Clinical research

Assessment of subclinical cardiac damage in chronic plaque psoriasis patients: a case control study

Hatice Kaya Ozden[1], Mualla Polat[2], Serkan Ozturk[3], Güler Bugdayci[4]

[1]Dermatology Department, Kocaeli Derince Education and Research Hospital, Kocaeli, Turkey
[2]Faculty of Medicine, Abant İzzet Baysal University, Bolu, Turkey
[3]Department of Cardiology, Medical Faculty, Abant Izzet Baysal University, Bolu, Turkey
[4]Department of Biochemistry, Abant Izzet Baysal University, Bolu, Turkey

Submitted: 1 November 2016
Accepted: 25 November 2016

Arch Med Sci Atheroscler Dis 2016; 1: e126–e132
DOI: 10.5114/amsad.2016.64165

Corresponding author:
Hatice Kaya Ozden
Dermatology Department
Kocaeli Derince Education and Research Hospital
Ibn-i Sina St
41900 Kocaeli, Turkey
Phone: +90 5052347287
E-mail: hatcek@gmail.com

Abstract

Introduction: Epidemiological studies have suggested that patients with psoriasis are at an increased risk of developing cardiovascular diseases. Chronic inflammation may play a role in the pathogenesis of atherosclerosis in psoriasis patients. Recent studies have evaluated the expression of plasma endocan and homocysteine levels. Endocan is a marker of vascular endothelial damage, and homocysteine plays a role in the development of atherosclerosis. Plasma endocan and homocysteine levels, as well as echocardiographic parameters, were evaluated in patients with psoriasis to assess cardiovascular disease risk.
Material and methods: This was a prospective cohort analysis of 40 patients who were diagnosed with psoriasis and 40 healthy controls matched to the patient group according to demographic and biochemical parameters.
Results: Serum endocan and homocysteine concentrations were significantly higher in the psoriasis group than the control group ($p < 0.001$). Serum endocan concentrations correlated positively with disease duration ($p < 0.001$; $r = 0.725$). The Tei index (myocardial performance) was elevated in psoriasis patients ($p < 0.001$). Additionally, the E/A (mitral valve early diastolic peak flow velocity/mitral valve late diastolic peak flow velocity) and E/Em (early diastolic myocardial velocity) ratios were reduced in psoriasis patients ($p < 0.001$). Parameters indicative of left ventricular asynchrony were elevated significantly in the psoriasis group versus the control group ($p < 0.001$).
Conclusions: We observed a substantial increase in serum endocan and homocysteine concentrations, and significant differences in key parameters of cardiac function, in psoriasis patients relative to controls. These results are consistent with the hypothesis that subclinical cardiac damage is increased in patients with psoriasis and that psoriasis itself may be a cardiovascular risk factor.

Key words: cardiovascular comorbidity, endocan, echocardiography, homocysteine, psoriasis.

Introduction

Psoriasis is a chronic, immune-mediated, relapsing inflammatory dermatosis characterized by hyperproliferation of the epidermis [1]. Recent publications support the hypothesis that psoriasis is a systemic condition associated with various comorbidities [2, 3]. Activation of inflam-

matory pathways in psoriasis may play a role in the development of atherosclerosis and vascular endothelial damage, independent of 'conventional' risk factors. Thus, psoriasis itself may be a cardiovascular risk factor [4, 5].

Serum concentrations of homocysteine and endocan, biomarkers of subclinical atherosclerosis and cardiovascular risk, play an important role in many vascular diseases [6, 7]. Hyper-homocysteinemia increases oxidative stress, activates the coagulation cascade, and causes endothelial dysfunction and atherogenesis [7, 8]. Expression of plasma endocan parallels the expression of other pro-angiogenic factors, such as the vascular endothelial growth factors vascular endothelial growth factor-A (VEGF-A) and VEGF-C, which play a role in the development of atherosclerosis. Vascular endothelial growth factor is expressed by keratinocytes, stimulates endothelial cell proliferation, and induces intimal hyperplasia. Endocan is considered a potential novel marker of endothelial dysfunction [9].

Cardiovascular diseases (stroke, atherosclerosis, myocardial infarction) occur more frequently in patients with psoriasis relative to the general population and independently of other cardiovascular risk factors (e.g., hypertension, dyslipidemia, type 2 diabetes, metabolic syndrome, obesity). Similarly, psoriasis and atherosclerosis share similar immunological pathogenesis mechanisms [2–4]. Antigen-presenting cells in lymph nodes activate naïve T cells, resulting in increased expression of lymphocyte function-associated antigen 1 (LFA-1). Activated T cells migrate to the blood vessels and adhere to endothelial cells. T cells extravasate through the endothelium via LFA-1 and intercellular adhesion molecule 1 (ICAM-1). These activated T cells interact with dendritic cells, macrophages, and keratinocytes in psoriasis, and smooth muscle cells in atherosclerosis. The resultant release of chemokines and cytokines initiates inflammation [10–12]. In addition to the effects of CD4 T lymphocyte infiltration, proliferation of monocyte/macrophage and dendritic cells in both psoriasis and in atherosclerotic plaques increases local concentrations of Th1- and Th17-type cytokines, such as interferon (INF)-γ, IL-2, and tumor necrosis factor (TNF)-α [2, 10, 11]. Vascular endothelial growth factor, a potent pro-angiogenic factor expressed at high levels in psoriasis and atherosclerosis, can cause intimal hyperplasia of endothelial cells, contributing to the development of atherosclerosis [11–13].

In the present study, we investigated serum endocan and homocysteine concentrations and echocardiographic parameters in patients with psoriasis who did not have 'traditional' cardiovascular risk factors to assess the role of psoriasis in cardiovascular disease.

Material and methods

The study was reviewed and approved by the local ethics committee. The study group included 40 patients who were diagnosed with psoriasis and 40 healthy controls with similar demographic characteristics. Exclusion criteria for the patient and control groups included the presence of psoriasis types other than chronic plaque, systemic treatment for psoriasis, history of myocardial infarction, stroke, peripheral artery disease, coronary heart disease, angina pectoris, heart failure, left ventricular ejection fraction (LVEF) < 50%, atrial fibrillation, ischemic electrocardiography results, presence of a pacemaker, prolonged QRS (≥ 120 ms), hypertrophic cardiomyopathy, valvular heart disease, congenital heart disease, diabetes mellitus, dyslipidemia, smoking, obesity, uncontrolled hypertension (resting blood pressure ≥ 140/90 mm Hg), hepatic or renal dysfunction (creatinine > 1.5 mg/dl, aspartate and amino transferase levels greater than twice the upper limit), history of malignancy, local or systemic infection, impaired thyroid function or other systemic inflammatory disease and/or a diagnosis of psoriatic arthritis, and receiving biologic agents, such as tumor necrosis factor-α blockers. Chronic plaque psoriasis was diagnosed by a clinical examination of patients. The severity of psoriasis was scored using the Psoriasis Area Severity Index (PASI) by a dermatologist. The same dermatologist examined all study participants.

Collection and evaluation of blood samples

Venous blood samples were obtained from participants following a 12-h overnight fast. Blood samples were stored at –80°C following centrifugation (1,250 g, 15 min) for the extraction of serum and plasma. A Bio-Rad Benchmark Plus (Bio-Rad Laboratories, Hercules, CA, USA) ELISA plate reader was used to measure plasma endocan and homocysteine levels. Endocan plasma concentrations were measured using the Cloud-Clone ELISA kit (Catalog No: SEC463; Hu Corp., Houston, TX, USA) and homocysteine plasma concentrations were measured using the DRG brand ELISA kit (Catalog No: EIA-2925; DRG Instruments GmbH, Marburg, Germany), according to the manufacturers' protocols.

Evaluation of cardiac functions

Standard echocardiography

Echocardiographic evaluations were processed using the GE Vivid-S6 system (GE Vingmed, Horten, Norway) with the probe set at a frequency of 2–4 MHz. M mode, two-dimensional (2D), pulse-wave Doppler, continuous-wave Doppler, color flow, tissue Doppler imaging (TDI), and tissue synchroni-

zation imaging (TSI) methods were used with the patient in a supine or left lateral decubitus position. Following these scans, stroke volume, systolic volume, end diastole volume, and ejection fraction were calculated according to the modified Simpson rule using the software on the echocardiography device. Diastolic functions and flow through the mitral valve were evaluated with Doppler measurements. Maximum flow velocity (velocities, cm/s) of early (E velocity) and late (A velocity) waves, deceleration time of E waves (DT, ms), and isovolumetric relaxation and contraction times (IVRT and IVCT, respectively) were calculated using point Doppler. Mitral flow parameters were measured at the end of expiration and are expressed as the mean values of three cardiac cycles.

Tissue Doppler echocardiography (TDE)

Wall filter and gain were maintained at the minimum during compression, and reflections from unwanted images were maximized. Sampling volume width was set by changing the Nyquist limit to 15–20 cm/s. Ultrasonographic waves were pointed parallel to the lateral mitral annulus. The echocardiographic images obtained consisted of positive systolic, negative early diastolic, and negative late diastolic waves, showing myocardium movements using pulse-wave tissue Doppler. Peak systolic (Sm), early peak (Em), and late peak (Am) diastolic velocities were measured. The IVCT, IVRT, acceleration time, and ejection time (ET) were measured. Myocardial performance index (MPI) was calculated using the formula (IVRT + IVCT)/ET. Myocardial performance index is an expression of ventricular performance, also known as the 'Tei index.' This simple index includes systolic and diastolic parameters and is applicable to both the right and left ventricles (LVs). The reference range for MPI is 0.39 ±0.05. Values > 0.45 are considered abnormal.

Tissue synchronization imaging (TSI)

Tissue synchronization imaging is a technique based on color-coded imaging of the time intervals required to reach peak systolic velocity in different myocardial segments using DTI data. At least three cardiac cycles were recorded in TVI mode for offline analysis. Recorded images were analyzed using EchoPAC (EchoPAC PC-SW, ver. 6.0.0; Vingmed-GE). Standard deviation values of 12-segment peak systole time (Zs-12-SD) > 31.4 ms were deemed to indicate left ventricular asynchrony [14].

Statistical analysis

The SPSS software package (ver. 22.0; SPSS Inc., Chicago, IL, USA) was used for all analyses. Numerical data were evaluated using the Kolmogorov-Smirnov normality test. Continuous variables with a normal distribution are expressed as means ± standard deviation. Medians and minimum and maximum values were used to express variables not compatible with a normal distribution. When analyzing variables with a normal distribution, Student's *t*-test for independent samples was used to evaluate differences between two groups. The non-parametric Mann-Whitney *U*-test and Kruskal-Wallis test for two independent samples were used to analyze variables inconsistent with a normal distribution. In this study, a power analysis was not performed due to the small sample size. Results were evaluated with a 95% confidence interval. *P*-values < 0.05 were considered to indicate statistical significance.

Results

The study cohort included 80 participants: 40 patients with chronic plaque psoriasis and 40 healthy individuals. The patient group consisted of 20 males and 20 females with a mean age of 35.93 ±9.79 years. The control group consisted of 21 females and 19 males with a mean age of 34.03 ±7.62 years. There was no statistically significant difference between the two groups in gender or age ($p > 0.05$).

The mean duration of disease in the psoriasis group was 168.13 ±89.30 months. The mean PASI value among the study participants was 8.24 ±8.14. The median PASI value among the male patients was 6.50, while the mean PASI value was 9.98 ±9.65. The median PASI value among female patients was 5, while the mean PASI value was 6.48 ±6.03. There was no statistically significant difference in PASI values between the female and male psoriasis patients ($p = 0.139$).

Serum endocan concentrations in the patient group ranged between 0.19 and 4.30 ng/ml, with a mean of 1.78 ±1.13 ng/ml. Serum endocan levels in the control group ranged between 0.38 and 2.30 ng/ml, with a mean of 0.85 ±0.42 ng/ml.

Homocysteine concentrations in the patient group ranged between 1.17 and 15.91 µmol/l, with a mean of 17.11 ±20.04 µmol/l. Homocysteine concentrations in the control group ranged between 5.46 µmol/l and 12.10 µmol/l, with a mean of 8.75 ±1.87 µmol/l. Serum endocan and homocysteine concentrations were significantly higher in the patient group than the control group ($p < 0.001$; Figure 1).

There was no statistically significant difference between the patient and control groups in terms of left ventricular end diastolic diameter (LVDD), left ventricular end systolic diameter (LVSD), interventricular septum (IVS), mitral valve early diastolic peak velocity (E), mitral valve late diastolic peak velocity (A), early diastolic myocardial velocity (Em),

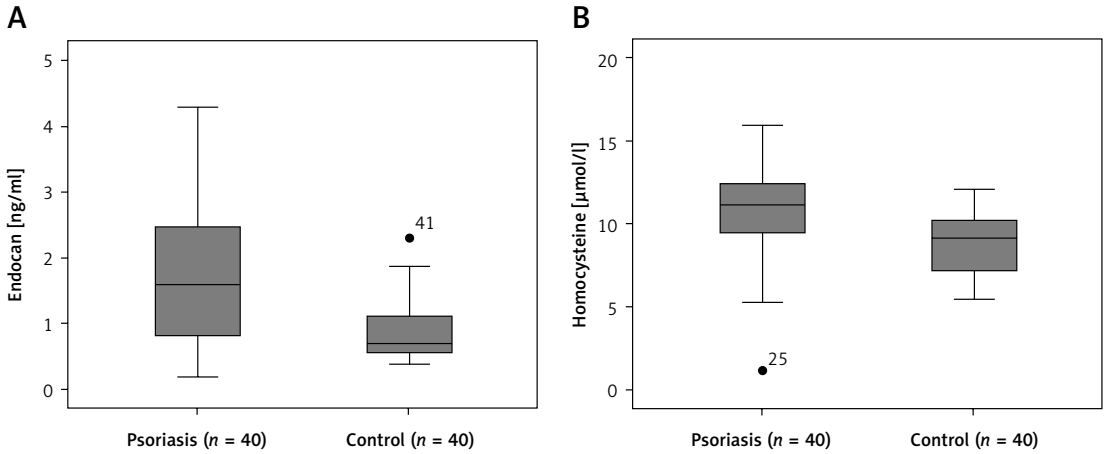

Figure 1. Endocan (**A**) and homocysteine (**B**) concentrations in patients with psoriasis

late diastolic myocardial velocity (Am), or Em/Am values (all $p > 0.05$), all of which reflect LV systolic and diastolic function, when tissue Doppler echocardiography and two-dimensional echocardiography findings were evaluated (Table I). When the Tei index values were compared, the mean of the psoriasis group was 0.47 ±0.08 and that of the control group was 0.41 ±0.037. This difference was statistically significant ($p < 0.001$; Figure 2). We observed a statistically significant difference in the E/Em and E/A values between the groups ($p = 0.028$, Figure 2; and $p < 0.001$, Figure 3, respectively). When the Zs-12, Zs-12-SD, Zs-6, and Zs-6-SD values, which quantify the time required by the LV myocardial segments to reach peak systolic velocity, were compared between the patient and control groups, the left ventricular systolic asynchrony values of the patient group were significantly higher than those of the control group ($p < 0.001$; Table II). A Zs-12-SD value greater than 31.4 ms defines LV systolic asynchrony. Asynchrony was present in 77.5% of the patients and 7.5% of the controls (Figure 3).

We found no evidence of a correlation between PASI values and serum endocan concentrations in the patient group ($p = 0.118$). Duration of disease

Table I. Echocardiographic parameters in patients and controls

Parameter	Psoriasis (n = 40)	Controls (n = 40)	P-value
LVDD [mm]	46.10 ±3.161	45.38 ±3.57	0.422
LVSD [mm]	28.35 ±3.19	27.88 ±3.00	0.495
IVS [mm]	8.10 ±1.23	7.93 ±1.73	0.893
E [cm/s]	70.98 ±20.46	72.20 ±10.74	0.052
A [cm/s]	65.48 ±18.77	50.20 ±10.20	0.262
E/A	1.16 ±0.46	1.50 ±0.39	0.001
E/Em	6.32 ±2.02	7.44 ±2.38	0.028
Tei index	0.47 ±0.08	0.41 ±0.037	< 0.001
Em [cm/s]	11.73 ±3.06	11.30 ±3.47	0.45
Am [cm/s]	9.35 ±2.09	9.85 ±2.22	0.33
Em/Am	1.32 ±0.45	1.24 ±0.58	0.35

LVDD – left ventricular end diastolic diameter, LVSD – left ventricular end systolic diameter, IVS – interventricular septum, E – mitral valve early diastolic peak velocity, A – mitral valve late diastolic peak velocity, Em – early diastolic myocardial velocity, Am – late diastolic myocardial velocity.

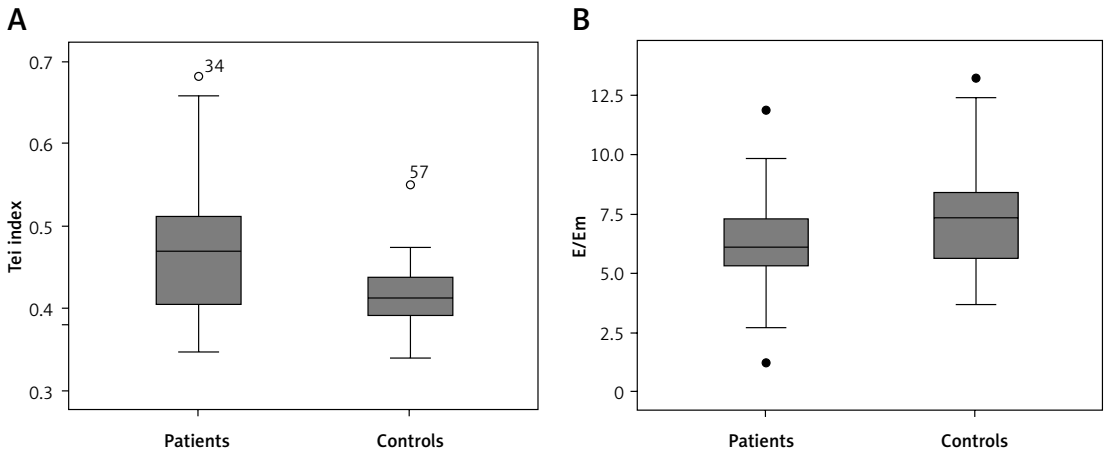

Figure 2. Distribution of Tei index (**A**) values and E/Em rates (**B**) in patient and control groups

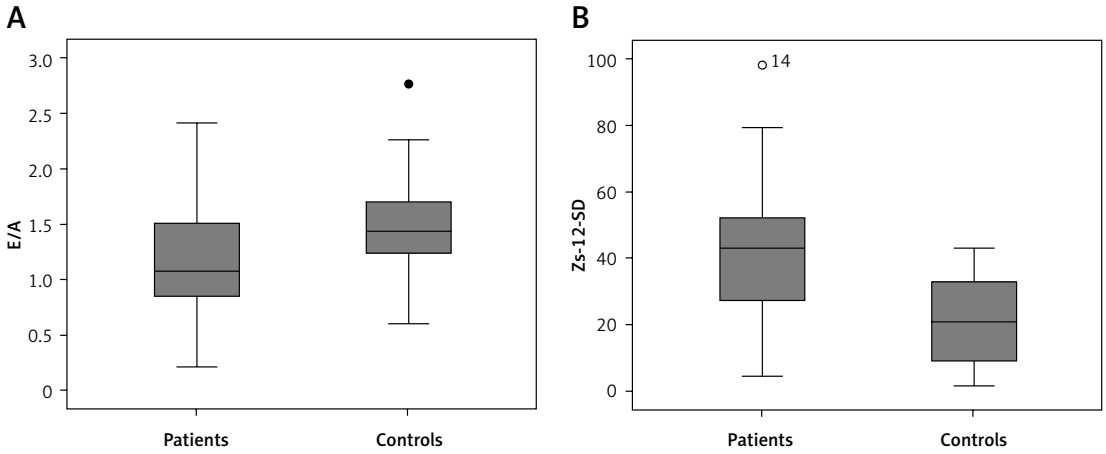

Figure 3. Distribution of E/A rates (**A**) and Zs-12-SD levels (**B**) in patient and control groups

Table II. Comparison of TSI parameters between patient and control groups

Parameter	Psoriasis (n = 40)	Controls (n = 40)	P-value
Zs-6	104.75 ±49.40	57.48 ±35.12	< 0.001
Zs-6-SD	42.18 ±21.26	22.00 ±13.17	< 0.001
Zs-12	139.73 ±56.84	65.65 ±37.53	< 0.001
Zs-12-SD	45.15 ±17.99	20.95 ±11.97	< 0.001

Zs-12 – maximal difference between any 2 of 12 basal left ventricle (LV) segments, Zs-12-SD – 12-segment peak systole time standard deviation, Zs-6 – maximal difference between any two of six basal LV segments, Zs-6-SD – standard deviation of 6-segment peak systole time.

was significantly correlated with serum endocan concentration (p < 0.001, r = 0.725; Figure 4). Separate analyses of male and female patients, for correlations between duration of disease and serum endocan concentrations, failed to demonstrate a significant correlation in either group (p > 0.05). There was no significant correlation between serum endocan or homocysteine and vitamin B_{12}, folate, triglycerides, very-low-density lipoprotein (VLDL), high-density lipoprotein (HDL), low-density lipoprotein (LDL), or body mass index (BMI) (p > 0.05).

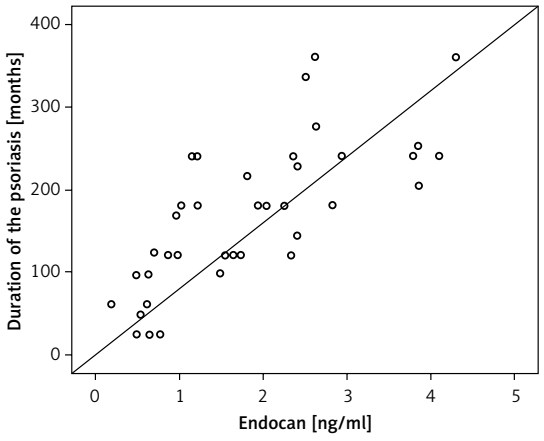

Figure 4. Correlation between duration of the disease and serum endocan levels

Discussion

Free oxygen radicals and pro-inflammatory cytokines generated under conditions of chronic inflammation are known to induce angiogenesis, insulin resistance, lipid metabolism, and epidermal hyper-proliferation [3, 4, 10]. These factors play essential roles in the pathogenesis of psoriasis and are known to cause cardiovascular diseases, such as atherosclerosis, dyslipidemia, and acute myocardial infarction [11, 15–17]. Considering the hypothesis that psoriasis may itself be a cardiovascular risk factor, previous studies have investigated serum homocysteine and endocan concentrations to determine subclinical atherosclerosis and cardiovascular risk [2–9]. Hyperhomocysteinemia is associated with an increased risk of atherosclerotic cardiovascular diseases, stroke, peripheral arterial occlusive diseases, and venous thrombosis [7, 8, 18]. Thus, some reports have concluded that high homocysteine levels in patients with psoriasis are positively correlated with PASI scores, even in patients who do not have accompanying hyperhomocysteinemia risk factors. Homocysteine levels may be an independent risk factor for cardiovascular disease [19, 20]. However, in the study by Giannoni *et al.*, patients with increased homocysteine levels also had decreased vitamin B_{12} and folate levels. These parameters (increased homocysteine and decreased vitamin B_{12} and folate) might be caused by the same determinant, which might be increased keratinocyte metabolic turnover rate in psoriasis patients [20]. On the other hand, in our study, increased homocysteine levels did not correlate with disease duration or severity, and these patients had normal vitamin B_{12} and folate values. So, we suggest that serum homocysteine concentration is an independent risk factor when assessing cardiovascular risk.

Another indicator of endothelial dysfunction is endocan [6, 9]. Endocan has been reported to promote the development of atheroma plaques by stimulating the proliferation and migration of vascular smooth muscle cells [21–23]. Balta *et al*. reported that serum endocan levels were significantly higher in psoriasis patients than control subjects. Additionally, serum endocan concentrations correlated positively with PASI, high-sensitivity C-reactive protein (hs-CRP), and carotid artery intima-media thickness (c-IMT), suggesting that endocan may be a new biomarker for assessing cardiovascular risk [9]. In our study it was found that endocan level is correlated with disease duration, as opposed to Balta's study, where endocan level was found to be correlated with disease severity (PASI). PASI scoring does not provide an objective evaluation of disease severity or reflect the chronic microvascular inflammation. It only represents the current status of the disease. The correlation of endocan concentration with duration of disease may indicate the cumulative effects of the inflammatory process and endothelial dysfunction and/or the development of atherosclerosis, caused by progressive endothelial damage. Thus, the relationship between disease duration and endocan elevation is a more accurate variable reflecting the chronic inflammatory injury in psoriasis.

Many studies using a variety of methods have evaluated objectively the underlying atherosclerotic status of patients with psoriasis [2, 24–26]. The most common approach is echocardiographic analyses. Some reports have indicated that standard echocardiography may be insufficient in some cases and early diagnosis of asymptomatic patients with high cardiovascular risk is difficult [27–30]. In recent studies, TDE, which evaluates global or regional systolic and diastolic functions of the ventricles, and TSI, which provides fast and reliable evaluation of synchronization, have been used successfully [28–32]. Using TDE and TSI methods, diastolic function can be evaluated readily without any influence of preload, and minimal regional dysfunction can be detected much earlier than when 'classical' pulsed-wave Doppler is used [30, 32]. Örem *et al*. compared left ventricular asynchrony (LVA) and systolic and diastolic dysfunction in patients with psoriasis using classical echocardiography, TDE, and TSI [25]. Among psoriasis patients, all TSI parameters of LVA were elevated compared to the control group. They found no correlation between LVA and PASI, but reported a positive correlation between the Tei index and age [25].

The present study is the second to evaluate LVA in patients with psoriasis. Our results were similar to those of Örem *et al*. [25]. However, the larger group of participants in the present study was selected after careful exclusion of individuals with known cardiovascular risk factors. Even smoking history was excluded in the current study. Data published by Örem *et al.* showed that 58% of patients with psoriasis and 64% of the controls reported positive smoking history. In our study, we tested more specific biomarkers, namely homocysteine and endocan, which have been previously shown to be strong biomarkers in subclinical atherosclerosis and cardiovascular risk development. Örem *et al.* tested non-specific biomarkers such as CRP and erythrocyte sedimentation rate, and presence of local or systemic infections was not excluded. The observation that the Tei index, E/Em, E/A, Zs-12-SD, and PASI were not associated with duration of the disease or biochemical parameters supports the hypothesis that psoriasis might be considered as an independent cardiovascular risk factor. In the present study, TDE and TSI were used with standard echocardiography to detect sub-clinical cardiac dysfunction. The Tei index, reflecting both systolic and diastolic function and global LV function, was elevated significantly in psoriasis patients compared to controls. In contrast, the E/A ratio, a parameter of LV diastolic dysfunction, was within normal limits in both groups, and the E/A ratio was lower in the patient group than the control group. The E/Em ratio was significantly lower in the patient group than the control group. The TSI values were significantly higher in the patient group than the control group, and asynchrony was detected in 77.5% of patients with psoriasis.

Major limitations of our study are the small sample size and single-center design. In this study, a power analysis was not performed due to small sample size.

In conclusion, serum endocan and homocysteine concentrations, markers of chronic inflammation, secondary vascular endothelial damage, and atherosclerotic pathogenesis, were significantly higher in psoriasis patients than in controls. We also observed a significantly higher rate of systolic and diastolic dysfunction in patients with psoriasis relative to the control subjects. Together, these data support the hypothesis that psoriasis might be considered as a cardiovascular risk factor. Although this study included a limited number of patients, our results suggest that larger case control studies with extended follow-up evaluations are warranted. We wanted to publish our work with the idea that it will support the studies done so far and that it will shed light on further research.

Conflict of interest

The authors declare no conflict of interest.

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