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Comparison of epicardial fat thickness between metabolically healthy and unhealthy obese women

Metabolik olarak sağlıklı ve sağlıksız obeziteye sahip kadınlar arasında epikardiyal yağ kalınlığının karşılaştırılması

Duygu Ersan Demirci, M.D., Deniz Demirci, M.D.

Department of Cardiology, Health Sciences University Antalya Training and Research Hospital, Antalya, Turkey

ABSTRACT

Objective: Epicardial adipose tissue is suggested to play an important role in the progression of metabolic syndrome (MetS). There is not enough evidence regarding the relationship between echocardiographically measured epicardial fat thickness (EFT) and metabolic health status in women with equal obesity. In this study, we aimed to compare the echocardiographically measured EFT between metabolically healthy and unhealthy obese women with similar body mass index (BMI) and waist circumference (WC) values.

Methods: A total of 90 women (mean age 51.7±8.6 years) with BMI ≥30 kg/m² were enrolled in the study. EFT was measured with transthoracic echocardiography in all participants. The patients were then classified into two groups; metabolically healthy obesity (MHO) and metabolically unhealthy obesity (MUO). EFT and clinical and biochemical parameters were compared between the two groups.

Results: Among the study participants, 46 (51.1%) patients were included in the MHO group. The groups were not different with respect to age, WC, waist to hip ratio, and BMI. The mean value of EFT was 5.53±1.42 mm in patients with MUO and 4.80±1.54 mm in patients with MHO with a statistically significant difference (p=0.022). EFT, fasting insulin, and vitamin D were found as independent variables associated with MUO in obese women.

Conclusion: This study demonstrates that EFT is increased in women with MUO, regardless of BMI and waist circumference, than in women with MHO.

ÖZET

Amaç: Epikardiyal yağ dokusunun metabolik sendrom (MetS) gelişiminde önemli bir rol oynadığı ileri sürülmektedir. Eşit obezitesi olan kadınlarda ekokardiyografi ile ölçülen epikardiyal yağ kalınlığı ile metabolik sağlık durumu arasındaki ilişki hakkında yeterli kanıt yoktur. Çalışmamızın amacı, benzer vücut kitle indeksi (VKİ) ve bel çevresi ölçülerine sahip metabolik olarak sağlıklı ve sağlıksız obez kadınlar arasında, ekokardiyografi ile ölçülen epikardiyal yağ kalınlığını karşılaştırmaktır.

Yöntemler: VKİ ≥30 kg/m² olan 90 kadın hasta (ortalama yaş: 51.7±8.6 yıl) çalışmaya dahil edildi. Tüm katılımcılara transtorasik ekokardiyografi ile epikardiyal yağ kalınlığı ölçümü yapıldı. Hastalar daha sonra metabolik olarak sağlıklı ve sağlıksız obeziteye sahip olmalarına göre 2 grup olarak sınıflandırıldılar. Gruplar arasında, epikardiyal yağ kalınlığı, klinik ve biyokimyasal parametreler karşılaştırıldı.

Bulgular: Çalışma katılımcıları içerisinde 46 (%51.1) hasta metabolik olarak sağlıklı obeziteye sahip idi. Hastalar her 2 grupta yaş, bel çevresi, bel-kalça oranı ve VKİ açısından benzer özelliklerde idi. Epikardiyal yağ kalınlığı ortalama değeri metabolik olarak sağlıksız obezite grubunda 5.53±1.42 mm, metabolik olarak sağlıklı obezite grubunda ise 4.80±1.54 mm olarak ölçüldü ve aradaki fark istatistiksel olarak anlamlı bulundu (p=0.022). Epikardiyal yağ kalınlığı, açlık insülini ve D vitamini düzeyleri metabolik olarak sağlıksız obezite ile ilişkili bağımsız değişkenler olarak saptandı.

Sonuç: Çalışmamız metabolik açıdan sağlıklı obez kadınlara kıyasla, metabolik açıdan sağlıksız obez kadınlarda epikardiyal yağ kalınlığının VKİ ve bel çevresinden bağımsız olarak arttığını göstermektedir.

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Correspondence: Duygu Ersan Demirci, M.D.; Department of Cardiology, Health Sciences University Antalya Training and Research Hospital, Antalya, Turkey
Tel: +90 505 684 73 21 e-mail: duygu_ersan@yahoo.com

Obesity is an increasing health problem worldwide. Obesity can be defined as excess body fat associated with comorbid conditions and increased cardiovascular and mortality risk.[1] However, patients with equal obesity show a remarkable heterogeneity in cardiovascular disease (CVD) risk. Thus, not every patient with obesity develops CVD risk factors.[2] Some investigators use the term "metabolically healthy obesity" (MHO) to describe this issue.[3] There are no clear accepted criteria on the definition of MHO as well as biological mechanisms to explain the phenotype. In different studies, more than 30 different definitions have been used for MHO. In most of the studies, it was defined as having less than or equal to two of the five metabolic syndrome (MetS) components, whereas many others define MHO using the homeostasis model assessment of insulin resistance (HOMA-IR).[4] Body mass index (BMI), blood pressure (BP), triglyceride, high-density lipoprotein cholesterol (HDL-C), fasting plasma glucose, low-density lipoprotein cholesterol (LDL-C), and C-reactive protein (CRP) have also been used as diagnostic criteria for determining obesity phenotype.[5] The prevalence of MHO varies according to the criteria used for the definition. The prevalence of MHO was reported as ranging between 3.3% and 32.1% in men and between 11.4% and 43.3% in women according to the criteria used.[6] As the incidence of obesity continues to rise, the importance of MHO phenotype is increasing.[7]

In clinical practice, the most common index used to estimate adiposity is BMI expressed in kg/m^2. Besides the amount of fat, body fat distribution is an important issue. It's known that visceral fat is metabolically more active and dangerous than subcutaneous fat.[8] It has been suggested that waist circumference (WC) and BMI are the most accurate surrogate markers of visceral obesity in young adults.[9] However, overweight subjects with similar BMI values have different levels of visceral adipose tissue (VAT).[10] Because of the significant contribution of visceral fat accumulation to the development of metabolic disorders, VAT is determined by different imaging modalities like computerized tomography (CT) or magnetic resonance imaging (MRI).[11] Epicardial adipose tissue (EAT) is a kind of VAT between the surface of the myocardium and the epicardium. It can easily be measured by standard two-dimensional (2D) echocardiography.[12] EAT serves as an endocrine organ that secretes hormones, inflammatory cytokines, and chemokines.[13] Previous data suggests that EAT can play an active role in the development of MetS, which is related to increased CVD risk.[14] MetS is also considered to be a pro-inflammatory condition. Most of the components of MetS, especially visceral obesity is associated with low-grade systemic inflammation.[15]

Previous studies have demonstrated the relationship between EAT and MetS.[16] However, in most of the studies, control groups without MetS consist of the healthy, lean subjects. There is lack of enough evidence investigating the impact of metabolic health status on EAT in women with equally obesity.

Therefore, in this study, we aimed to compare echocardiographically measured EAT between women with metabolically healthy and unhealthy obesity, who had similar BMI and WC values.

Abbreviations:

2D	*Two-dimensional*
ATP III	*Adult Treatment Panel III*
BMI	*Body mass index*
BP	*Blood pressure*
CI	*Confidence interval*
CRP	*C-reactive protein*
CT	*Computerized tomography*
CVD	*Cardiovascular disease*
DBP	*Diastolic BP*
DM	*Diabetes mellitus*
EAT	*Epicardial adipose tissue*
EFT	*Epicardial fat thickness*
GLP-1	*Glucagon-like peptide 1*
HC	*Hip circumference*
HDL-C	*High-density lipoprotein cholesterol*
HOMA-IR	*Homeostasis model assessment of insulin resistance*
hs-CRP	*High sensitive C-reactive protein*
HT	*Hypertension*
LDL-C	*Low-density lipoprotein cholesterol*
MetS	*Metabolic syndrome*
MHO	*Metabolically healthy obesity*
MUO	*Metabolically unhealthy obesity*
NCEP	*National Cholesterol Education Program*
NLR	*Neutrophil lymphocyte ratio*
SBP	*Systolic BP*
SD	*Standard deviation*
SGLT-2	*Sodium glucose cotransporter 2*
TTE	*Transthoracic echocardiography*
VAT	*Visceral adipose tissue*
WC	*Waist circumference*

METHODS

Study group

In this cross-sectional study, 90 women (>18 years) with BMI ≥30 kg/m^2 who presented to the obesity management center of Antalya Training and Research Hospital between January and June 2019 were included. Patients with established heart disease such as coronary heart disease, cardiac failure, cardiac valve disease or arrhythmia, renal failure, hepatic failure, presence of active infection, chronic systemic

inflammatory disease, pulmonary disease, malignancy, and inadequate transthoracic echocardiographic images were excluded. The principles of the Helsinki Declaration was followed throughout the study. The study protocol was approved by the Clinical Research Ethics Committee of Antalya Training and Research Hospital (Approval Date: December 26, 2019; Approval Number: 27/6) and registered to Clinical Trials (NCT04437979). Informed consent was obtained from each patient.

Clinical information and current cardiovascular medication use were provided by each patient. Height, weight, WC, and hip circumference (HC) were measured when fasting and standing up with standard measuring tools. Waist circumference was measured to the nearest 0.5 cm on bare skin during mid-respiration at the natural indentation between the tenth rib and the iliac crest. BMI was calculated as body weight divided by height squared (kg/m^2). Waist to hip ratio was calculated as WC divided by HC. BP was measured after at least 10 minutes rest in sitting position. The mean of three measurements of each patient was recorded. Patients were defined as having hypertension (HT) if their systolic BP (SBP) was >140 mmHg, their diastolic BP (DBP) was >90 mmHg, or they were using an antihypertensive medication.[17] Blood samples were obtained after overnight fasting. Fasting blood glucose, urea, creatinine, total cholesterol, LDL-C, HDL-C, triglycerides, CRP ratio, fasting and postprandial insulin, C-peptide levels, vitamin D, ferritin, and complete blood counts were measured using standard methods. HOMA-IR was calculated using the method described by Matthews et al.[18] Neutrophil lymphocyte ratio (NLR) was defined as the log e neutrophil count/log e lymphocyte count within the peripheral blood. Patients were defined as having diabetes mellitus (DM) if they had a history of taking an oral antidiabetic or insulin medication, or if their fasting plasma glucose was ≥126 mg/dL.[19]

We defined MetS according to the National Cholesterol Education Program (NCEP) Adult Treatment Panel III (ATP III)[20] criteria, but waist circumference >80 cm was accepted as MetS criterion for Turkish women.[21]

Participants were divided into 2 groups: those with MHO and metabolically unhealthy obesity (MUO). Subjects with MHO had less than three of the following disorders, whereas subjects with MUO had at least three of the following abnormalities: SBP ≥130 mmHg or DBP ≥85 mmHg and/or use of antihypertensive medications; fasting glucose ≥100 mg/dL and/or use of anti-diabetic medications; hypertriglyceridemia ≥150 mg/dL, HDL-C levels <50 mg/dL, and WC >80 cm.[22] Patients in the MUO group were also evaluated according to how many MetS criteria they had. MetS score was defined as the number of criteria present.

Transthoracic echocardiography

Transthoracic 2D and Doppler echocardiographic examinations were performed in all patients according to the recommendations of American Society of Echocardiography and European Association of Cardiovascular Imaging.[23] Standard parasternal and apical views were obtained in the left lateral decubitus position using a Phillips iE33 ultrasound machine (Andover, USA) with a 3.5 MHz transducer.

Epicardial fat thickness (EFT) was identified as the echo-free space in the pericardial layers on 2D echocardiography.[24] EFT was measured on the free wall of the right ventricle at end-diastole from both parasternal long axis and parasternal short axis views using the mean of three consecutive beats. All measurements were performed by a single investigator who was aware of the clinical data of the patients, before the classification of the patients according to metabolic health status. For the reliability of the EFT average measurement, the interclass correlation coefficient for the intraobserver variability was 0.969 [95% confidence interval (CI) 0.953-0.979; p<0.001].

Statistical analysis

The arithmetic mean±standard deviation (SD) for normally distributed continuous variables, median (interquartile range) for non-normally distributed or ordered variables, frequency, and percentage for categorical variables were used. The Kolmogorov-Smirnov test was used to determine the normality assumption of the continuous variables. The chi-squared test was used to compare categorical variables. The Fisher's exact test was used when the expected count was less than five. Comparisons of normally distributed continuous variables were performed with the Student's t-test. Mann-Whitney U test was used for continuous variables that were not distributed normally. Correlation coefficients between variable pairs with linear correlation were calculated according to Pear-

son's correlation test, and correlation coefficients between variable pairs without linear correlation were calculated according to Spearman's correlation test. Multivariate logistic regression analysis was performed with variables determined as p<0.25 as a result of univariate statistical analysis. Using forward logistic regression, it was determined whether EFT is an independent factor in predicting the presence of MHO. Statistical analyses were performed using SPSS v25.0 (IBM Corp.; Armonk, NY, USA). P value <0.05 was considered statistically significant.

RESULTS

A total of 90 women (mean age 51.7±8.6 years) with obesity were included in the study. The demographic and clinical characteristics of the study population are shown in Table 1.

Table 2 presents the comparison of MHO and MUO groups. Among the study participants, 46 (51.1%) patients were in MHO group. Patients with MHO were not different from those with MUO in terms of age, WC, waist to hip ratio, and BMI. Systolic and diastolic blood pressure values were significantly higher in the MUO group. There was not difference between the groups in terms of smoking status and heart rate. The mean value of EFT was 5.53±1.42 mm in patients with MUO and 4.80±1.54 mm in patients with MHO with a statistically significant difference (p=0.022). Antihypertensive and antidiabetic medication use was significantly higher in the MUO group as expected; however, the difference in the use of medications which can modulate the EFT values was not statistically significant between the groups.

In the laboratory tests, we found that patients in the MUO group had significantly higher values of fasting glucose, HOMA-IR, C-peptide, triglycerides and lower values of HDL-C as expected. Fasting and postprandial insulin values were higher in patients with MUO but was not statistically significant. Vitamin D was significantly lower in the MUO group. Ferritin, total cholesterol, and LDL-C values did not differ between the two groups. We evaluated neutrophils, lymphocytes, NLR, and CRP as inflammation markers between the groups. CRP values were significantly higher in patients with MUO than in those with MHO (6.0 [4.0-6.6] vs. 4.54 [3.22-5.22], p=0.040), whereas there was no significant difference in NLR between the groups (Table 3).

Table 1. General characteristics of the study population (n=90)

Age, years, (mean±SD)	51.7±8.6
Hypertension, n (%)	37 (41.1)
Current smoker, n (%)	19 (21.1)
Diabetes mellitus, n (%)	32 (35.6)
Epicardial fat thickness (mm), (mean±SD)	5.16±1.52
Body mass index (kg/m²), (median Q1-Q3)	36.7 (33.3-40.2)
Waist circumference (cm), (median Q1-Q3)	106.7 (100.0-113.3)
Waist to hip ratio, (median Q1-Q3)	0.91 (0.88-0.95)
Systolic blood pressure (mmHg), (median Q1-Q3)	120 (110-123)
Diastolic blood pressure (mmHg), (median Q1-Q3)	80 (70-80)
Heart rate (beats/m), (median Q1-Q3)	76 (68-88)
Drug therapy	
Antihyperlipidemics	8 (8.9)
Statins, n (%)	5 (5.6)
Fenofibrates, n (%)	3 (3.3)
Oral antidiabetics, n (%)	24 (26.7)
Biguanide, n (%)	22 (24.4)
SGLT-2 inhibitors, n (%)	5 (5.6)
DPP4 inhibitors, n (%)	6 (6.7)
Tiazolidindiones, n (%)	2 (2.2)
Sulfonamides, n (%)	1 (1.1)
Antihypertensives, n (%)	32 (35.6)
ACE inhibitors, n (%)	10 (11.1)
Angiotensin receptor blockers, n (%)	18 (20.0)
Calcium channel blockers, n (%)	11 (12.2)
Diuretics, n (%)	22 (22.4)
Beta-blockers, n (%)	13 (14.4)

ACE: angiotensin converting enzyme; DPP4: dipeptidyl peptidase-4; SD: standard deviation; SGLT-2: sodium-glucose cotransporter-2.

Correlations between EFT values and selected variables are presented in Table 4. There were positive correlations between EFT and MetS scores of the patients, as well as EFT and CRP, ferritin, SBP, and DBP.

Using forward logistic regression analysis, the independent determinants of MUO were investigated. In the final model, EFT, fasting insulin, and vitamin D were found as MUO-related independent variables (Table 5).

Table 2. Comparison of groups with MHO and MUO

	MHO (n=46)	MUO (n=44)	*p*
Age, years, (mean±SD)	50.5±8.6	52.8±8.5	0.207
Current smoker, n (%)	9 (19.6)	10 (22.7)	0.891
Epicardial Fat Thickness (mm) (mean ± SD)	4.80±1.54	5.53±1.42	0.022
Body mass index, (kg/m²), (median Q1-Q3)	36.4 (32.7-40.2)	37.1(33.9-40.4)	0.392
Waist circumference, (cm), (median Q1-Q3)	105 (100-114)	108 (99.8-113)	0.796
Waist to hip ratio, (median Q1-Q3)	0.90 (0.88-0.92)	0.91 (0.88-0.96)	0.405
Systolic blood pressure (mmHg), (median Q1-Q3)	120 (110-123)	128 (120-140)	0.002
Diastolic blood pressure (mmHg), (median Q1-Q3)	75 (70-80)	80 (76-80)	0.042
Heart rate (beats/m) (median Q1-Q3)	75 (68-86)	80 (76-80)	0.490
Drug therapy			
Antihyperlipidemics	2 (4.3)	6 (13.6)	0.153
Antihypertensives	6 (13.0)	26 (29.1)	<0.001
Antidiabetics	5 (10.9)	19 (43.2)	0.001
EFT modulating drug therapy			
Statins, n (%)	1 (2.2)	4 (9.1)	0.198
DPP4 inhibitors, n (%)	2 (4.3)	4 (9.1)	0.469
SGLT-2 inhibitors, n (%)	1 (2.2)	4 (9.1)	0.198

DPP4: dipeptidyl peptidase-4; EFT: epicardial fat thickness; MHO: metabolically healthy obesity; MUO: metabolically unhealthy obesity; SD: standard deviation; SGLT-2: sodium-glucose cotransporter-2.

Table 3. Laboratory findings of the study population

	MHO (n=46)	MUO (n=44)	*p*
Neutrophil to lymphocyte ratio, (mean±SD)	1.72±0.56	2.04±1.04	0.090
Neutrophils (x 10^3/μL), (mean±SD)	4.13±1.3	4.30±1.5	0.232
Lymphocytes (x 10^3/μL), (mean±SD)	2.50±0.67	2.31±0.75	0.146
C-reactive protein (mg/dL), (median Q1-Q3)	4.54 (3.22-5.22)	6.0 (4.0-6.6)	0.040
Vitamin D (μg/L), (median Q1-Q3)	21.9 (13.7-26.1)	16.5 (11.3-19.8)	0.035
Ferritin (μg/L), (median Q1-Q3)	23.29 (12.0-29.5)	28.0 (14.0-46.5)	0.159
Fasting insulin (uIU/mL), (median Q1-Q3)	8.1 (5.5-11.4)	9.3 (5.7-14.1)	0.101
Postprandial insulin (uIU/mL), (median Q1-Q3)	24.1 (9.6±46.4)	25.41±(20.6-47.1)	0.375
HOMA-IR (%), (median Q1-Q3)	1.7 (1.3-2.4)	2.24 (1.48-4.65)	0.015
C– Peptide (μg/L), (median Q1-Q3)	2.4 (2.1-3.2)	3.1 (2.3-4.0)	0.006
Fasting glucose(mg/dL), (median Q1-Q3)	92.5 (87.0-97.3)	109.0 (97.3-102.0)	<0.001
Total Cholesterol (mg/dL), (median Q1-Q3)	208.0 (187.7-243.3)	210.0 (189.3-234.0)	0.958
LDL–Cholesterol (mg/dL), (median Q1-Q3)	126.0 (112.8-153.8)	128.5 (110.0-152.3)	0.744
HDL–Cholesterol (mg/dL), (median Q1-Q3)	56.0 (53.0-62.3)	49.5 (44.0-64.09)	0.004
Triglycerides (mg/dL), (median Q1-Q3)	91.5 (70.5-120.25)	175.5 (100.5-175.5)	<0.001

HDL: high density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; LDL: low-density lipoprotein; MHO: metabolically healthy obesity; MUO: metabolically unhealthy obesity; SD: standard deviation.

DISCUSSION

This study indicated the association of metabolic health status and echocardiographically measured EFT in women with equal obesity. EFT, fasting insulin, and vitamin D were found as independent variables associated with MUO. Our findings emphasize the relationship between increased EFT with MUO regardless of BMI and WC in women with obesity.

Table 4. Correlations between epicardial fat thickness and selected variables

	r	*p*
MetS score	0.279	0.012
HOMA-IR	-0.009	0.938
Fasting glucose	0.122	0.256
C-peptide	0.089	0.417
Fasting insulin	-0.054	0.615
Post prandial insulin	0.023	0.817
C-reactive protein	0.208	0.049
Neutrophil to lymphocyte ratio	0.016	0.885
Neutrophils	-0.016	0.878
Lymphocytes	-0.065	0.558
Total cholesterol	-0.061	0.568
LDL-Cholesterol	-0.034	0.752
HDL-Cholesterol	-0.012	0.908
Triglycerides	0.113	0.288
Ferritin	0.316	0.007
Vitamin D	0.032	0.776
Aspartate transaminase	-0.131	0.223
Alanine aminotransferase	-0.073	0.499
Systolic blood pressure	0.366	<0.001
Diastolic blood pressure	0.237	0.024
Heart rate	-0.027	0.800

HDL: high-density lipoprotein; HOMA-IR: homeostasis model assessment of insulin resistance; LDL: low-density lipoprotein; MetS: metabolic syndrome.

The risks of CVD and all-cause mortality were found to be greater in people with MUO than in those with MHO.[4] The risk of developing cardio metabolic diseases in people with obesity is associated with the severity and number of metabolic abnormalities. The exact mechanisms responsible for metabolic health in patients with MHO are not known. Excess adiposity per se is not responsible for unhealthy metabolism, although there are differences in adipose tissue distribution between MHO and MUO phenotypes. Therefore, the classification of obesity by BMI status alone does not provide adequate information about current metabolic health status and potential risk of adverse outcomes.[4] EAT is suggested to play an important role in the progression of MetS.[25] EFT measurement with transthoracic echocardiography (TTE), as an objective marker of the visceral fat level and as an effective predictor of MetS development risk,[26] could be used to identify individuals at risk.

Several studies investigated the association of EFT with MetS. However, in the vast majority of the studies, there was a significant difference in BMI values between patients with and without MetS. In a study, Liang et al.[27] have compared men with obesity and MetS and lean controls. They showed a significant increase of MRI measured EFT in the group with obesity and MetS. Demir et al.[28] have demonstrated that patients with chronic obstructive pulmonary disease with MetS had a higher mean EFT value than those without MetS. Another study by Calabuig et al.[29] has suggested that increased EFT was associated with a higher prevalence of MetS, with lower HDL-C, hypertriglyceridemia, and the presence of abdominal obesity. In all these studies, the patients with MetS had significantly higher BMI and WC values compared with the controls. A study involving the Korean population, in which the cut-off point of obesity was decided as ≥27 kg/m^2 instead of 30 kg/m^2 demonstrated no significant difference in the median

Table 5. Independent variables associated with MUO in obese women

			95% CI		
	Wald	OR	Lower	Upper	*p*
Epicardial fat thickness	6.686	1.614	1.127	2.311	0.009
Fasting insulin	5.377	1.123	1.018	1.239	0.020
Vitamin D	4.147	0.942	0.889	0.998	0.042

MUO: metabolically unhealthy obesity; OR: odds ratio; CI: confidence interval.

EFT between patients with and without MetS in the higher BMI group. Their possible explanations for this were that the difference of EFT in patients with and without MetS might have been obscured by the change of EFT by obesity in the high BMI group and might be a different proportion of the EAT to total amount of VAT according to BMI.[30] In contrast to this study, we found a significant difference in EFT between the MHO and MUO groups, in women with BMI ≥30 kg/m^2. According to our knowledge, scarce evidence is available regarding the comparison of echocardiographically measured EFT between the MHO and MUO groups in women. Our results state a significant difference of EFT between the groups regardless of BMI and WC, and also suggest that EFT is an independent predictor of MUO.

Several studies have shown a correlation between MetS components and inflammatory mediators. Buyukkaya et al.[31] have indicated a significant correlation between the criteria of MetS and inflammation on the basis of NLR. Tok et al.[16] have demonstrated that EFT is increased in patients with MetS; and in addition, high sensitive c-reactive protein (hs-CRP) and MetS are independent predictors of this increment. In another study, Bahadır et al.[32] have stated that NLR is not a good indicator of inflammation, whereas leukocyte and hs-CRP are more useful biomarkers to indicate inflammation in non-diabetic patients with obesity and MetS. In this study, we found that CRP values were significantly higher in the MUO group than in women with MHO, whereas there was no significant difference in NLR. Furthermore, they were not determined as independent variables associated with MUO in regression analysis.

The exact etiology of visceral adiposity related metabolic complications is not fully understood. One of the suspected mechanisms is VAT, acting as an endocrine organ and contributing to systemic inflammation.[33] VAT is more strongly associated with an adverse metabolic risk profile than subcutaneous abdominal tissue.[34] As individuals with equally obesity have different levels of VAT, BMI and WC measurements are not enough for assessing VAT and related metabolic risk profile in patients with obesity. In a review by Neeland et al.,[35] the authors have indicated the need to develop methods for identifying subjects with excess visceral adiposity and ectopic fat in clinical practice and further refine the definition of high-risk overweight and obesity. EAT is a measurable and modifiable target, correlated with VAT; and measurement of EAT with echocardiography is a reproducible, easily accessible, and cost-effective method. It is suggested that EAT measurement serves as a powerful potential diagnostic tool in assessing CVD risk and for risk stratification of MetS.[36] In a study by Manno et al.,[37] including seemingly healthy overweight and obese subjects, a direct relation between para- and peri-renal fat and epicardial fat, measured by ultrasounds, independently of age, BMI, WC, and insulin resistance was shown.

Recent studies investigating the effects of therapy with antidiabetic drugs, such as glucagon-like peptide 1 (GLP-1) receptor agonists and sodium glucose cotransporter 2 (SGLT-2) inhibitors showed that EAT thicknesses decreased significantly after these therapies.[38,39] There are also data indicating that statin therapy modulates the thickness and inflammatory profile of EAT.[40] In this study, antihypertensive, antidiabetic, and antihyperlipidemic medications were higher in the MUO group, as expected. The difference in the use of medications, which can modulate the EFT values, was not significant between the groups. The regression model in our study found them not effective in the association of EFT with MUO.

There is no exact value that indicates the normal for EFT. There are discrepancies in the literature regarding EFT. Iacobellis et al.[12] have found that EAT thickness measured during end-systole to be minimum 1 mm and maximum 22.6 mm with a mean value of 7 mm in men and 6.5 mm in women among individuals evaluated by echocardiography for standard clinical indications. It should be underlined that end-systolic measurements will reveal higher values than end-diastolic measurements. Nelson et al.[41] have found a mean of 4.7±1.5 mm in 356 asymptomatic patients when measured at end-diastole. Mookadam et al.[42] have reported that an EFT >5 mm during end-diastole was associated with cardiac abnormalities that have been detected by echocardiography. A study in the Turkish population found the mean EFT value to be 4.8±0.1 mm for healthy participants.[16] Bertaso et al.[43] have suggested that measurements >5 mm should indicate an appropriate cut-off value to define increased EFT, especially in low-risk

populations. Eroğlu[44] also reported that although it should be supported by large studies, measurements >5 mm during end-diastole could be a cut-off value for increased epicardial fat. In this study, the mean EFT value in women with MHO was 4.80±1.54 mm, whereas it was 5.53±1.42 mm in those with MUO, similar to the cut-off values of these studies.

In this study, in addition to EFT, fasting insulin and vitamin D were found to be independent variables associated with MUO. Hyperinsulinemia and insulin resistance are components of MetS and occur as a result of insulin responsiveness of metabolic tissues.[45] It has been reported that obesity is a risk factor for the deficiency of vitamin D.[46] However, the associations of vitamin D deficiency with insulin resistance and other aspects of MetS have not been proven yet. There are studies demonstrating an inverse correlation between serum vitamin D levels and MetS, CVD, and their complications.[47] The probable mechanisms were reported as improving insulin sensitivity, reducing inflammation that directly improves insulin resistance, and pancreatic β-cell function. Furthermore, vitamin D may also play a role in influencing insulin secretion by the regulation of plasma ionized calcium levels.[48] There are also studies not demonstrating this relationship.[49] Data are also conflicting regarding the treatment effect of vitamin D.[50] We need more data to determine whether maintaining an adequate serum vitamin D level by exposure to sunlight and oral intake of vitamin D has an impact on reduction of the incidence of metabolic disorders. Large-scale, prospective studies are needed to determine causality.

The findings of this study emphasize the independent association between EFT measured by echocardiography and metabolic health in women with obesity. The unique character of our study design was that both the groups of participants were equally obese in terms of BMI and WC. Classification of obese individuals based on their metabolic phenotype may be important for treatment planning. High-risk obese individuals can be given priority in terms of pharmacological treatment and lifestyle intervention. Assessment of VAT by measuring EFT using echocardiography can be an easy method for determining metabolic risk profile in clinical practice. Considering that there is no clear definition of MHO, it can also be a useful indicator for MHO.

Limitations

Our study had some limitations. First, the sample size of the study population was relatively small. Second, our findings can only be applied to women with obesity, not to obese men. Third, we assessed inflammation by CRP, instead of hs-CRP. The absence of a healthy, lean control group can be considered as another limitation; however, the mean EFT value of the MHO group was close to the cut-off values reported in the previous studies. The main purpose of this study was to demonstrate the difference of EFT values between metabolically healthy and unhealthy groups of women with obesity. Finally, echocardiography may not be the optimal technique for quantification of epicardial fat. It is a linear measurement, and therefore may not correlate with the total volume. However, owing to the limitations of MRI and CT, such as high costs, experience requirements, and radiation exposure; echocardiography is a reliable, easier, and accurate method. Further large scale studies are needed to determine the exact interaction among EFT, inflammation, and MUO to elucidate the clinical implications relevant to these associations.

Conclusion

This study proposes that echocardiographically measured EFT is increased in women with MUO than in those with MHO, regardless of BMI and WC. EFT, fasting insulin, and vitamin D were found as independent variables associated with MUO in obese women.

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