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Relationship between epicardial adipose tissue and body muscle-to-fat ratio in patients with type 2 diabetes mellitus

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Abstract

Type 2 Diabetes mellitus (T2DM) is shown as an important risk factor for the development of cardiovascular diseases worldwide. Epicardial adipose tissue (EAT) has been associated with cardiovascular diseases. The body muscle-to-fat ratio measured by bioelectric impedance (BIA) is associated with cardiac dysfunction. In this study, we aimed to evaluate the relationship between EAT and body muscle-to-fat ratio in T2DM patients. The 125 consecutive T2DM patients and 46 healty volunteers included in the study. EAT was measured by using transthorasic echocardiograph (TTE). Data were obtained BIA analysis in all patient. The muscle-to-fat ratio measured by BIA and EAT was compared between the two groups. There was a significant difference between the groups in terms of waist circumference (WC), fat mass, fat mass ratio, muscle mass and muscle-to-fat ratio. E ($p<0.001$), Em wave ($p<0.001$), E/A ratio ($p<0.001$) and E/Em ratio ($p=0.014$) were significantly lower in the DM group compared to controls. Also, EAT thickness was higher in the DM group (5.78 ± 0.7 vs 4.89 ± 0.7 $p <0.001$). While a positive correlation was observed between EAT and BMI ($r = 0.445$, $p <0.001$), WC ($r = 0.401$, $p < 0.001$), Age ($r = 0.237$, $p = 0.008$) and disease duration ($r = 0.199$, $p = 0.049$), EAT and muscle-to-fat ratio were negatively correlated ($r = -0.615$, $p <0.001$). Age and muscle-to-fat ratio were found to be independent predictors for EAT ($\beta= 0.037$; $p<0.001$; $\beta=-1.403$, $p<0.001$ respectively). The muscle-to-fat ratio measured by bioelectrical impedance technique in type 2 DM patients may provide a more accurate estimate for EAT, which has been shown to be associated with cardiovascular events.

Keywords: Diabetes mellitus, epicardial adipose tissue, muscle-to-fat ratio

Introduction

Obesity and fat deposition are closely related due to their effect on insulin resistance in the pathogenesis of Type 2 Diabetes mellitus (T2DM) [1,2]. In addition to the traditional risk factors such as obesity and dyslipidemia, recently identified risk factors including chronic low-grade inflammation and endothelial dysfunction are also quite common and play a significant role in the development of vascular disease in patients with diabetes [2]. Although body mass index or body weight are commonly utilized as a measure of excessive bodyweight, these do not accurately reflect the fat mass.

Epicardial adipose tissue (EAT) is a mass of visceral fat around the heart and coronary arteries that is known to exert various paracrine, vasocrine and inflammatory effects. Furthermore, EAT is also considered to reflect the cardiometabolic risk [3]. An association between cardiac visceral fat stores and cardiovascular disorders has been established [3]. Increasing visceral adiposity is linked with pro-inflammatory activity, risk of atherosclerosis, and higher mortality. Furthermore, EAT is now considered to represent a novel cardiovascular risk factor in the general population [4]. EAT functions like a very active organ producing numerous bioactive adipokines and it is also able to secrete proinflammatory cytokines and may utilize free fatty acids (FFAs) [5,6].

Body composition analyzers based on bioelectrical impedance analysis (BIA) are widely used in the clinical practice as well as for investigational purposes [7] and offer a non-invasive, practical, and rapid means for estimating the fat and muscle composition in the body [8].

In our study, we planned to evaluate the relationship between musle-to-fat ratio obtained with bioelectrical impedance and epicardial adipose tissue in T2DM patients.

Materials and Methods

A total of 125 consecutive patients meeting the diagnostic criteria of the American Diabetes Association [9] for T2DM and 46 healthy controls were included in this study. Inclusion criteria were age between 18 and 80 years, meeting ADA criteria for T2DM, and willingness for study participation [9]. Patients with suspected

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coronary artery disease or objective ischemia (wall motion defect in echocardiography, evidence of ischemia in treadmill exercise test or myocardial single-photon emission computed tomography), cardiac valvular disease, hypertension, rheumatologic or collagen tissue disorder, hepatic or renal disease, malignancy, pulmonary hypertension, chronic obstructive pulmonary disease, dysthymia, Individuals with body mass index under 18 or above 35, and more than 10% change of bodyweight in the past year were excluded. The study protocol was approved by the institutional ethics committee and all patients provided written informed consent before the study.

Study protocol

The following demographic data were recorded for all patients: age, gender, duration of diabetes, use of insulin, BMI, and heart rate. Anthropometric (height, weight, and waist circumference) and blood pressure (BP) measurements were performed during the physical examination. The weight was measured using a mechanical scale nearest to 100 g. The waist circumference was the smallest diameter between the lower rib line and the superior iliac spine. BMI was recorded as the weight (kg) divided by the square meter of the height. BP measurements (in mmHg) were performed in supine position after 5 minutes of rest using a mercury sphygmomanometer. Furthermore, the following blood chemistry tests were performed after at least 8 hours of overnight fasting in automated analyzers: glycosylated hemoglobin (HbA1c), total cholesterol (TC), triglycerides (TG), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C), alanine aminotransferase (ALT), aspartate aminotransferase (AST).

Muscle mass and fat mass measurements with bioelectric impedance analyzer (BIA)

All anthropometric measurements were performed using BIA. Data were obtained bioelectrical impedance analysis in all patient (TANITA BC 601 body composition analyzer, Biospace, Tokyo, Japan). The analyzer measures the resistance at different frequencies (1, 5, 50, 250, 500 KHz, and 1 MHz) and responds at certain frequencies (5.50 and 250 KHz). BIA is generally considered an accurate method for the assessment of body composition [2], with the output data consisting of body weight, body fat mass, and skeletal muscle mass. Then, the fat mass ratio was obtained by dividing the body fat mass to total body mass. Muscle-to-fat ratio was obtained by dividing the body muscle mass to body fat mass.

Echocardiographic Examination

Transthoracic echocardiographic assessments were performed using a 2.5 MHz S5-1 probe (Philips Medical Systems, Ie33, Bothell, USA) with the patient being in left lateral decubitus position. During echocardiographic assessment, all patients were kept under cardiac monitoring. Using standard echocardiographic techniques (parasternal long axis, short axis, apical 4-chamber and 2-chamber), images were acquired. Transthoracic echocardiographic measurements were performed according to the AHA and ESC Cardiac Chamber Measurement guidelines. Left atrial (LA) diameter, Left ventricular (LV) end-diastolic dimension (LVEDD), LV end-systolic dimension (LVESD), interventricular septal diameter (IVSD), and posterior wall diameter (PWD) were measured using the M-Mode technique. Ejection fraction was estimated with Simpson's methodology. During the apical 4-chamber imaging, the flow Doppler transmitral flow waves (E and A) were measured and the E/A ration was estimated. Again, using the same methology the mitral lateral annular peak early diastolic (Em), peak late diastolic (Am) velocities in cm/s were obtained in the apical 4-chamber view with tissue Doppler. EAT is observed as an echo-free space in the pericardial layer in 2D echocardiography. The EAT thickness was measured during diastole in the free wall of the right ventricle, using the parasternal long and short axis images. The average of 3 separate measurements performed in long and short parasternal axis were recorded (10).

Statistical Analysis

The data analyses were performed using SPSS 21.0 software pack. The descriptive statistics included mean ± SD for continuous variables, and number and percentage for categoric variables. Kolmogorov-Smirnov test was used to test the normal distribution in the study groups. Significant measurement differences between the groups were detected with Student's t test or Mann Whitney U test. The significance of the linear relationship between BMI, fat tissue ratio, muscle-to-fat ratio, waist circumference, and EAT was tested with Pearson's or Spearman's correlation tests. Categorical comparisons were performed using chi-square test. All variables showing significance values of <0.05 on univariate analysis (BMI, Waist circumference, Muscle to fat ratio, Age, Disease duration) were included in the multivariate model. A p value of less than 0.05 was considered statistically significant.

Results

The comparison of demographic, clinical features and laboratory parameters of all individuals included in the study is shown in Table 1. The two groups were comparable with respect to age, gender, systolic and diastolic blood pressures, LDL, HDL, triglyceride, creatinine, height, weight, and BMI. Fasting glucose was significantly higher in the T2DM group (161 ± 64.2 vs 89.0 ± 7.9 $p <0.001$). There was a significant difference between the groups in terms of waist circumference, fat mass, fat mass ratio, muscle mass and muscle-to-fat ratio. The results of 2D and tissue Doppler echocardiography measurements are shown in Table 2. LV end systolic and end diastolic diameter, LVEF, LA diameter, interventricular septum (IVS), posterior wall diameter (PWD), A and Am wave were similar between the groups. On the other hand E wave ($p<0.001$), Em wave ($p<0.001$), E/A ($p<0.001$) and E/Em ratio ($p=0.014$) were significantly lower in the T2DM group compared to controls. Also, EAT thickness was higher in the T2DM group (5.78 ± 0.7 vs 4.89 ± 0.7 $p <0.001$).

The results of the correlation and linear regression analyses are given in Table 3. While a positive correlation was observed between EAT and BMI ($r = 0.445$, $p <0.001$), WC ($r = 0.401$, $p <0.001$), Age($r= 0.237$, $p=0.008$) and disease duration ($r = 0.199$, $p = 0.049$), EAT and muscle-to-fat ratio were negatively correlated ($r = -0.615$, $p < 0.001$). In the multivariate linear regression analysis, age and muscle to fat ratio ($\beta= 0.037$; $p<0.001$; $\beta=-1.403$, $p<0.001$ respectively) were found to be independent predictors for EAT.

Table 1. Basal demographic, clinic and biolectrical impedance datas of the study groups

	Control group N:46	DM group N:125	P Value
Age (year)	56.1 ± 6.7	55.5 ± 5.7	0.560
Sex (male %)	21 (45.7)	46 (36.8)	0.296
DM duration (years)		8.4±1.7	-
SBP (mmHg)	115 ± 12	118 ± 17	0.334
DBP (mmHg)	82 ± 11	82 ± 7	0.675
HbA1c (%)	5.2 ± 0.1	7.5± 1.2	<0.001
LDL cholesterol (mg/dL)	112 ± 38	118 ± 32	0.276
HDL cholesterol (mg/dL)	37 ± 6	38 ± 7	0.650
Triglycerides (mg/dL)	187 ± 48	197 ± 62	0.315
Fasting glucose (mg/dL)	89.0 ±7.9	161 ± 64.2	<0.001
Creatinine (mg/dL)	0.82 ± 0.15	0.92 ± 0.28	0.076
Height (cm)	166.9 ± 6.85	166.1 ± 7.7	0.678
Weight (kg)	84.6 ± 14.5	80.1 ± 14.9	0.098
BMI (kg/m^2)	28.7 ± 4.4	28.8 ± 4.4	0.876
Waist circumference (cm)	99.3 ± 9.6	102.6 ± 8.66	0.032
Fat mass (kg)	25.4 ± 3.3	28.7 ± 4.5	<0.001
Fat mass ratio (%)	31.0 ± 4.7	36.7 ± 4.8	<0.001
Muscle mass (kg)	53.4 ± 12.8	46.7 ± 10.4	<0.001
Musle to fat ratio	2.1 ± 0.56	1.6 ± 0.25	<0.001

The bold values indicate a statistically significant difference between groups
DM: Diabetes mellitus; SBP: Systolic blood pressure; DBP: Diastolic blood pressure; HbA1c: Glycated hemoglobin; LDL: low-density lipoprotein; HDL: high-density lipoprotein; BMI: Body Mass Index

Table 2. Comparison to echocardiographic parameters between two groups

	Control group N:46	DM group N:125	P Value
LVEF (%)	59.0 ± 2.8	59.5 ± 1.5	0.193
LAD (mm)	37.7 ± 1.8	38.6 ± 5	0.861
LVEDD (mm)	45.4 ± 1.9	44.0 ± 1.2	0.100
LVESD (mm)	32.0 ± 2.1	32.3 ± 2.7	0.650
PWD (mm)	10.3 ± 0.8	10.1 ± 0.7	0.212
IVSD (mm)	10.6 ± 0.9	10.4 ± 0.8	0.151
E wave (mm/sec)	72 ± 18	61 ± 9	<0.001
A wave (mm/sec)	76 ± 10	78 ± 13	0.543
Em (cm/sec)	8.0 ± 2.5	7.1 ± 1.2	<0.001
Am (cm/sec)	9.9±2.2	10 ± 2.8	0.893
E/A ratio	0.96 ± 0.2	0.74 ± 0.1	<0.001
E/Em ratio	10.1 ± 3.7	8.9 ± 1.3	0.014
EAT (mm)	4.89 ± 0.7	5.78 ± 0.7	<0.001

The bold values indicate a statistically significant difference between groups. A-wave: Late diastolic filling; E-wave: Peak early filling velocity; Em: Velocity of the mitral annulus early diastolic wave; Am: Velocity of the mitral annulus late diastolic wave; EAT: Epicardial adipose tissue; IVSD: Interventricular septum diameter; LAD: left atrium diameter; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; LVESD: Left ventricular endsystolic diameter; PWD: Posterior wall diameter

Table 3. Independent predictors of Epicardial Adipose Tissue in multivariate linear regression analysis

Parameters	Univariate analysis		Multivariate analysis	
	r	p	β(95 %CI)	P value
Body mass Index	0.445	<0.001	-0.24(-0.052-0.003)	0.085
Waist circumference	0.401	<0.001	-0.13 (-0.027-0.001)	0.061
Muscle-to-fat ratio	- 0.615	<0.001	-1.403(-1.88--0.944)	<0.001
Age	0.237	0.008	0.037(0.18-0.55)	<0.001
Disease duration	0.199	0.049	0.054(-0.03-0.111)	0.065

The bold values indicate a statistically significant difference between groups.

Discussion

Our findings suggest that muscle-to-fat ratio as measured by bioelectric impedance technique may be superior to BMI and waist circumference in reflecting EAT in T2DM patients who have no coronary artery disease and cardiac symptoms. With the recent recognition of the importance of the body composition in the pathogenesis of diabetes, we have witnessed an increase in the number of studies investigating the role of body composition in this condition [11]. Although an association between increased BMI and diabetes risk was established [12,13], failure of BMI to provide adequate information regarding the fat distribution, and fat ratio in relation to inflammatory mediators appears to be a significant limitation of this parameter. Accordingly, visceral adiposity index was shown to be closely related to cerebrovascular and cardiovascular events [11]. The investigators of the latter study also showed that among the commonly utilized measures of body fat such as waist circumference or waist to hip ratio, visceral adiposity index showed better correlation with cardiovascular events [14]. In a study by Naburo et al, body fat ratio was found to be associated with insulin resistance [15]. Again, in another study by the same authors, muscle to fat ratio was found to be linked with the requirement for higher insulin doses among a group of diabetic patients [16].

The relationship between diabetes mellitus and cardiac diastolic dysfunction has been shown in many studies. Various studies in DM patients have shown diastolic dysfunction as the earliest functional change during diabetic cardiomyopathy [17-20]. In our study, we evaluated diastolic dysfunction in the light of this information. We detected a statistically significant reduction in E wave, Em wave, E / A ratio and E / Em ratio in DM patients. These findings may indicate early diastolic dysfunction.

EAT covers a significant proportion of the cardiac surface and accounts for 20% of the total cardiac weight. It is present in the atrio-ventricular and interventricular sulci, along the major branches of the coronary arteries, around atria, on the free wall of the right ventricle, and apex of the left ventricle. Similar to an active endocrine organ, EAT produces several hormones, cytokines, and other vasoactive substances that have an effect on coronary atherogenesis and myocardial functions. This direct effect is thought to result from the diffusion of free fatty acids and adipokines found between EAT and the vessel wall as well as the myocardium underneath [21-23]. These adipocytes may affect the function of myocytes and cardiovascular outcomes. In one study by Baloglu et al. the visceral adiposity index determined by anthropometric measurements in T2DM was found to be associated with the increase in EAT thickness [24]. In contrast, in our study the fat tissue ratio and muscle-to-fat ratio measurements were based on the bioelectrical impedance method, which has a proven record rapidity and reliability.

In previous study in which 56 subjects from autopsies were examined, there was a relationship between age and epicardial adipose tissue [25]. In another study investigating the relationship of epicardial adipose tissue with age, it was shown that age correlated positively with EAT [26]. Our study supports these studies and it was observed that age was an independent predictor of EAT in T2DM patients.

Our results suggest that the body fat ratio and muscle to fat ratio may be superior to the commonly utilized parameters such as BMI and waist circumference in reflecting the EAT. In support of this view, Hatani et al. also found a significant relationship between subclinical left ventricular dysfunction and body fat ratio and muscle to fat ratio [27]. Again, in another study increased epicardial adiposity was associated with left ventricular dysfunction [28]. It is plausible to assume that one of the pathophysiological mechanisms responsible for the effects on the left ventricle may involve the increase in EAT, which is known to be metabolically active. This observed association between body fat ratio and EAT may provide further information as to why diabetic patients have an increased risk of cardiovascular and cerebrovascular conditions.

Study Limitations

Our study suffers certain limitations. Firstly, our sample size was small and the study was a cross-sectional study. Secondly, our measurements were not tested against the gold standard method for body composition estimations, i.e. computed tomography.

Conclusion

Utilization of muscle-to-fat ratio in T2DM patients as measured by bioelectrical impedance technique instead of body weight or BMI may provide a more accurate estimation of EAT. It has also been shown that muscle-to-fat ratio and age are the independent predictors of EAT which is known to be linked with cardiovascular events in patients with T2DM.

Conflict of interests
The authors declare that they have no conflict of interest and any financial disclosures.

Financial Disclosure
All authors declare no financial support.

Ethical approval
The study was approved by the local ethics committee.

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