0.084
Smoker, n (%)	10 (45.5)	56 (53.3)	0.501
Hypertension, n (%)	14 (63.6)	69 (65.7)	0.852
CAD, n (%)	20 (90.9)	58 (55.2)	**0.002**
HbA1c	7.65 (6.3-12.1)	7.2 (5.9-12.2)	0.243
Glucose (mg/dL)	147.5 (106-412)	145 (91-371)	0.621
Creatinine (mg/dL)	0.8 (0.3-1.7)	0.6 (0.3-1.7)	**0.001**
Uric acid (mg/dL)	5.3±1.15	5.16±1.36	0.660
Total cholesterol (mg/dL)	215.4±56.8	184.2±41.3	**0.003**
LDL (mg/dL)	133.2±46.3	108.6±36.8	**0.007**
HDL (mg/dL)	40±9.3	45.3±9.4	**0.017**
Triglyceride (mg/dL)	188.5 (65-864)	150 (48-445)	**0.012**
CRP (mg/L)	1.97±0.85	1.44±0.69	**0.002**
EAT volume (mL)	159.5±51.2	106.9±34.2	**<0.001**

Data are presented as a percentage, mean±SD, or median (minimum-maximum). Bold indicated statistically significant values.
CAD: coronary artery disease; CRP: C-reactive protein; EAT: epicardial adipose tissue; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipoprotein; MACE: major adverse cardiovascular event.

To investigate the predictive value of EAT volumes for MACE in patients with T2-DM, the ROC curve was generated for sensitivity and specificity using the respective areas under the curve (AUCs) (Fig. 2). The analysis indicated that EAT volumes >123.2 mL had a 72.7% sensitivity and a 77.1% specificity for predicting long-term MACE in patients with T2-DM without previous CAD (AUC: 0.820; 95% CI: 0.733–0.908). Its positive and negative predictive values were 40% and 93.1%, respectively, and accuracy was 76.4%. Kaplan–Meier cumulative survival curves for MACE by using the EAT cut-off value are presented in Fig. 3. Kaplan–Meier curves showed that patients with EAT ≥123.2 mL had a significantly higher incidence of MACE (Log-rank test, p<0.001).

Table 2. Univariate and multivariate regression analysis for the predictors of MACE

	Univariate analysis		Multivariate analysis	
Variables	OR (95% CI)	*p*	OR (95% CI)	*p*
Age	1.043 (0.986-1.103)	0.143	1.003 (0.927-1.085)	0.943
Sex (male)	2.255 (0.884-5.749)	0.089	1.209 (0.312-4.691)	0.784
Smoker	0.729 (0.290-1.835)	0.502	—	
Hypertension	0.913 (0.350-2.379)	0.852	—	
CAD	8.103 (1.802-36.448)	0.006	2.147 (0.372-12.383)	0.393
HbA1c	1.269 (0.935-1.722)	0.127	1.171 (0.798-1.720)	0.420
Glucose	1.004 (0.998-1.011)	0.212		
Creatinine	14.719 (1.855-116.796)	0.011	6.463 (0.488-85.669)	0.157
Uric acid	1.081 (0.765-1.528)	0.658	—	
Total cholesterol	1.014 (1.004-1.025)	0.007	—	
LDL	1.016 (1.004-1.028)	0.010	1.015 (1.000-1.030)	0.050
HDL	0.932 (0.879-0.989)	0.020	—	
Triglyceride	1.006 (1.001-1.011)	0.016	—	
CRP	2.392 (1.328-4.309)	0.004	0.903 (0.344-2.367)	0.835
EAT volume	1.029 (1.016-1.043)	<0.001	1.027 (1.010-1.044)	0.002

CAD: coronary artery disease; CI: confidence interval; CRP: C-reactive protein; EAT: epicardial adipose tissue; HbA1c: hemoglobin A1c; HDL: high-density lipoprotein; LDL: low-density lipo-protein; MACE: major adverse cardiovascular event; OR: odds ratio.

DISCUSSION

In our study, we found that EAT volume was an independent predictor of long-term MACE in patients with T2-DM without previous coronary events. EAT volumes >123.2 mL had a 72.7% sensitivity and a 77.1% specificity for predicting MACE (AUC: 0.820; 95% CI: 0.733–0.908). In addition, LDL was an independent predictor of MACE for our study population.

EAT is a visceral adipose tissue that acts as an endocrine and inflammatory organ, which locally affects the cardiac morphology and function by secreting proatherogenic and proinflammatory cytokines. EAT can be measured noninvasively by echocardiography, cardiac magnetic resonance, or multislice computed tomography (MSCT). MSCT provides more accurate measurements than other techniques because of its high temporal resolution.[5] MSCT volumetric measurements are found to be more reproducible[9,10] and reliable than echocardiographic thickness measurements.[11] Our study was designed to evaluate EAT with MSCTs as volumetric measurements.

Strong correlations between EAT volumes measured by MSCT and cardiometabolic risk factors,[12] coronary calcium score,[13] and CAD[2,14–16] have been shown in previous studies. Tanindi et al. [17] have shown that EAT thickness measured by conventional 2-dimensional echocardiography may be used to predict MACE, including MI and cardiovascular death, and Altin et al. [18] showed that EAT thickness is associated with even prediabetic status. In addition, there are some studies designed with CT showing the relationship between EAT volumes and MACE in the general population.[8,19] Cheng et al.[20] evaluated 2,751 asymptomatic patients without CAD from a registry, comparing 58 patients who had MACE with 174 age- and sex-matched event-free individuals. They reported that patients with MACE showed higher pericardial fat volume on pre-MACE CT, and pericardial fat volume helped with the prediction of MACE after adjustment for the Framingham risk score, coronary calcium score, and body mass index (BMI).[20] The Heinz–Nixdorf Recall Study, one of the largest studies on the relationship between EAT volume measured by CT and coronary events, showed that EAT was associated with fatal and nonfatal coronary events in the general population, regardless of the presence of classical risk factors.[3] Our study also confirmed the results of previous studies in a select-

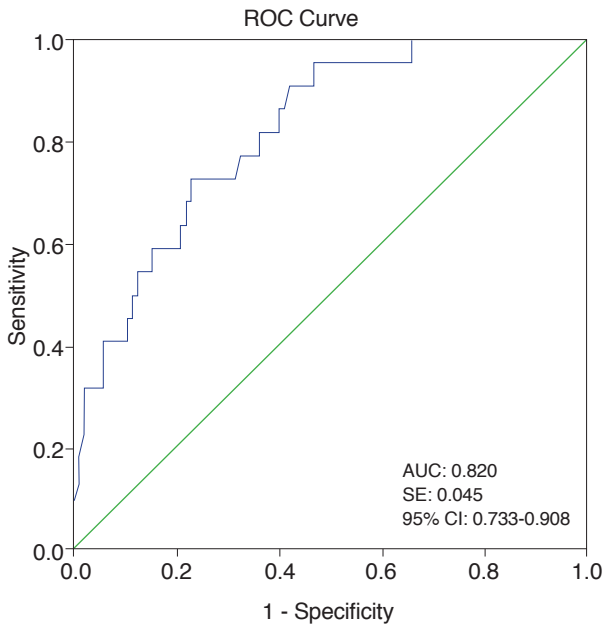

Figure 2. Receiver operator characteristic curve for total epicardial adipose tissue volumes. AUC: area un-der the curve; CI: confidence interval; SE: standard error.

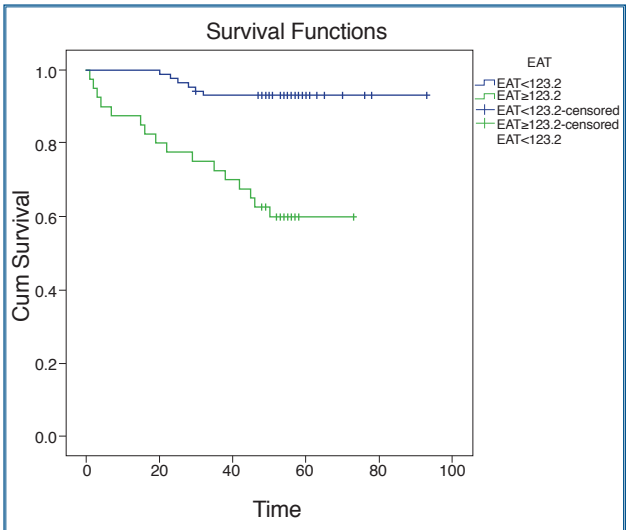

Figure 3. Kaplan–Meier curves for major adverse cardiovascular events stratified by epicardial adipose tissue.

ed patient group. According to our study findings, EAT volume was a predictor of long-term MACE in patients with T2-DM without previous coronary events, independent from well-known cardiovascular risk factors. The distinctive point of our study was the specific study population. We included only patients with T2-DM without previous CAD. The most recent study published by Christensen et al.[21] also investigated the relationship between EAT diameter measured by echocardiography and MACE in patients with diabetes; they included all patients with T2-DM. They found that higher EAT was associated with MACE and mortality similar to the findings of our study. Our study differed from their study by measuring EAT volume using CT, which is superior to 1-dimensional echocardiographic measurement, and in addition, our study population was different because it only included patients with T2-DM without previous CAD history.

Our study showed that patients with T2-DM who experienced MACE had significantly higher EAT volume than patients who did not experience MACE. EAT volume ≥123.2 mL was independently associated with MACE, consistent with previous studies.[3,20,22] Considering the study by Altin et al.,[23] which presented improvement in EAT measurements in patients who underwent laparoscopic sleeve gastrectomy, EAT can be evaluated as a modifiable cardiovascular risk factor. As a result, the volumetric CT measurements of EAT can give additive information in the cardiovascular risk assessment of patients with T2-DM.

In our study, 20 of 22 patients who experienced MACE had CAD on CCTA, which was defined as the presence of plaque or any degree of stenosis. In the univariate analysis, CAD was found to be associated with MACE, but in a multivariate analysis, it lost significance. The fact that even the presence of plaque was defined as CAD could be the reason why the presence of CAD was not associated with MACE in this patient population. EAT was found to be a strong predictor for MACE independent of the presence of CAD.

Limitation

Our study had some limitations. First, our study was designed retrospectively and involved a single center with a small study population. Second, BMI and waist circumference, which are indicators of cardiovascular risk, were missing. Finally, although MSCT is the most accurate method for EAT measurement, high costs, experience requirement, and radiation exposure limit its clinical use.

Conclusion

In our study, EAT volume was an independent predictor of long-term MACE in patients with T2-DM without previous coronary events. EAT can have an

important role in risk stratification for MACE besides the well-known risk factors in patients with T2-DM, and patients with high EAT volumes can be candidates for more aggressive risk reduction strategies.

Ethics Committee Approval: Ethics committee approval for this study was received from the Ethics Committee of University of Health Sciences Mehmet Akif Ersoy Thoracic and Cardiovascular Surgery Training and Research Hospital (Approval Date: October 30, 2018; Approval Number: 2018-52).

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