Epicardial fat thickness in patients with psoriasis vulgaris

Psoriasis vulgarisli hastalarda epikardiyal yağ kalınlığı

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ABSTRACT

Objectives: Psoriasis vulgaris is one of the most common skin disorders. Patients with psoriasis carry an excessive risk of coronary artery disease. Visceral adipose tissue around the heart affects the heart and coronaries by secreting proatherogenic mediators. It can be evaluated easily by measurement of epicardial fat thickness (EFT). The aim of this study was to investigate EFT in patients with psoriasis vulgaris.

Study design: One hundred and fifteen adult patients (62 male; mean age 33.6±6.0 years) with psoriasis vulgaris (Group 1) and 60 age- and sex-matched healthy individuals (28 male; mean age, 32.5±8.3 years) (Group 2) were included in this study. EFT was obtained by transthoracic echocardiography. Disease-specific characteristics of the patients were recorded. Serum glucose, lipid profile and high-sensitive C-reactive protein (hs-CRP) levels were measured.

Results: EFT and hs-CRP were significantly higher in Group 1 than in Group 2 (5.7±1.2 *vs.* 4.1±1.0 mm, p<0.001 and 0.52±0.45 mg/dl *vs.* 0.19±0.17 mg/dl, p<0.001, respectively). The psoriasis disease activity score and hs-CRP were found to be independent predictors of EFT in patients with psoriasis vulgaris (β=0.21, t=2.67, p=0.01 and β=0.62, t=7.72, p=0.001, respectively).

Conclusion: Our findings indicate that EFT was significantly higher in patients with psoriasis vulgaris compared with the controls. It was more prominent in patients with severe disease.

ÖZET

Amaç: Psoriazis sık görülen bir cilt hastalığıdır. Bu hastalarda koroner arter hastalığı riski artmıştır. Kalbi saran yağ dokusu salgıladığı proaterojenik maddeler ile hem kalbi hem de koronerleri etkiler ve transtorasik ekokardiyografi ile epikardın yağ kalınlığı (EYK) ölçülerek kolayca değerlendirilebilir. Bu çalışmada, psoriazis hastalarının EYK'ları ölçülerek sağlıklı kişilerle karşılaştırıldı.

Çalışma planı: Yüz on beş erişkin hasta (62 erkek; ort. yaş 33.6±6.0 yıl) (1. grup) ve benzer yaş ve cinsiyette 60 sağlıklı gönüllü (28 erkek; ort. yaş 32.5±8.3 yıl) (2. grup) çalışmaya alındı. Transtorasik ekokardiyografi ile EYK ölçüldü. Psoriazisin değerlendirilmesinde kullanılan ölçütler kullanılarak hastalığın şiddeti ve yaygınlığı değerlendirildi. Ayrıca, serum açlık glukozu, lipit profili ve yüksek duyarlıklı C-reaktif protein (hs-CRP) seviyeleri ölçüldü.

Bulgular: Psoriazis hastalarında EYK ve hs-CRP kontrol grubuna göre daha yüksekti (sırasıyla, 5.7±1.2 mm ve 4.1±1.0 mm, p<0.001 ve 0.52±0.45 mg/dL ve 0.19±0.17 mg/dL, p<0.001). Psoriazis aktivite skoru (PASI) ve hs-CRP, psoriazis hastalarında EYK'nın bağımsız ön gördürücüleriydi (sırasıyla, β=0.21, t=2.67, p=0.01 ve β=0.62, t=7.72, p=0.001).

Sonuç: Bu çalışma, psoriazisi bulunanlarda sağlıklı kişilere göre EYK'nın arttığını ve bu artışın hastalığın şiddetiyle ilişkili olduğu göstermiştir.

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Psoriasis vulgaris is one of the most prevalent T-cell-mediated, chronic, multisystemic, inflammatory diseases, and is characterized by epidermal hyperproliferation, abnormal keratinocyte differentiation, T-lymphocyte infiltration, and increased expression of cytokines, which results in the formation of inflamed plaque affecting the skin, scalp, nails, and joints.[1] Although the pathogenesis of psoriasis is still not fully understood, systemic inflammatory response and oxidative stress are considered the most important mechanisms in the development of the disease.[2] Studies have shown that psoriasis vulgaris is associated with atherosclerosis and related disorders, which result in excessive cardiovascular morbidity and mortality.[3-8] This association is not only the result of the fact that cardiovascular risk factors like hypertension (HT), diabetes mellitus, obesity, smoking, and dyslipidemia have been found to be more prevalent in patients with psoriasis vulgaris, since psoriasis confers an independent risk even after compensating for these risk factors.[9]

Abbreviations:

BMI	*Body mass index*
BSA	*Body surface area*
CAD	*Coronary artery disease*
COV	*Coefficient of variations*
CT	*Computed tomography*
EFT	*Epicardial fat thickness*
EST	*Exercise stress test*
hs-CRP	*High-sensitive C-reactive protein*
HT	*Hypertension*
IL	*Interleukin*
MRI	*Magnetic resonance imaging*
NAPSI	*Nail Psoriasis Severity Index*
PASI	*Psoriasis Area and Severity Index*
PSI	*Psoriasis Severity Index*
TNF	*Tumor necrosis factor*
TTE	*Transthoracic echocardiography*

Visceral adipose tissue encircling the heart and coronaries, namely epicardial fat, acts as a local energy supply for the adjacent myocardium and as a buffer against toxic levels of free fatty acids.[10] It also serves as a potential endocrine organ by secreting several cytokines, chemokines, and proinflammatory hormones.[11] Previous studies have demonstrated its association with obesity, metabolic syndrome, HT, atrial fibrillation, and atherosclerosis.[11-13] Its close anatomical location proximally to the adventitia of the coronary arteries and secretory function as an important source of proatherogenic mediators were suggested as the underlying pathophysiology of its strong correlation with coronary artery disease (CAD).[14] A recent meta-analysis proved its value as an effective marker in the prediction of CAD.[15] Although computed tomography (CT) and magnetic resonance imaging (MRI) can demonstrate epicardial fat tissue more precisely, transthoracic echocardiography (TTE) has been validated instead as a noninvasive, feasible, and reproducible method for quantification by measuring epicardial fat thickness (EFT).[16]

The aim of this study was to evaluate EFT in patients with psoriasis vulgaris.

PATIENTS AND METHODS

Patients

This study enrolled consecutive patients with psoriasis vulgaris over 18 years of age with a minimum disease duration of 0.5 years who admitted to the Dermatology Department, Faculty of Medicine, BezmiÂlem Foundation University, Istanbul, Turkey (Group 1). Age-, sex- and body mass index (BMI)-matched healthy individuals recruited from hospital staff and their relatives were included in this study as the control group (Group 2). None of the patients or control subjects had a history of CAD or other atherosclerotic diseases (cerebrovascular, peripheral artery disease, etc.). All the participants underwent treadmill exercise stress test (EST) in order to rule out CAD. Any participants with ischemic electrocardiographic changes (horizontal or downsloping ST-segment depression by 1 mm or more), complex arrhythmias, or symptoms of ischemia during the EST were excluded from the study. Participants with past or concurrent diseases, such as HT, diabetes mellitus, dyslipidemia, lung diseases and/or pulmonary HT, valvular heart diseases, liver or kidney diseases, collagen vascular diseases, rhythms other than sinus, any cardiovascular drug use including statins, and abnormal thyroid function or serum electrolyte values were also excluded from the study. Obese subjects (BMI $\geq$30 kg/m^2) were excluded from the study to rule out the effects of obesity. All subjects provided their informed consent and the study was approved by the local ethics committee.

The age, gender, age of onset, duration of disease, and drug history of each patient were recorded. Height, weight, BMI, and waist circumference were assessed in all patients. Biochemical variables such as fasting glucose levels and lipid panel were analyzed. Serum high-sensitive C-reactive protein (hs-CRP) level was obtained by the nephelometric method using a Dade Behring Cardio Phase kit (Dade Behring Inc.; Newark, DE, USA).

Echocardiography

Each patient underwent a complete TTE performed

using a Philips iE55 echocardiograph (Philips Medical Systems; Andover, MA, USA) and a 3.5 MHz transducer. Standard parasternal and apical views were obtained in the left lateral decubitus position and analyzed according to current guidelines.[17] Images were digitally stored and reviewed by two experienced cardiologists (EE, ES) blinded to the patients' information. One week after the first measurement, echocardiograms of 10 patients and 10 controls were randomly selected, and EFT was measured a second time to assess intraobserver variability.

To obtain a reliable measurement of EFT, we used the method described by Iacobellis et al.[11] EFT was defined as the relatively echo-free space between the outer wall of the myocardium and the visceral layer of the pericardium. EFT was measured at the point on the free wall of the right ventricle at end systole, perpendicular to the aortic annulus for parasternal long-axis view and perpendicular to the interventricular septum at mid chord and tip of the papillary muscle level for parasternal short-axis view. The average value of three cardiac cycles from each echocardiographic view was determined as EFT.

Evaluation of disease activity

The diagnosis of psoriasis vulgaris was based on dermatologist diagnosis and/or description of characteristic lesions. These lesions were most frequently well-demarcated bright red plaques covered by adherent silver-white scales, often symmetric, especially on the scalp and extensor surfaces of limbs. The disease duration of the patients ranged from 0.5 to 40 years (mean, 12.2±8.4). Clinical severity was determined according to the Psoriasis Area and Severity Index (PASI).[18] The PASI assesses four body regions: head, trunk, upper extremities, and lower extremities. For each region, the surface area involved is graded from 0 to 6, and each of the three variables (erythema, thickness and scaling of the plaques) is graded from 0 to 4. The scores from the regions were summed to determine a PASI score ranging from 0 to 72. The Psoriasis Severity Index (PSI) was also used to evaluate clinical signs (erythema, thickness and scaling) on a scale of 0 (absent) to 3 (severe).[19] The affected body surface area (BSA) was also evaluated. The Nail Psoriasis Severity Index (NAPSI) was used to quantify the degree of nail changes.[20] The NAPSI was assessed separately for each fingernail and toenail. It is a numeric, simple tool for evaluation of nail psoriasis. This scale is used to evaluate the severity of nail bed psoriasis and nail matrix psoriasis. Each nail is evaluated for the presence or absence of nail matrix disease (pitting, leukonychia, red spots in the lunula, nail plate crumbling) and nail bed disease (oil drop/salmon patch discoloration, onycholysis, nail bed hyperkeratosis, and splinter hemorrhage). The sum of the scores for all of the nails is the patient's NAPSI. Nail involvement was considered for patients with a NAPSI score ≥1. The disease-specific characteristics (age of onset, duration of psoriasis, mean PASI, mean PSI, mean NAPSI, and number of patients with nail involvement) of the psoriasis patients are summarized in Table 1. Most of the patients had mild psoriasis (58 patients (50.8%), mean PASI score, 3.8±4.1) and received local treatment.

Statistical analysis

Continuous variables were reported as mean±standard deviations (SD) and categorical variables were ex-

Table 1. Disease specific characteristics of patients with psoriasis vulgaris

	Mean±SD / (Median)
Mean age of onset of psoriasis (years)	22.3±8.5 (1-43)
Mean duration of disease (years)	12.2±8.4 (0.5-40)
Mean PASI score	3.8±4.1 (0.0-18.6)
Mean PSI score	1.6±0.8 (0-3)
Mean Affected BSA (%)	6.8±10.3 (0-90)
Mean NAPSI score	23.4±20.9 (0-87)
% of patients with nail involvement	62.6 (72/115)

Continuous variables were presented as mean, standard deviation and range; categorical variables were presented as percentage and proportion. SD: Standard deviation; PASI: Psoriasis area and severity index; PSI: Psoriasis severity index; BSA: Body surface area; NAPSI: Nail psoriasis severity index.

pressed as percentages. The variables between the two groups were compared using the χ^2 and unpaired t-tests. The correlations between EFT and clinical variables were assessed by Pearson and Spearman correlation tests. A stepwise linear regression analysis was performed to identify the independent relationships of EFT with other variables. A value of $p<0.05$ was considered statistically significant. The Statistical Package for the Social Sciences (SPSS) 19.0 for Windows program was used for the statistical analysis. Intra- and interobserver agreements of the EFT measurement were tested according to the statistical methods proposed by Bland and Altman. The intraobserver agreement was 94.6% and coefficient of variations (COV) was 3.8% ($p<0.01$). The interobserver agreement was 92.8% and COV was 4.8% ($p<0.01$).

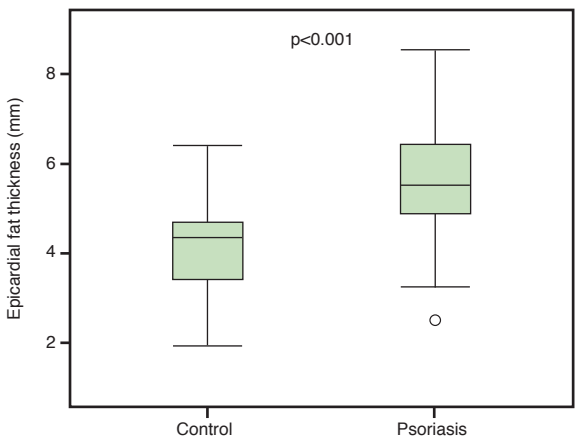

Figure 1. Epicardial fat thickness values in patients with psoriasis vulgaris and controls.

RESULTS

The descriptive demographical characteristics of the groups are shown in Table 2. One hundred and fifteen patients (62 male; mean age, 33.6±6.0 years) and a control group of 60 participants (28 male; mean age, 32.5±8.3 years) were included in this observational study. There were no statistically significant differences between groups in terms of age, gender, smoking ratio, family history of CAD, BMI, and waist circumference. The mean systolic and diastolic blood pressure and heart rate were also similar. Biochemi-

Table 2. Demographic characteristics of the study population

	Group 1 (Psoriatic) (n=115)	Group 2 (Control) (n=60)	*p*
	Mean±SD	Mean±SD	
Age (years)	33.6±6.0	32.5±8.3	NS
Male gender	62 (53.9)	28 (46.7)	NS
Current smoker	46.9 (54/115)	38.3 (23/60)	NS
Family history of CAD	18.3 (21/115)	16.7 (10/60)	NS
BMI (kg/m^2)	26.1±3.1	25.2±3.2	NS
Waist circumference (cm)	92.3±10.1	88.7±11.9	NS
Office systolic BP (mmHg)	121.9±10.6	118.3±11.6	NS
Office diastolic BP (mmHg)	75.8±8.7	73.2±9.6	NS
HR (beat/minute)	78.5±9.9	74.1±11.5	NS
Fasting glucose (mg/dL)	92.2±11.6	88.5±12.7	NS
Total cholesterol (mg/dL)	185.4±37.4	179.1±33.8	NS
Serum LDL cholesterol (mg/dL)	129.4±33.7	127.7±26.1	NS
Serum HDL cholesterol (mg/dL)	49.2±12.9	48.4±13.5	NS
Serum triglycerides (mg/dL)	125.3±77.3	126.2±67.0	NS
Sedimentation (mm/h)	14.4±10.2	11.0±9.6	NS
hs-CRP (mg/dL)	0.52±0.45	0.19±0.17	**0.001**

Continuous variables were presented as mean±standard deviation (SD), and categorical variables were presented as frequencies with percentages. CAD: Coronary artery disease; BMI: Body mass index; BP: Blood pressure; HR: Heart rate; HDL: High-density lipoprotein; LDL: Low- density lipoprotein; hs-CRP: High sensitive C-reactive protein; NS: Non-significant.

Table 3. Bivariate correlations of anthropometric and laboratory variables with epicardial fat thickness

	Correlation coefficient (r)	*p*
Age	0.128	0.091
Weight	0.316	**0.001**
Body mass index	0.300	**0.001**
Waist circumference	0.297	**0.001**
Low-density lipoprotein-cholesterol	0.088	0.285
High sensitive C-reactive protein	0.451	**0.001**

Table 4. Bivariate correlations of disease specific characteristics with epicardial fat thickness in patients with psoriasis vulgaris

	Correlation coefficient (r)	*p*
Psoriasis area and severity index	0.703	**0.001**
Body surface srea	0.481	**0.001**
Psoriasis severity index	0.665	**0.001**
Nail Involvement	0.315	**0.001**
Nail psoriasis severity index	0.237	0.045
Duration	0.032	0.733

cal data including serum glucose, lipid profile and erythrocyte sedimentation rate were not significantly different between groups, but hs-CRP levels were significantly higher in patients with psoriasis compared to controls (0.52±0.45 *vs.* 0.19±0.17 mg/dl, p=0.001).

As shown in Fig. 1, EFT was significantly increased in Group 1 compared to Group 2 (5.7±1.2 mm *vs.* 4.1±1.0 mm, p<0.001). When all participants were evaluated, EFT was correlated with weight, BMI, waist circumference, and hs-CRP levels (Table 3). In patients with psoriasis, EFT was also correlated with disease-specific indexes (Table 4) (Fig. 2). After stepwise linear regression analysis, hs-CRP and PASI were found to be independent predictors of EFT in patients with psoriasis vulgaris (β=0.21, t=2.67, p=0.01; β=0.62, t=7.72, p=0.001, respectively).

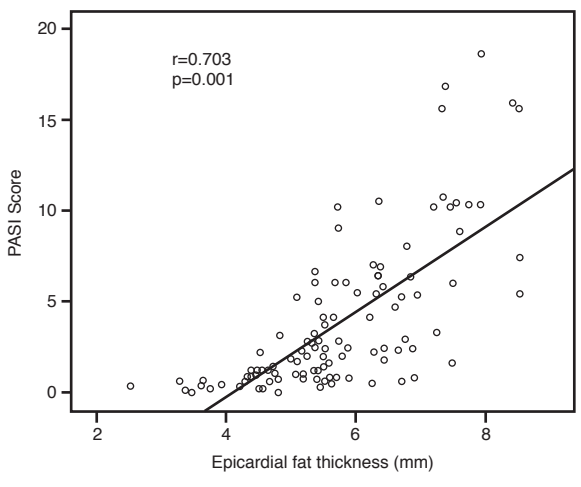

Figure 2. Scatter plot of the PASI score against EFT (mm) (r=0.703, p=0.001).

DISCUSSION

The principal new finding of this study is that EFT was significantly increased in patients with psoriasis vulgaris compared with the control group. To the best of our knowledge, this is the first study to evaluate the potential association between psoriasis and EFT as a marker of atherosclerosis.

Ectopic fat around the heart, a type of regional fat distribution in the human body, has gained clinic attention recently.[11,12,15] It covers nearly 80% of the heart's surface and extends into the myocardium following the adventitia of the coronaries.[21] Accumulated data have revealed that it has some other functional and metabolic properties that go beyond the mechani-

cal protection of the heart from trauma and storage of excess calories.[11,12] By secretion of proinflammatory molecules such as cytokines like interleukin (IL)-1β, IL-6 and tumor necrosis factor (TNF)-α, leptin, plasminogen activator inhibitor-1, and monocyte chemoattractant protein-1, it contributed to promotion of atherosclerosis, which further leads to CAD.[22] A close association between epicardial fat tissue and subclinical atherosclerosis, coronary calcium score, and presence and severity of coronary stenosis was reported in several observational studies.[14,15,23-26] Eroglu et al.[27] evaluated EFT in patients with CAD and found that EFT was significantly higher in these patients compared to subjects with normal coronary arteries. In addition, EFT emerged as an independent predictor of microvascular dysfunction identified with reduced coronary flow reserve in women with chest pain and angiographically normal coronaries.[28] Xu et al.[15] reviewed the literature about epicardial adipose tissue and CAD, including 2872 patients. They concluded that EFT could be used as an effective marker to assess atherosclerosis and predict CAD. Furthermore, after adjustment of other cardiovascular risk factors like BMI, waist circumference, and CRP level, EFT was still significantly associated with calcified coronary plaque burden.[25,26]

Psoriasis vulgaris is a chronic inflammatory skin disease affecting nearly 3% of the global population, including 125 million persons worldwide.[4] Papulosquamous plaque symmetrically located on extensor surfaces of the joints is the most common clinical manifestation. Not just a skin disease, it is also a systemic inflammatory condition, similar to other inflammatory immune disorders, such as rheumatoid arthritis and systemic lupus erythematosus.[5] Atherosclerosis shares the same pathogenetic mechanisms: chronic inflammation, endothelial dysfunction, and increased oxidative stress.[6] A higher prevalence of atherosclerotic diseases, not only of CAD, but also of cerebrovascular and peripheral vascular diseases, is reported in patients with psoriasis compared with controls after controlling for diabetes, HT, dyslipidemia, and smoking.[5] Although patients whose psoriasis develops at a young age and those with more severe disease are at the greatest risk, even patients with mild-to-moderate disease had an increased risk of myocardial infarction with a hazard ratio of 1.54 (95% confidence interval [CI], 1.24-1.91) as compared to patients without psoriasis.[8] Existing data are also sufficient to indicate that atherosclerosis should be considered as systemic involvement of psoriasis, and numerous studies have demonstrated manifestations of atherosclerosis, such as increased carotid intima-media thickness, arterial stiffness and endothelial dysfunction, in these patients.[29-32] To the best of our knowledge, this is the first study that evaluates the association between psoriasis and EFT, as a marker of atherosclerosis.

Patients with psoriasis vulgaris had significantly increased EFT, and it was correlated with severity of the disease. In previous studies, many individual risk factors that compose metabolic syndrome, such as visceral obesity, dyslipidemia, HT, and impaired glucose tolerance, were associated with EFT.[12,15] Therefore, our study group did not include patients with these comorbidities in order to rule out possible effects of accompanying diseases. We used a number of indexes (PASI, PSI, BSA, and NAPSI) to evaluate the disease severity in psoriatic patients, and only PASI was correlated with EFT. Despite some disadvantages, PASI is the most widely used instrument in clinical practice to evaluate psoriasis disease severity.[33]

Some authors have reported a correlation between CAD risk and severity of psoriasis.[8] Data in the literature have pointed to a pivotal role of chronic systemic inflammation in the pathogenesis of atherosclerosis, although the etiology is multifactorial. Higher PASI scores indicate more severe psoriasis, and PASI was found to be correlated with serum levels of systemic inflammatory cytokines, such as TNF-α and IL-6.[34] Similarly, in this study, serum hs-CRP level, as an indicator of proinflammatory state, was increased in patients with psoriasis vulgaris compared to healthy controls and was correlated with EFT.

Study limitations

Some limitations of the present study were the relatively small number of participants and lack of follow-up to look for development of overt atherosclerotic disease. We performed TTE to measure EFT. Failure to measure EFT with several other imaging technologies, such as CT and MRI, which allow direct visualization of epicardial adipose tissue, was another limitation of the study. However, TTE-derived EFT measurements were correlated highly with MRI-determined EFT in a previous study.[35] Moreover, we do not have data before and after initiation of therapy to

determine whether this treatment affects EFT.

In conclusion, we have shown that patients with psoriasis vulgaris have higher EFT compared to control subjects without psoriasis. Moreover, serum hs-CRP level and PASI score, which represent the severity of the disease, were demonstrated as independent predictors of EFT in psoriatic patients. Although the exact mechanism remains unclear, chronic systemic inflammation may be responsible for the increased EFT in these patients. Further long-term prospective studies are needed to clarify the clinical utility and prognostic importance of EFT in patients with psoriasis vulgaris.

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