Determination of subclinical atherosclerosis in plaque type psoriasis patients without traditional risk factors for atherosclerosis

Klasik aterosklerotik risk faktörü bulunmayan plak tipi psoriasisi olan hastalarda subklinik aterosklerozun değerlendirilmesi

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ABSTRACT

Objectives: Systemic inflammation plays an important role in the pathogenesis of atherosclerosis in psoriasis patients. Therefore, persistent skin inflammation in psoriasis patients may contribute to the development of premature atherosclerosis, as it occurs in rheumatoid arthritis and systemic lupus erythematosus. We aimed to evaluate the relationship between subclinical atherosclerosis and psoriasis by using pulse wave velocity (PWV) and the measurement of carotid intima media thickness (CIMT) in psoriatic patients.

Study design: Fifty-seven plaque-type psoriasis patients (31 males, 26 females; mean age 41±10.8 years) and 60 healthy individuals (32 males, 28 females; mean age 40±9.4 years) were included. Atherosclerotic risk factors were excluded in both of the groups. Demographic, bio-chemical data, psoriasis area and severity index (PASI) score of the psoriasis group, and disease duration were recorded. Carotid-femoral artery PWV and CIMT values were compared.

Results: PWV, and the maximum and average CIMT values of psoriasis patients were higher than those of the healthy group (PWV: 7.04±1.1 m/sn *vs.* 6.03±0.61 m/sn, p<0.001; maximum CIMT: 0.86±0.09 mm *vs.* 0.77±0.06 mm, p<0.001; mean CIMT: 0.73±0.09 mm *vs.* 0.66±0.06 mm p<0.001, respectively). Although there was no difference in the lipid levels of the groups, total/HDL cholesterol (4.40±1.26 vs. 3.88±1.18, p=0.02, respectively), and LDL/HDL cholesterol ratios (2.78±0.98 vs. 2.32±0.92, p=0.01, respectively) of the psoriasis group were higher than those of the healthy group. A positive correlation was observed between PASI and the PWV (r=0.417, p=0.001).

Conclusion: Despite the nonexistence of atherosclerotic risk factors, the risk of development of atherosclerosis is higher in psoriasis patients compared to healthy individuals. In addition to damage of the artery wall caused by systemic inflammation, lipid metabolism disorders may contribute to the development of atherosclerosis in these patients.

ÖZET

Amaç: Psoriasisli hastalarda görülen sistemik enflamasyon ateroskleroz gelişiminde önemli rol oynayabilir. Bu hastalarda görülen kronik enflamasyon, romatoid artrit ve sistemik lupus eritamozuslu hastalarda olduğu gibi erken ateroskleroz gelişimine katkıda bulunabilir. Çalışmamızda, nabız dalga hızı (NDH) ve karotis intima medya kalınlığı (KİMK) ölçüm yöntemleri kullanarak, psoriasis ile subklinik ateroskleroz arasındaki ilişkinin araştırılması amaçlandı.

Çalışma planı: Klasik ateroskleroz risk faktörleri bulunmayan, plak tipi psoriasisi olan 57 hasta (31 erkek, 26 kadın; ort. yaş 41±10.8 yıl) ve 60 sağlıklı birey (32 erkek, 28 kadın; ort. yaş. 40±9.4 yıl) çalışmaya alındı. Çalışmaya alınan bireylerin demografik, biyokimyasal verilerine ek olarak, hastalıklı bireylerde psoriasis alanını ve ciddiyet indeksini ölçen PASİ skoru ve hastalığın süresi kayıt edildi. Sağlıklı ve psoriasisli olgularda karotis ve femoral arterlerde yapılan NDH ve KİMK ölçümleri karşılaştırıldı.

Bulgular: NDH, maksimal ve ortalama KİMK değerleri psoriasis grubunda, sağlıklı gruptan fazla bulundu (sırasıyla, NDH: 7.04±1.1 m/sn ve 6.03±0.61 m/sn, p<0.001; maksimum KİMK: 0.86±0.09 mm ve 0.77±0.06 mm, p<0.001; ortalama KİMK: 0.73±0.09 mm ve 0.66±0.06 mm, p<0.001). Grupların lipit düzeyleri arasında fark olmamasına rağmen, total/HDL kolesterol (sırasıyla, 4.40±1.26 ve 3.88±1.18, p=0.02) ve LDL/HDL kolesterol (sırasıyla, 2.78±0.98 ve 2.32±0.92, p=0.01) oranları psoriasis grubunda daha yüksek bulundu. PASİ skoru ile NDH arasında pozitif korelasyon gözlendi (r=0.417, p=0.001).

Sonuç: Klasik aterosklerotik risk faktörleri bulunmayan psoriasisli hastalarda ateroskleroz gelişme riski sağlıklı kişilerden daha fazla olabilir. Sistemik enflamasyonun arter duvarında neden olduğu hasara ek olarak, lipit metabolizması bozuklukları da ateroskleroz gelişimine katkıda bulunabilir.

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Psoriasis is a chronic, multigenic immune/inflammatory-mediated disorder associated with serious medical comorbidities. In previous clinical studies, the relationship between psoriasis and an increased risk of cardiovascular disease has already been demonstrated.[1,2] Inflammation and the accompanying elevation in the homocysteine and C-reactive protein (CRP) levels, the increased platelet activation, and cytokine imbalance between coagulation-fibrinolysis seem to be responsible for this relationship. The increase in the incidence of classic atherosclerotic risk factors and treatment with immunosuppressive agents contribute to the development of atherosclerosis in patients with psoriasis.[3,4]

Carotid intima-media thickness (CIMT), flow-mediated dilation (FMD) and pulse wave velocity (PWV) measurements are methods used to determine subclinical atherosclerosis in inflammatory diseases such as rheumatoid arthritis (RA) or systemic lupus erythematosus (SLE).[5-7] Endothelial dysfunction is a marker of the vascular damage preceding the development of the atherosclerotic plaques. The inhibition of nitric oxide (NO) synthesis by chemical or mechanical stimulation - or of the vascular response to NO - is the mechanism responsible for the endothelial dysfunction. Endothelial injury results in reduced arterial elasticity and increased arterial stiffness. Arterial stiffness is assessed by the degree of increase in the PWV. Previous studies have demonstrated that increased arterial stiffness is a marker of increased cardiovascular mortality and morbidity.[8,9]

The increase in the CIMT develops subsequent to intimal smooth muscle proliferation and the accumulation of atherogenic particles. Measurement of the CIMT can be used for an early diagnosis of atherosclerosis, risk stratification and the assessment of the response to treatment. CIMT was found to be increased in patients with psoriatic arthritis independently from the atherosclerotic risk factors. However, the presence of coexisting atherosclerotic risk factors may further increase the CIMT. Proinflammatory cytokines produced by type 1 T-helper lymphocytes such as TNF-α and interferon are important participants in plaque formation and in the development of endothelial dysfunction and atherosclerosis in patients with psoriasis.[10-12]

This study aimed to investigate the relationship between subclinical atherosclerosis and plaque-type psoriasis without the traditional risk factors for atherosclerosis. In addition, the contribution of the atherosclerotic risk factors within the normal range to the condition using the PWV analysis and CIMT measurement methods were investigated.

Abbreviations:

BMI	*Body mass index*
CIMT	*Carotid intima-media thickness*
CRP	*C-reactive protein*
FMD	*Flow-mediated dilation*
NO	*Nitric oxide*
PASI	*The psoriasis area and severity index*
PWV	*Pulse wave velocity*
RA	*Rheumatoid arthritis*
SBP	*Systolic blood pressure*
SLE	*Systemic lupus erythematosus*

PATIENTS AND METHODS

For the purposes of this study, 57 consecutive patients with plaque-type psoriasis (31 males, 26 females; mean age 41±10.8 years) and 60 healthy, sex- and age-matched individuals (32 males, 28 females; mean age 40±9.4 years) were enrolled between October 2008 and November 2009. The psoriatic patients were clinically diagnosed, and the diagnosis was confirmed through a histopathological examination in rare cases. Informed consent forms were obtained from every individual included in the study. The study was approved by the local ethics committee of the university.

The exclusion criteria for the study included hypertension, hyperlipidemia, diabetes mellitus, any malignancies, systemic inflammation associated with the disease, previous history of cardiovascular disease, renal and liver insufficiency, psoriatic arthritis, severe forms of psoriasis such as erythrodermic psoriasis, systemic immunosuppressive therapy within the last 6 months, smoking, and a body mass index (BMI) >30 kg/m^2. In the patient group, the severity of the psoriasis was evaluated using the psoriasis area and severity index (PASI) score. The blood pressure and heart rate of all the individuals were measured after a 15-minute rest. The biochemical parameters were obtained from venous blood samples drawn after an 8-hour fasting period.

Pulse wave velocity and carotid intima-media thickness measurement

CIMT measurements of the individuals were performed by a physician blinded to the patients and the obtained PWV values. Both common carotid arteries were visualized using the Toshiba Powervision 7500 (Toshiba AG) ultrasound device with a 7.5 MHz linear probe. The maximum and mean thicknesses were calculated based on the values obtained from a pre-de-

termined 1 cm segment of the common carotid artery located 2-3 cm distal to the bulbus and using the far edge measurement method through the CIMT measurement program M'Ath® standard version 2.0.1.0 (Metris AG., France). This method was applied for the measurement of both common carotid arteries and the averages of the measured values were calculated.

The measurement of the PWV was carried out with the help of the SphygmoCor (Artcore, Sydney, Australia) device. Before the procedure, blood pressure readings were taken from every patient. The distance between the palpable point of the femoral artery and the sternal notch, and the distance between the most distal palpable part of the carotid pulse and the sternal notch were entered into the system. The applanation tonometry was applied to these points sequentially through the skin. The recording was made after the most appropriate waveform amplitude and shape were observed. Simultaneous ECG readings were also taken from the patients. The pulse transit times, i.e. the PWV, were calculated automatically by the SphygmoCor device by subtracting the time between the ECG and the proximal pulse from the time between the ECG and the distal pulse.

Statistical analysis

Study data were analyzed with the SPSS 16.0 for Window (SPSS Inc., Chicago, USA) and MedCalc 10.4.0 (Mariakerke, Belgium) software packages. Continuous variables were expressed as mean±standard deviation, while the categorical data were expressed as percentages. The Kolmogorov-Smirnov test was used to analyze the normality of the data. In order to compare the continuous variables, Student's t-test or the Mann-Whitney U-test were used. Pearson's or Spearman's correlation analyses were used to analyze the correlation between the two groups. All hypotheses were constructed in two-ways and the critical value for alpha was accepted as 0.05.

RESULTS

No difference was observed among the groups in terms of the demographic and biochemical data. Although there was no difference between the lipid parameters in the psoriasis and control groups, the total cholesterol/HDL cholesterol (TC/HDL) and the LDL cholesterol/HDL-cholesterol (LDL/HDL) ratios in the psoriasis group were higher than the control

Table 1. Demographic and biochemical data comparision of study groups

	Control (n=60) Mean±SD	Psoriasis (n=57) Mean±SD	*p*
Age (years)	40.0±9.4	41.8±10.8	0.17
Body mass index (kg/m^2)	25.18±2.14	25.85±2.31	0.06
Systolic blood pressure (mmHg)	119.96±8.2	119.1±7.8	0.76
Diastolic blood pressure (mmHg)	74.9±5.2	75±5.0	0.81
Fasting blood glucose (mg/dl)	87.1±11.1	88.9±9	0.40
Total cholesterol (mg/dl)	172.1±30.4	170.1±27.9	0.97
LDL-cholesterol (mg/dl)	106.7±26.1	110.9±26.2	0.34
HDL-cholesterol (mg/dl)	48.1±13.7	46.0±11.8	0.49
Triglyceride (mg/dl)	122.9±46.5	123.6±49.1	0.91
Total cholesterol/HDL cholesterol	3.88±1.18	4.40±1.26	0.022
LDL cholesterol/HDL cholesterol	2.32±0.91	2.78±0.98	**0.01**
Triglyceride/HDL cholesterol	2.83±1.64	3.2±1.66	0.229
Hemoglobin (gr/dl)	13.9±1.2	12.7±1.3	**0.001**
Leukocyte(1000/mm^3)	6635±1640	7742±1803	**0.01**
PASI score	N/A	7.8±7.4	
Psoriasis duration (month)	N/A	136.6±102	

Mean±SD: Mean±standart deviation; N/A: Non-appropriate: PASI: Psoriasis area severity index.

Table 2. Comparision of groups in terms of carotid intima media thickness and pulse wave velocity

	Control (n=60) Mean±SD	Psoriasis (n=57) Mean±SD	*p*
Pulse wave velocity (m/sn)	6.03±0.61	7.04±1.1	**<0.001**
Maximum carotid intima media thickness (mm)	0.77± 0.06	0.86 ± 0.09	**<0.001**
Mean carotid intima media thickness (mm)	0.66±0.06	0.73±0.09	**<0.001**

Mean±SD: Mean±standart deviation.

Table 3. The relationship of pulse wave velocity and carotid intima media thickness with disease duration and severity and atherosclerotic risk factors

	Maximum CIMT		PWV	
	r	p	r	p
Age	0.470	<0.001	0.395	0.002
Glucose	0.344	0.009	0.404	0.002
BMI	0.346	0.008	0.264	0.047
SBP	0.032	0.032	0.299	0.024
PASI score	0.108	0.423	0.417	0.001
Psoriasis duration	0.018	0.893	0.031	0.819
T. chol/HDL	0.122	0.366	0.274	0.039
LDL/HDL	0.117	0.386	0.264	0.047

BMI: Body mass index; CIMT: Carotid intima media thickness; LDL/HDL: LDL cholesterol/HDL cholesterol ratio; PWV: Pulse wave velocity; T. chol/HDL: Total cholesterol/HDL cholesterol ratio.

group. The triglyceride/HDL cholesterol (TG/HDL) ratio was also higher in the patients with psoriasis, but the difference was statistically insignificant. The leukocyte level was observed to be higher in the psoriasis group in comparison to the healthy controls, while the haemoglobin level was lower (Table 1).

The mean and maximum CIMT and the PWV values were found to be higher in the psoriasis group than the control group (Table 2). Correlation analyses were performed among the CIMT and PWV values and the age, fasting glucose levels, blood pressure readings, lipid parameters, BMI, PASI scores and the duration of disease in the psoriasis group. Both the CIMT and PWV were found to be correlated with the age, glucose level, BMI, and systolic blood pressure (SBP) values. Although a correlation was observed among the PWV, the PASI score, and the TC/HDL, LDL/HDL ratios (Fig. 1), no correlation was found between the duration of the disease and the PWV. CIMT was not observed to be correlated with the PASI score, duration of the disease or lipid ratios (Table 3). The CIMT ($p=0.001$ - $r=0.419$) and PWV ($p<0.001$ - $r=0.5$) were correlated with age in the healthy control group, but no such relationship was observed with the other parameters.

DISCUSSION

Systemic inflammation plays an important role in the pathogenesis of atherosclerosis in patients with psoriasis. Thus, the persistent skin inflammation in

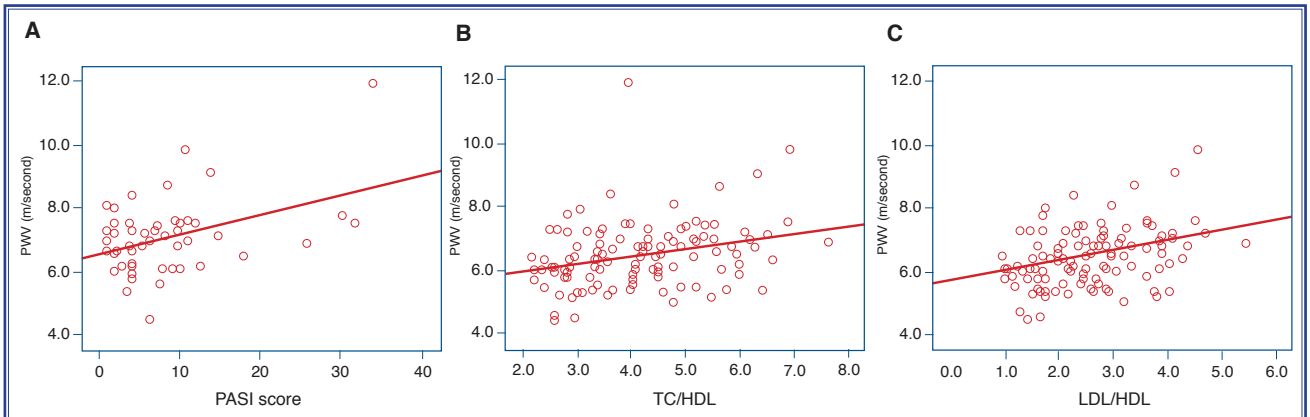

Figure 1. (A) Correlation between the PWV and PASI score, **(B)** and TCHDL, **(C)** and LDL/HDL. PWV: Pulse wave velocity; TCHDL: Total cholesterol and high density lipoprotein ratio; LDLHDL: Low density lipoprotein and high density lipoprotein ratio.

these patients may contribute to the development of premature atherosclerosis, as is the case in rheumatoid arthritis and SLE.[13-15] The inflammation process responsible for the disease also plays a role in the development of risk factors for atherosclerosis and cardiovascular complications. Histologically, psoriasis and atherosclerosis show common features like infiltrating T-cells, monocytes/ macrophages, neutrophils, dendritic cells (DCs) and mast cells. The IL-1, IL-6, TNF-α, IFN-γ, CRP and adhesion molecules are synthesized as a result of the inflammatory cascade which is initiated by the introduction of autoantigens to the Th-1 and Th-17 cells. These inflammatory mechanisms seem to be responsible for the formation of the psoriatic plaques and atherosclerosis.[16,17] Although the inflammation parameters were not directly investigated in our study, the low haemoglobin and high leukocyte levels observed in the psoriasis group intensify the inflammatory reactions observed in psoriatic patients.

Although there were no demographic or biochemical differences between the groups in our study, the TC/HDL, LDL/HDL and TG/HDL ratios in the psoriasis group were significantly higher than the control group, and the difference was statistically significant except for the TG/HDL ratio. The maximum and mean CIMT values were also higher than the control group. The age, BMI, SBP and glucose levels were found to be factors affecting the CIMT in psoriatic patients. No correlation was observed between the CIMT and the duration of the disease or the PASI score.

The CIMT, which was associated with subclinical atherosclerosis in previous studies, was found to be increased in psoriatic patients in comparison to the healthy individuals. Although common results from the previous studies point out an increase in CIMT in psoriatic patients, there are also conflicting results in terms of the factors leading to increased CIMT values. In a study by Mongy et al.,[18] the CIMT, sedimentation rate and CRP levels were found to be increased in patients with psoriatic arthritis and plaque-type psoriasis without any accompanying risk factors for atherosclerosis. In their study, the age, disease duration and severity of disease were associated with the CIMT, but there was no relationship between the acute phase reactants and CIMT. Gonzales et al.[19] have found a correlation between the CIMT and the disease duration, age, LDL and total cholesterol levels in patients with psoriatic arthritis without any accompanying risk factors for atherosclerosis or proven history of cardiovascular disease. Despite the high sedimentation rate and CRP values in the patient group, no relationship was established between these parameters and the CIMT. The PASI scores and inflammation markers reported in these studies were associated with an instant activation of the disease. Because psoriasis is characterized by periods of exacerbation, the level of inflammation may vary according to the period.

The CIMT indicates the degree of the atherosclerosis caused by the chronic inflammation and it is expected to increase parallel to the duration of the inflammation. Therefore, the relationship between the CIMT and the disease duration can be more apparent than the relationship with the level of inflammation. Balci et al.[20] did not observe any relationship between the CIMT and the duration and severity of the disease in plaque-type psoriatic patients. When the previous studies focusing on the relationship between the CIMT and the duration and severity of the disease were considered, it was observed that the mean age and the PASI scores were higher in the patient group. Also, the patients had more severe forms of the disease like psoriatic arthritis and higher atherosclerotic risk factors. No other relationship was observed between the CIMT and atherosclerosis in the studies investigating the relationship between inflammatory diseases and CIMT in younger patient groups.[6,18,21,22] In our study, the lack of a relationship between the CIMT and the duration and severity of the disease can be attributed to the low mean PASI score, lower mean age of the participants, and the exclusion of the patients with more severe forms of the disease or under immunosuppressive treatment.

Endothelial damage caused by subclinical atherosclerosis and inflammatory diseases were examined using the FMD and PWV measurement methods in several studies. As a result of these, the parameters associated with the development of atherosclerosis and its complications have already been described.[9,10] In our study, the PWV was higher in the psoriasis group compared to the control group. Although a relationship was observed between the PWV and the SBP, glucose level, BMI, the TC/HDL and LDL/HDL ratios, and the PASI score, no relationship was found between the PWV and the duration of the disease. In a study by Gisondi et al.[23] conducted in patients

with psoriasis, the carotid-femoral artery PWV was higher and a correlation was observed between the duration of the disease and the PWV. In the study by Martyn-Simons et al.,[24] the FMD values were found to be similar in patients and healthy individuals, and there was no correlation between the FMD and the duration and severity of the disease. A study by Yiu et al.,[25] which investigated the relationship between endothelial dysfunction and inflammation, revealed that the hs-CRP levels and PWV were higher in psoriatic patients compared to healthy individuals. Also in their study, the PWV was observed to correlate with the hs-CRP, although there was no correlation with either the PASI score or the disease duration. The reason for the different results obtained from similar studies can be explained with the heterogeneity of the patient characteristics, administered medications, and accompanying atherosclerotic risk factors in the enrolled patients. Although PWV was correlated with the PASI score, we did not find any correlation between the PWV and the disease duration. The PASI score is an indirect measure of the inflammation level in psoriasis. In our study, through the exclusion of the patients under immunosuppressive treatment or with atherosclerotic risk factors, we were able to observe the relationship between inflammation and endothelial dysfunction more clearly. Thus, we found a correlation between the PWV and the PASI score. In psoriasis, the effect of the cytokines like TNF-α and CRP bring about a decrease in both the NO synthesis and endothelial response, leading to arterial stiffness and an increase in the PWV.[26]

Although our study included patients without risk factors for atherosclerosis, the CIMT and PWV were found to be correlated with the glucose level, BMI and blood pressure besides the age. Coexistence of psoriasis with these factors associated with atherosclerosis has already been demonstrated in the previous studies.[27-29] Although the lipid parameters of the patients and the healthy individuals were not different, the TC/HDL and LDL/HDL ratios were higher in the psoriatic patient group compared to the controls. HDL cholesterol prevents atherosclerosis by transporting the free lipid particles from the arterial system to the liver. It also hinders endothelial dysfunction by inhibiting the oxidation of the LDL and triggering prostacyclin release from the endothelium.[30,31] The correlation of the PWV with the TC/HDL and LDL/HDL ratios suggests that the endothelial damage occurs parallel to the decrease in the HDL cholesterol in lipid particles due to the inflammation.

The small population size and absence of serum inflammation markers like the CRP and sedimentation rate were the limitations of our study. Instead of those markers, we used the PASI score as an indirect marker of the severity of the inflammation.

As a result of our study, we have demonstrated that even in the absence of atherosclerotic risk factors, psoriatic patients are at a higher risk for the development of atherosclerosis and endothelial dysfunction compared to healthy individuals. Besides, the correlation of the PWV with increased TC/HDL and LDL/HDL ratios in the case of a normal lipid profile points to a relationship among atherogenic dyslipidemia, endothelial dysfunction and inflammation. In order to reduce cardiovascular mortality, determination of the atherosclerotic risk factors and risk stratification are also important issues as well as the treatment of the primary disease. CIMT and PWV evaluations are useful tools to detect subclinical atherosclerosis and conduct the risk stratification.

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Key words: Atherosclerosis/epidemiology; carotid arteries/pathology/ultrasonography; C-Reactive Protein; lipid metabolism disorders; platelet activation; psoriasis/blood/epidemiology; pulse; risk factors.

Anahtar sözcükler: Ateroskleroz/epidemiyoloji; karotis arter/patoloji/ultrasonografi; C-reaktif protein; lipit metabolizması bozuklukları; trombosit aktivasyonu; psoriasis/kan/epidemiyoloji; atım; risk faktörü.