

## Original Article

# An indicator of subclinical cardiovascular disease in patients with primary osteoarthritis: epicardial fat thickness

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**Abstract:** Osteoarthritis (OA) is one of the most common chronic diseases seen in the elderly, and it is associated with increased cardiovascular morbidity and mortality. The cause of this association is not fully known. We aimed to investigate the relationship between epicardial fat and the presence and the grade of primary knee OA for analyzing the relationship between visceral adiposity and primary OA, thereby revealing the increased subclinical atherosclerosis and cardiovascular risk in OA patients. In this cross-sectional study, subjects with primary knee osteoarthritis and a control group were compared with regard to epicardial fat thickness through transthoracic echocardiography. In addition, OA was divided into four stages and the relationship between the grade of OA and epicardial fat thickness was analyzed. Eighty subjects with primary knee OA and 50 controls were analyzed. There was no difference between groups with regard to age, gender and BMI. Epicardial fat thickness was greater in patients in the primary OA group compared to the control group ( $3.73 \pm 1.08$  vs  $3.30 \pm 0.61$ , respectively,  $P=0.005$ ). In-group comparison of OA patients revealed that epicardial fat thickness was detected to increase as the grade of OA increased ( $P=0.001$ ). A relationship was detected between the presence of OA and epicardial fat thickness and CRP levels in multivariate logistic analysis ( $P=0.017$ ,  $P=0.047$ , respectively). There is a significant relationship between primary OA and epicardial fat thickness, which is a part of visceral adipose tissue. These results may indicate the relationship between OA and visceral fat tissue and, consequently, cardiovascular risk, so body weight alone may not be an identifying co-factor.

**Keywords:** Atherosclerosis, cardiovascular risk, epicardial fat, osteoarthritis

## Introduction

Osteoarthritis (OA) is one of the most common chronic diseases seen in the elderly. Approximately 9.6% of all men and 18% of all women worldwide are estimated to suffer from symptomatic hip or knee OA, making it the leading cause of physiological problems with daily activities and quality of life. Although obesity and related mechanical wear and tear are defined as the causes of OA, the roles of inflammation and free radical injury are also important [1]. There is extensive data on the relationship between OA and increased cardiovascular morbidity and mortality [2, 3]. Although the cause of this relationship is not fully known, it is considered to be multifactorial.

Epicardial fat (EF) is a visceral fat deposit, located between the heart and the pericardium, which shares many of the pathophysiological properties of other visceral fat deposits. Various bioactive molecules are released from this metabolically active tissue [4]. Visceral fat tissues like EF are known to have more proinflammatory and proarrhythmogenic effects compared to other fat stores [5, 6]. In previous studies, an association was detected between EF and coronary artery disease (CAD) [7], increased cardiometabolic risk [8] and inflammatory markers [9].

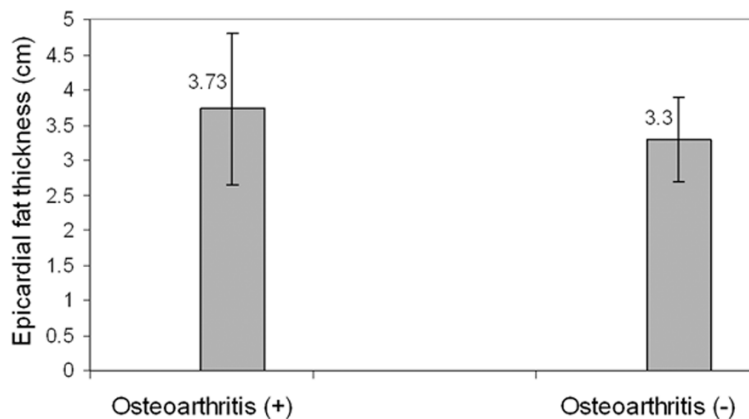
An association was detected between visceral obesity and hand OA [10]. To the best of our knowledge, there are no studies investigating

## Epicardial fat thickness in primary osteoarthritis

**Table 1.** Assessment of descriptive characteristics, biochemical parameters and epicardial fat measurements with regard to the presence of osteoarthritis

		Presence of osteoarthritis		P
		Osteoarthritis (+) (n=80)	Osteoarthritis (-) (n=50)	
		Mean±SD	Mean±SD	
Age (year)		56.81±5.36	54.82±7.03	0.090
BMI (kg/m <sup>2</sup> )		27.56±1.82	27.24±1.75	0.291
Gender	Female	50 (62.5%)	28 (56%)	0.581
	Male	30 (37.5%)	22 (44%)	
Hypertension	No	55 (68.8%)	37 (74%)	0.658
	Yes	25 (31.3%)	13 (26%)	
Glucose (mg/dL)		90.99±11.42	87.34±9.77	0.064
Creatinine; (Median) (mg/dL)		0.88±0.23 (0.80)	0.91±0.20 (0.98)	0.106
LDL (mg/dL)		102.89±19.77	96.18±18.68	0.057
HDL (mg/dL)		47.16±7.75	50.04±7.89	0.043
Triglyceride (mg/dL)		129.99±33.30	127.06±35.07	0.434
CRP; (Median) (mg/L)		4.03±4.14 (2.85)	2.42±1.63 (2.00)	0.033
Epicardial fat thickness (cm)		3.73±1.08	3.30±0.61	0.005

BMI: body mass index; CRP: C reactive protein; LDL: low density lipoprotein; HDL: high density lipoprotein.



**Figure 1.** Distribution of epicardial fat measurements with regard to the presence of osteoarthritis.

the association between OA and EF, a part of visceral obesity. We aimed to investigate the association between EF and the presence and the degree of OA both for better understanding the relationship between visceral adiposity and OA and revealing the subclinical atherosclerosis and increased cardiovascular risk.

### Materials and methods

#### Study design and study population

Eighty primary OA patients and 50 controls were included in the study. Osteoarthritis

patients who meet the inclusion criteria were included in the study consecutively, so as to ensure equal numbers of patients in each OA subgroup. Age- and sex-matched individuals served as controls, with no history of trauma to the knees or familial predisposition to OA, knee pain or clinical signs of knee osteoarthritis and grade 0 on the Kellgren-Lawrence scale on the knee and hip X-rays. The study protocol was approved by the local ethics committee, and written informed consent was obtained from each subject.

Age, sex, body mass index (BMI), and admission biochemical measurements [fasting blood glucose, creatinin, C-reactive protein (CRP), high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol and triglyceride levels] were recorded.

Patients were excluded if they had coronary artery disease, severe valvular disease, hypertrophic cardiomyopathy, chronic obstructive pulmonary disease, malignancy, congenital heart disease, chronic heart failure, cardiac rhythm other than sinus, uncontrolled hypertension prior to study, systemic disease such as

## Epicardial fat thickness in primary osteoarthritis

diabetes mellitus, collagenosis, chronic autoimmune disease, infectious diseases, hemolytic, hepatic and chronic renal disease, or history of alcohol abuse. Smokers were also excluded in addition to patients presenting with inadequate transthoracic echocardiographic images. Causes of secondary OA (previous knee operation, intra-articular fracture, major knee trauma) were also excluded.

### *Diagnosis and grading of OA*

Diagnosis and grading of primary OA was done according to Kellgren-Lawrence classification which is the radiologic diagnostic criteria [11].

- Grade 0-No radiographic features of OA are present.
- Grade 1-Doubtful joint space narrowing (JSN) and possible osteophytic lipping.
- Grade 2-The presence of definite osteophytes and possible JSN on anteroposterior weight-bearing radiograph.
- Grade 3-Multiple osteophytes, definite JSN, sclerosis, possible bony deformity.
- Grade 4-Large osteophytes, marked JSN, severe sclerosis and definitely bony deformity.

### *Measurement of EF with transthoracic echocardiography*

Transthoracic echocardiography was performed in all participants in the left lateral position according to the American Society of Echocardiography guidelines using the VIVID 3 (GE Medical Systems, USA). The echo-free space between visceral and parietal pericardium on the anterior wall of the right ventricle was diagnosed as EF thickness. EF thickness was measured perpendicularly on the free wall of the right ventricle on parasternal long-axis and short-axis views at end-diastole over 3 cardiac cycles [12]. Mean value of these 3 EF values which were measured by a cardiologist blinded to the degree of OA was calculated.

### *Statistical analysis*

NCSS (Number Cruncher Statistical System) 2007 & PASS (Power Analysis and Sample Size) 2008 Statistical Software (Utah, USA) was used for statistical analysis. In order to com-

pare variables between groups with OA and controls, a student's t-test was used for normally distributed parameters and the Mann Whitney U test was used for parameters not normally distributed (mean, standard deviation, median, frequency, and ratio). To determine the differences between the variables among the four subgroups of OA, a one-way ANOVA test for normally distributed variables and a Kruskal Wallis test for variables that were not normally distributed were used. Then, a Tukey HSD test (for normally distributed variables) and a Mann Whitney U test (for variables not normally distributed) were applied for single comparisons between subgroups. The Yates Continuity Correction test was used for comparison of qualitative data. Variables with a  $p$  value  $<0.25$  in univariate analysis were incorporated in the multivariate model. Multivariate regression analysis was used for analyzing the independent factors related with OA.  $P$  levels of  $<0.01$  and  $0.05$  were accepted as statistically significant.

### **Results**

A total of 130 subjects (80 OA and 50 control) were included in the study. The mean age of the control group was  $54.82 \pm 7.03$  years, and the mean age of the OA group was  $56.81 \pm 5.36$  years. The patient group consisted of 30 men (37.5%) and 50 women (62.5%). A statistically significant difference was not detected between OA and control groups with regard to age, gender, presence of HT and BMI (**Table 1**).

When patients were analyzed with regard to the grade of OA; 25% ( $n=20$ ) were seen to have grade 1; 25% ( $n=20$ ) grade 2; 25% ( $n=20$ ) grade 3 and 25% ( $n=20$ ) grade 4 OA.

EF thickness is significantly higher in the OA group than in the control group ( $P=0.005$ ) (**Table 1; Figure 1**). CRP levels are significantly higher in the OA group than in the control group ( $P=0.033$ ).

When the OA group was analyzed according to grade, glucose, creatinine, LDL, HDL and CRP values were not statistically significant ( $P>0.05$ ) (**Table 2**).

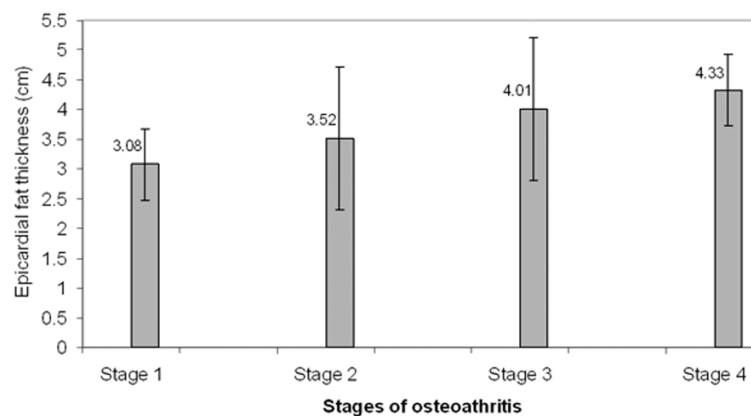
A statistically significant difference was detected between EF thickness measurements when analyzed according to OA grade ( $P=0.001$ )

## Epicardial fat thickness in primary osteoarthritis

**Table 2.** Analysis of laboratory findings and epicardial fat thickness with regard to the grade of osteoarthritis

	Osteoarthritis (+)				P
	Grade 1 (n=20)	Grade 2 (n=20)	Grade 3 (n=20)	Grade 4 (n=20)	
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	
Glucose (mg/dL)	96.35±6.4	88.05±9.5	88.25±12.3	91.30±14.5	0.072
Creatinine; ( <i>Median</i> ) (mg/dL)	0.90±0.21 (0.80)	0.84±0.25 (0.80)	0.84±0.18 (0.85)	0.95±0.27 (0.90)	0.480
LDL (mg/dL)	94.40±8.4	106.15±20.1	102.50±20.2	108.5±24.8	0.117
HDL (mg/dL)	47.90±4.7	46.7±7.8	46.90±11.2	47.15±6.3	0.966
CRP; ( <i>Medyan</i> ) (mg/L)	3.48 (3.23)	3.06 (1.75)	4.16 (2.72)	5.42 (3.31)	0.253
Epicardial fat thickness (cm)	3.08±0.6	3.52±1.2	4.01±1.2	4.33±0.6	0.001

CRP: C reactive protein; HDL: high density lipoprotein; LDL: low density lipoprotein.



**Figure 2.** Measurement of epicardial fat thickness with regard to the grade of osteoarthritis.

**Table 3.** Independent correlates of osteoarthritis in multivariate logistic regression analysis

	Odds ratio (95% CI)	P value
Epicardial fat	1.77 (1.11-2.85)	0.017
HDL	0.96 (0.91-1.01)	0.204
CRP	1.19 (1-1.42)	0.047

Note: Dependent variable: Presence of osteoarthritis.

(**Table 2; Figure 2**). According to paired comparisons in the evaluation of the group that has led to the difference, EF thickness measurements in grade 4 OA patients were statistically significantly higher than those in grade 1 and 2 OA ( $P=0.001$ ;  $P=0.045$ , respectively). In addition, EF thickness measurements in grade 3 OA patients were statistically significantly higher than those in grade 1 OA ( $P=0.001$ ).

An association was identified between the presence of OA and EF thickness and CRP levels in multivariate logistic regression analysis (**Table 3**).

### Discussion

In our study, EF thickness was greater in the OA group compared to the control group, although the groups were similar with regard to BMI, age and gender. In-group comparison of the OA group revealed that EF thickness was seen to increase as OA grade increased.

The relationship between OA and increased cardiovascular risk is not fully known. There is extensive data on the role of inflammation, although OA

is generally accepted as a degenerative disease [1]. In addition to the manifestation of synovial inflammation during early onset of knee and hip OA [13, 14], systemic low-grade inflammation has also been identified with serum CRP levels [15]. EF is a constituent of visceral adiposity, metabolically active and the source of various adipokines [16, 17]. It is closely related with CAD, subclinical atherosclerosis, coronary calcium score, insulin resistance and metabolic syndrome [18, 19]. Adipokines are mainly produced in adipose tissue and released into circulation [20]. OA-related adipokines were detected with in vitro tests and include mainly leptin, adipopectin, resistin, nicotinamide, visfatin, and chemerin. These adipokines also affect the distant joints [21, 22]. In a study, a relationship was identified between serum adipopectin levels and initial and six-year disease progression in 174 hand OA patients [23]. On the other hand, although Choe et al. [24] showed that radiological subchondral erosion is higher in patients

whose serum resistin levels are high, this was not observed for adipoectin. A relationship was detected between baseline serum leptin receptor levels and low N-terminal type IIA procollagen propeptide (cartilage formation biomarker), increased cartilage defect score and increased cartilage volume loss [25]. When preoperative radiographies of the patients who underwent total knee replacement were analyzed, adipokine levels were seen to be higher in patients with advanced OA [26]. However, Boer et al. [27] did not detect a difference between cartilage injury and adipoectin and resistin levels in their study conducted with 172 patients. In our study, we detected that CRP levels of knee OA patients were higher than those of the control group. EF thickness was also related to advanced OA grade. These high EF levels suggest that subclinical atherosclerosis is more severe in high-grade OA compared to low-grade OA besides the effects of visceral adiposity and inflammation on OA. This condition may be helpful in explaining increased cardiovascular morbidity and mortality in OA patients.

Recovery from OA may be impaired or the injury may be aggravated due to visceral adiposity. In vitro tests have shown that cartilage recovery is impaired [28] and cartilage degeneration is greater [29] in test animals fed a high fat-diet, excluding body weight as a co-factor. Moreover, the effects of a high-fat diet were inhibited in rats that were administered anti-inflammatory drugs (rosuvastatin, rosiglitazone) as shown histologically [30].

In addition, increase in serum nitrite and malondialdehyde levels and the reduction in vitamin E, Trolox Equivalent Antioxidant Capacity, and Ferric Reducing Antioxidant Power levels indicate the role of oxidative stress in OA [31]. Besides, the higher oxidative stress in EF than in subcutaneous tissue is striking [32]. Increased oxidative stress may play a role in both OA progression and subclinical atherosclerosis.

Our study has some limitations. It is impossible to precisely identify the beginning point of OA pathology and its total duration. In addition, small sample size and inability to completely eliminate the previous causes that could affect the relationship between EF and OA are the main limitations. The gold standard for EF mea-

surement is MRI, not echocardiography. However, echocardiographic measurements are well correlated with MRI ( $r=0.91$ ,  $P=0.001$ ) [8]. Its mainstream availability, in addition to being noninvasive and inexpensive, are the major advantages of echocardiography.

### Conclusions

In our study, we detected thicker EF values in OA patients compared to the control group, independent of BMI. In addition, EF thickness was seen to gradually increase as OA grade increases. The results indicate that the effect of obesity on OA is not only mechanical, but it also increased cardiovascular morbidity and mortality, suggesting an association with visceral adiposity and the inflammatory process. EF thickness may be a simple but important indicator for detection of subclinical atherosclerosis in OA patients.

### Disclosure of conflict of interest

None.

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