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Subclinical Left Ventricular Dysfunction in Patients with Psoriasis Assessed Using Speckle Tracking Echocardiography

Psöriyazis Hastalarında Subklinik Sol Ventriküler Disfonksiyonun Speckle Tracking Ekokardiyografi ile Değerlendirilmesi

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ABSTRACT Objective: Psoriasis, which is a chronic inflammatory disease is associated with an increased risk of cardiovascular (CV) diseases (CVD). Currently, no method is available to evaluate subclinical CV dysfunction in patients with psoriasis. The aim of the study was to evaluate left ventricular (LV) function in patients with untreated psoriasis but no risk factors for CV disease (CVD). **Material and Methods:** Thirty patients with psoriasis without any CVD or risk factors for CVD and 20 age- and gender-matched controls were recruited. All patients underwent detailed transthoracic echocardiography, including speckle tracking-derived strain analysis. **Results:** Speckle tracking echocardiography showed significantly lower global circumferential strain in psoriatic patients compared to healthy controls (mean ±SD: -23.34±6.74% vs. -27.53±4.11%, respectively, p<0.001). No significant differences were found in terms of global longitudinal strain, aortic flow velocity, pulmonary arterial flow velocity, LV end-systolic volume, LV end-diastolic volume, LV ejection fraction, peak of early diastolic (E) and late diastolic (A) flow velocity, E/A ratio, and levels of biochemical markers, including C-reactive protein, between the patients and controls (p>0.05). **Conclusion:** Subclinical myocardial dysfunction was seen in the patients with psoriasis who had no conventional risk factors for CVD using two-dimensional strain imaging. We believe that this imaging technique may be useful for early detection of CVD development in patients with psoriasis.

Keywords: Cardiovascular diseases; psoriasis; two-dimensional strain imaging

ÖZET Amaç: Kronik, inflamatuar bir hastalık olan psöriyazis artmış kardiyovasküler (KV) hastalık (KVH) riski ile ilişkilidir. Şu anda, psöriyazis hastalarında subklinik KV disfonksiyonu inceleyen bir yöntem bulunmamaktadır. Bu çalışmanın amacı, tedavi almayan ve KVH gelişimi açısından hiçbir risk faktörü bulunmayan psöriyazisli hastalarda sol ventrikül fonksiyonunu incelemektir. **Gereç ve Yöntemler:** Bilinen KVH öyküsü veya KVH gelişimi için hiçbir risk faktörü bulunmayan 30 psöriyazis hastası ve yaş ve cinsiyet açısından uyumlu 20 sağlıklı kontrol çalışmaya dahil edildi. Tüm hastalara speckle traking derivasyonlar da dahil olmak üzere detaylı transtorasik ekokardiyografi yapıldı. **Bulgular:** Speckle traking ekokardiyografi ile global sirkümferensiyal gerilme, psöriyazis hastalarında kontrollere göre belirgin olarak daha düşük saptandı (ortalama ±SS: -23,34±%6,74 vs.-27,53±%4,11, sırasıyla, p<0,001). Global longitudinal gerilme, aort akım hızı, pulmoner arter akım hızı, sol ventrikül sistolsonu hacmi, sol ventrikül ejeksiyon fraksiyonu, erken diyastolik akım hızı (E) ve geç diyastolik (A) akım hızı tepe noktası sistol sonu volüm, E/A oranı ve C-reaktif protein de dahil olmak üzere biyokimyasal parametreler açısından psöriyazis hastaları ve kontrol grubu arasında anlamlı fark saptanmadı (p>0,05). **Sonuç:** Kardiyovasküler hastalık gelişimi açısından geleneksel risk faktörü bulunmayan psöriyazis hastalarında iki-boyutlu gerilme görüntüleme kullanılarak subklinik myokard disfonksiyonu saptandı. Bu görüntüleme tekniğinin psöriyazis hastalarında KVH gelişimini erken dönemde belirlemek açısından faydalı olabileceğini düşünmekteyiz.

Anahtar Kelimeler: Kardiyovasküler hastalık; psöriyazis; iki boyutlu gerilme görüntüleme

Psoriasis which is a common chronic inflammatory skin disease, affects 2%-3% of the general population; it is associated with an increased risk of cardiovascular disease (CVD), but it cannot be explained by the presence of traditional risk factors.[1-6] Currently, data regarding the pathogenesis of myocardial impairment in patients with psori-

asis are insufficient.[7] Although some studies have shown that psoriasis does not impair left ventricular (LV) systolic function, recent reports have suggested a higher incidence of subclinical LV dysfunction in patients with psoriatic arthritis (PsA) and psoriasis than in those without.[8-11] Ejection fraction (EF) measurement, tissue Doppler imaging (TDI), Doppler strain imaging, and, more recently, speckle tracking echocardiography (STE) are commonly used for assessing LV function.[12] STE is a new noninvasive ultrasound imaging modality based on two-dimensional (2D) echocardiography and relatively angle-independent technology; it has been proposed as a reliable and sensitive method for assessing subclinical myocardial dysfunction.[13] STE also shows preclinical myocardial dysfunction before changes appear in the LV ejection fraction (LVEF) in patients who have diseases accompanied with systemic inflammation, eg. rheumatoid arthritis, systemic sclerosis, PsA, and psoriasis.[7,11,10,14,15] However, insufficient data are available on subclinical CVD-related comorbidities in patients with psoriasis who are otherwise symptom-free.

The present study aimed to evaluate the role of 2D strain imaging for assessing subclinical LV systolic dysfunction in untreated patients with psoriasis without risk factors for CVD and the relationship between STE measurements and psoriasis.

MATERIAL AND METHODS

STUDY POPULATION AND PROTOCOLS

The study group comprised 30 patients with untreated psoriasis, no risk factors for CVD, and no systemic disease, as confirmed by a physical examination, laboratory tests, and imaging studies. The subjects were recruited from the Department of Dermatology. For comparison, 20 healthy controls without psoriasis or other systemic inflammatory disease were enrolled from among hospital staff volunteers. The body mass index (BMI), biochemical measurements, and serum C-reactive protein (CRP) levels were recorded. Subjects with a history of topical or systemic psoriasis therapy were excluded. Only those with a normal BMI (18.5-25 kg/m^2) were included. The controls had normal findings on performing physical examination, chest roentgenography, and electrocardiography, and none had CVD or a disease in any other organ system. Subjects were excluded if they had a documented history of CVD. Subjects with a habit of smoking and/or alcohol consumption were also excluded. BMI and conventional risk factors for CVD, such as history of smoking, diabetes mellitus, hypercholesterolemia, and hypertension were excluded.

The study protocol was approved by the local ethics committee (date of approval: 06/01/2015, number of issue: 426) and conducted in accordance with the principles expressed in the Declaration of Helsinki. All subjects provided written informed consent.

Demographic data, disease characteristics, biochemical test results, and transthoracic echocardiograms of all subjects were prospectively obtained on the same day following overnight fasting. Serum levels of glycated hemoglobin, fasting glucose, creatinine, total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, and CRP were measured in all subjects using fasting venous blood samples. Psoriasis was graded according to the Psoriasis Area Severity Index (PASI), as calculated at the time of blood collection by a single dermatologist.[16]

CONVENTIONAL ECHOCARDIOGRAPHY

Conventional echocardiography was performed using the Philips iE33 ultrasound system (Koninklijke Philips Electronics N.V., Amsterdam, Netherlands). All subjects underwent M-mode, 2D Doppler (continuous and pulsed wave), and color Doppler examinations in the left lateral position. The structure of the mitral, aortic, tricuspid, and pulmonary valves and the pericardial space were examined by echocardiography to detect pericardial effusion. The following variables were assessed: LV end-diastolic and end-systolic volume, thickness of the interventricular septum, thickness of the LV posterior wall, right ventricular end-diastolic volume, and LVEF. Doppler echocardiography was used to determine transmitral flow, and

the apical four-chamber view was used to determine pulmonary venous flow. The following variables were examined using Doppler recordings as parameters of LV filling: peak of early diastolic (E) and late diastolic (A) flow velocity, E/A ratio, deceleration time of flow velocity in early diastole, isovolumic relaxation time, and peak pulmonary arterial flow velocity during ventricular systole.

2D SPECKLE TRACKING STRAIN ANALYSIS

STE is a new 2D echocardiographic technique. It gives a meticulous evaluation of the damage of the LV myocardium through following the acoustic markers- called speckles-within the cardiac movement. The speckles were defined as standard gray-scale 2D images.[17] Longitudinal strain, as an evaluation of the length changes of the myocardium, was assessed from the three apical views, each involves different walls of the myocardium and a total of 18 segmental strain curves were obtained by dividing each wall into three parts (basement, middle, apex), and the mean peak systolic strain value of these 18 segments was the global longitudinal strain. The circumferential strain used to evaluate myocardial shortening/ lengthening along the LV curvature was measured from the LV mid-ventricular short-axis view. The global circumferential strain was calculated from the average peak systolic strain value of six segments. Negative values were used to determine global longitudinal and circumferential strains, and less negative values indicated lower strains. All echocardiographic studies and measurements were performed by an experienced cardiologist who was blinded to the clinical characteristics of the subjects.

STATISTICAL ANALYSES

Statistical analyses were performed using SPSS software version 15 (SPSS, Inc., Chicago, IL, USA). Data were compared using the Mann–Whitney U test and are presented as mean ± standard deviation (SD). Correlations were identified by Spearman's correlation analysis. A p-value of <0.05 was considered significant.

RESULTS

CLINICAL CHARACTERISTICS

No significant differences were observed between the patients with psoriasis and healthy controls with regard to age and gender ($p > 0.05$). The mean age of the patients with psoriasis and controls was 34.63±10.2 and 33.1±7.22 years, respectively. The average Psoriasis Area Severity Index of the patients with psoriasis ranged from 1.8 to 52.5, with a mean of 13.23±10.36. The mean disease duration was 9.6 years. The BMI of all subjects was within the normal limits. No subjects had undergone psoriasis therapy and none had risk factors for CVD or any other accompanying disease. No significant differences were observed in biochemical parameters, including CRP, between the patients with psoriasis and controls.

The clinical characteristics of the patients with psoriasis and controls are shown in Table 1.

TABLE 1: Demographic features of the patients and controls.

	Psoriasis (n= 30)	Controls (n= 20)	p
Age (years)	34.63±10.2	33.1±7.22	[a]0.691
Gender	18 male 12 female	10 male 10 female	[b]0.49
Body mass index (kg/m^2)	23.1±1.79	22.6±2.07	[a]0.336
Fasting glucose	85.6±9.41	89.35±9.34	[a]0.084
C-reactive protein	5.07±3.41	4.41±2.98	*[a]0.014**
Creatinine	0.84±0.17	0.9±0.15	[a]0.208

[a]p value for the Mann-Whitney U test comparing age, body mass index, fasting glucose C-reactive protein and creatinine among patients with psoriasis and healthy control subjects.
[b]p value for the Pearson chi square test comparing gender ratio among patients with psoriasis and healthy controls. *p<0.05.

ECHOCARDIOGRAPHIC PARAMETERS

Myocardial strain was measured in two different directions using speckle tracking analysis to investigate myocardial function impairment. The STE analysis results showed that the patients with psoriasis had significantly lower global circumferential strain than the controls (mean±SD:- 24.13± 7.03% vs, -27.45±4.05 %, respectively; *p*=0.024). The EF values were statistically significantly higher in psoriasis patients than in controls (mean±SD: 70.53±7.17, 66.7±4.65, respectively p= 0.018). Pulmonary arteria flow velocity was also higher in psoriasis patients than in controls (mean±SD: 1.06±0.16, 0.97±0.14, respectively p= 0.029). No significant differences were found in terms of global longitudinal strain, aortic flow velocity, LV end-systolic and end-diastolic volume, E flow velocity, A flow velocity, or E/A ratio (p>0.05). None of the subjects had disorders involving the valves.

There was no correlation between the circumferential strain and age, lipids, or serum levels of fasting glucose, creatinine, or CRP (*p*>0.05, for all). In addition, there was no association between the results of global circumferential analysis and other disease-related factors, such as the disease severity score and disease duration (p>0.05). The STE results of LV systolic and diastolic function are shown in Table 2.

DISCUSSION

In the present study it was observed that despite the absence of a difference between the two groups in terms of EF and diastolic dysfunction, as examined by conventional echocardiography technique, a significant impairment was observed in the LV global circumferential strain, as evaluated through 2D speckle tracking study in untreated psoriasis patients, compared to healthy subjects, which is consistent with LV systolic dysfunction.

Psoriasis is an immune-mediated inflammatory skin disease of unknown etiology. Immunoinflammatory mechanisms shared by psoriasis and atherosclerosis may be the reason for the association between CVD and psoriasis.[18-20]

Although the association between psoriasis and CVD has been previously reported, few studies have used STE to assess subclinical myocardial impairment in psoriasis.[2-4,7,11,21,22] Zhao et al. conducted detailed echocardiographic examinations in 74 patients with severe psoriasis and reported significant dysfunctioning in LV global longitudinal and circumferential strains in all subjects; this finding was proposing the presence of subclinical myocardial dysfunction.[7] Bülbül Şen et al. evaluated STE images of 40 patients with psoriasis and found diastolic dysfunction to be more common in patients with psoriasis than in controls.[11] In the same

TABLE 2: Echocardiographic parameters of controls and of psoriatic patients

	Psoriasis (mean±SD)	Controls (mean±SD)	P
Aort flow velocity	1.27±0.23	1.28±0.2	0.857
Pulmonary arteria flow velocity	1.06±0.16	0.97±0.14	0.029*
Left ventricular end systolic volume (mL)	28.66±3.83	30.85±3.28	0.054
Left ventricular end diastolic volume (mL)	48.95±3.74	48.90±4.17	0.913
EF	70.53±7.17	66.7±4.65	0.018
E` velocity (cm/s)	0.72±0.16	0.74±0.097	0.648
A	0.57±0.15	0.54±0.13	0.677
E`/A	1.33±0.36	1.43±0.39	0.276
Speckle tracking derived strain			
Global longitudinal strain (%)	- 23.4±4.49	- 21.15±3.44	0.143
Global circumferential strain (%)	- 24.13±7.03	- 27.45±4.05	0.024*

E: peak of early diastolic flow velocity, A: late diastolic flow velocity P value for the Mann-Whitney U test comparing echocardiographic parameters among patients with psoriasis and healthy control subjects. *p < 0.05.

study, LV strain and all strain rate values were significantly lower in patients with psoriasis than in controls.[11]

In most of the aforementioned studies, subjects who were being evaluated for myocardial dysfunction had risk factors for CVD. We believe that this is a limitation for assessment of the relationship between subclinical myocardial dysfunction and psoriasis. Previously, the increased risk of CVD was considered to be due to an increased prevalence of risk factors associated with psoriasis, such as obesity, diabetes mellitus, hypertension, dyslipidemia, metabolic syndrome, peripheral vascular disease, atherosclerosis, alcoholism, and smoking.[23-29] As data on CVD manifestations in patients with psoriasis without clinically evident CVD or related risk factors are insufficient, it is unclear whether psoriasis or its comorbidities are an independent risk factor for CVD. Therefore, we excluded the patients with risk factors for CVD in the present study. Still, systolic function was found to be impaired in patients with untreated psoriasis, suggesting that psoriasis is a risk factor for CVD. Similarly, another study reported that psoriasis is an independent risk factor for myocardial infarction, even after controlling for conventional risk factors for CVD.[30] In the present study, the mean age of the subjects was 34 years, which may be considered to be an early age for CVD development. In other studies evaluating subclinical myocardial dysfunction with STE imaging in patients with psoriasis or PsA, the mean age of the subjects was 46, 41.1, 51.8, 41, and 51.5 years.[7,11,21,22,31] In the present study, although the subjects had no risk factors for CVD and were relatively young, myocardial dysfunction was still assessed using STE.

Adverse LV remodeling may be due to chronic systemic inflammation in patients with psoriasis.[10] The current study failed to find an association between CRP levels and 2D speckle tracking-derived strains, which brings up the hypothesis that myocardial dysfunction starts even in the absence of systemic inflammation in patients with psoriasis. Further studies are required to determine if myocardial dysfunction in patients with psoriasis is related to the inflammatory nature of the disease.

The results of the present study are unique in some aspects. To date, among reports in the literature, the subjects included in the present study were the youngest to have psoriasis with myocardial dysfunction. The development of CVD at the age of 34 years is uncommon.[24] None of the subjects had risk factors for CVD; this was not based on the patients' declaration but was rather confirmed based on physical examination, laboratory testing, and imaging analysis results. Moreover, EF values of psoriasis patients were higher than in controls, still STE revealed systolic dysfunction in patients presented as lower global circumferential strain. This may emphasize the fact that STE showing subclinical systolic dysfunction even in psoriasis patients with higher EF values. Also, the patients did not receive topical and/or systemic treatment for psoriasis in the last 6 months prior to the study. The aforementioned criteria were employed to investigate the systemic inflammatory effects of uncontrolled psoriasis on the myocardium. We believe that on the basis of these data, patients with psoriasis even without any risk factors for CVD at early ages should be carefully monitored to prevent CVD-related comorbidities. Further studies with more subjects and long follow-up periods are needed to clarify whether cardioprotective treatment is useful to prevent the development of CVD in the early stages of psoriasis.

This study was limited by the small sample size.

CONCLUSION

In conclusion, by comparing untreated psoriasis patients with controls, we found that patients with untreated psoriasis were significantly more likely to have LV systolic dysfunction, which manifested as reduced global circumferential strain values. Our results suggest that not only clinical but also subclinical cardiac dysfunction is more frequent in patients with psoriasis. We believe that a superiority of the study is that the patient group had no other medical problems than psoriasis, which allowed for the determination of whether psoriasis alone leads to impairment of myocardial functions even at an

early age. It may be concluded that 2D strain imaging, as used in the present study, is an objective technique for the diagnosis of LV systolic function in patients with psoriasis. Subclinical CVD-related morbidities should be carefully evaluated in patients with psoriasis.

Source of Finance

During this study, no financial or spiritual support was received neither from any pharmaceutical company that has a direct connection with the research subject, nor from a company that provides or produces medical instruments and materials which may negatively affect the evaluation process of this study.

Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

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