ORIGINAL ARTICLE

Assessment of subclinical atherosclerosis in psoriatic arthritis patients without clinically overt cardiovascular disease or traditional atherosclerosis risk factors

Klinik olarak aşikar kardiyovasküler hastalığı ya da geleneksel ateroskleroz risk faktörü bulunmayan psöriatik artritli hastalarda subklinik aterosklerozun değerlendirilmesi

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ABSTRACT

Objective: Cardiovascular disease (CVD) is more prevalent in almost all patients with chronic inflammatory musculoskeletal diseases than in their healthy counterparts. The aim of this study was to assess the presence of subclinical atherosclerosis in patients with psoriatic arthritis (PsA) in comparison with patients with rheumatoid arthritis (RA) and healthy controls.

Methods: A total of 30 patients with PsA, 30 patients with RA, and 30 healthy controls were enrolled in this parallel group study. Demographic, clinical, and laboratory data of the groups were recorded. The Disease Activity Score-28 tool was used for joint assessment. The erythrocyte sedimentation rate and C-reactive protein level were measured as acute phase reactants. Flow-mediated dilatation (FMD) and carotid intima media thickness (CIMT) were also measured in all participants.

Results: The median duration of disease in patients with PsA was 60 months (range: 8–216 months). A total of 22 of 30 (73.3%) PsA patients had a diagnosis of psoriasis and 13 (48.1%) had active disease. The study groups were similar with regard to age, gender, and body mass index data. In all, 23 (76.7%) of the PsA patients and 5 (16.7%) of the RA patients were using an anti-tumor necrosis factor alpha therapy ($p<0.001$). The FMD percentage was significantly smaller in both the PsA and the RA patients than in the healthy controls ($p<0.001$). The median CIMT was greater in the RA patients compared with the PsA patients and the healthy controls ($p=0.008$). There was no significant difference in FMD or CIMT between patients with and without an active joint lesion.

Conclusion: Endothelial functions were impaired in PsA, as in RA, in the absence of conventional risk factors or overt CVD. This finding may show a potential association between PsA, atherosclerosis, and CVD.

ÖZET

Amaç: Kardiyovasküler hastalıklar kronik enflamatuvar kas-iskelet hastalığı olan hastaların hemen hepsinde sağlıklı akranlarına göre daha sıktır. Bu çalışmada psöriatik artritli (PsA) hastalarda subklinik ateroskleroz varlığı hem romatoid artrit (RA) hem de sağlıklı kontrol bireyleri ile karşılaştırılarak değerlendirilmiştir.

Yöntemler: Paralel grup çalışmamıza PsA bulunan 30 hasta, RA bulunan 30 hasta ve 30 sağlıklı kontrol bireyi alındı. Katılımcıların tüm demografik, klinik ve laboratuvar verileri kaydedildi. Eklem aktivitesi hastalık aktivite skoru (DAS)-28 ile değerlendirildi. Eritrosit sedimentasyon hısı (ESH) ve C-reaktif protein (CRP) düzeyleri akut faz reaktanı olarak ölçüldü. Tüm katılımcılarda akım aracılı dilatasyon (AAD) ve karotis intima mediya kalınlığı (KİMK) ölçüldü.

Bulgular: Psöriatik artritli hastalardaki ortanca hastalık süresi 60 (dağılım, 8–216) aydı. 22/30 (%73.3) PsA'lı hastalarda psöriasis tanısı daha önce konmuştu ve bunların 13/30'unda (%48.1) hastalık aktifti. Çalışma grupları yaş, cinsiyet ve vücut kitle indeksi açısından benzerdi. Yirmi üç (%76.7) PsA'lı hasta ve RA'lı beş (%16.7) hastaya anti-tümör nekrozis faktör (TNF)-alfa tedavisi uygulanıyordu ($p<0.001$). AAD yüzdesi hem PsA'lı hem de RA'lı hastalarda sağlıklı kontrollere göre belirgin olarak düşüktü ($p<0.001$). Ortanca KİMK ise RA'lı hastalarda PsA'lı hastalar ve sağlıklı gruba göre belirgin yüksekti ($p=0.008$). Aktif eklem lezyonu olan ve olmayan hastalarda hem AAD yüzdesi hem de ortanca KİMK benzerdi.

Sonuç: Geleneksel risk faktörleri ya da aşikar kardiyovasküler hastalık olmaksızın PsA'da RA'ya benzer şekilde endotel fonksiyonları bozulmuştur. Bu durum PsA ile ateroskleroz ve KVH arasındaki potansiyel ilişkiyi gösterebilir.

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Psoriatic arthritis (PsA) is a well-known chronic inflammatory arthropathy affecting approximately 40% of patients with psoriasis.[1,2] Cardiovascular disease (CVD) is prevalent in almost all chronic inflammatory musculoskeletal diseases.[3] It has been well established that rheumatoid arthritis (RA) (relative risk 3.0) and systemic lupus erythematosus (relative risk 6.0) are independent risk factors for coronary heart disease.[1] Recently published data revealed that patients with PsA also had an increased risk for endothelial dysfunction and CVD, although the relative risk of CVD was only 1.6[2,4] and CVD accounted for approximately one-third of all deaths among PsA patients.[5] However, it was unclear if such an increased risk for CVD and mortality in PsA was entirely because of traditional atherosclerotic risk factors.[6]

Chronic inflammatory status is a well-defined nontraditional risk factor for atherosclerosis.[7] During an inflammatory state, the expression and activation of several proinflammatory cytokines, including interleukin (IL)-1, IL-6, and tumor necrosis factor (TNF) alpha have been documented in the pathogenesis of both atherosclerosis and PsA.[1] As a result of all those common pathways, endothelial function, as a hallmark of atherosclerosis, is impaired.[8,9] To address this issue in detail, previous studies have investigated the association of PsA with subclinical atherosclerosis, as a well-known indicator of CVD.[10,11] Subclinical atherosclerosis can be assessed by measuring either flow-mediated dilatation (FMD)[12] and/or carotid intima media thickness (CIMT).[13] However, there have been conflicting results regarding such an association between PsA and markers of subclinical atherosclerosis. This research was designed to assess the presence of subclinical atherosclerosis using FMD and CIMT in patients with PsA in comparison with patients with RA and with healthy control subjects.

METHODS

Study population

In this parallel group observational study, a total of 30 patients with PsA diagnosed according to the classification of psoriatic arthritis criteria,[1] 30 patients with RA diagnosed according to the American College of Rheumatology/European League Against Rheumatism criteria,[14] and 30 healthy control subjects who were admitted to a tertiary center rheumatology outpatient clinic were enrolled. Gender, age, and body mass index (BMI)-matched RA patients and healthy controls were selected as comparison groups for the study. Healthy control subjects were randomly selected from the patients of our check-up unit. Patients with the diagnosis of any CVD (stable coronary artery disease, peripheral artery disease, cerebrovascular disease, acute coronary syndrome); preexisting traditional cardiovascular risk factors, such as arterial hypertension, diabetes mellitus, family history of premature coronary heart disease, or dyslipidemia; chronic infectious or inflammatory disease; or liver or kidney failure were excluded from the study.

Abbreviations:

BMI	*Body mass index*
CIMT	*Carotid intima media thickness*
CRP	*C-reactive protein*
CVD	*Cardiovascular disease*
ESR	*Erythrocyte sedimentation rate*
FMD	*Flow-mediated dilatation*
HDH	*High-density lipoprotein*
IL	*Interleukin*
LDL	*Low-density lipoprotein*
PsA	*Psoriatic arthritis*
RA	*Rheumatoid arthritis*
TNF	*Tumor necrosis factor alpha*

Informed consent was obtained from each patient before enrollment. The study was conducted in compliance with the principles outlined in the Declaration of Helsinki and was approved by the Institutional ethics committee.

Demographic data (gender, age), BMI, smoking history, and disease characteristics of the patients were recorded. A tender joint count, swollen joint count, and the Disease Activity Score (DAS)-28 tool were used for joint activity assessment. Erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) measurements were used for acute phase reactants. The last visit fasting glucose level and lipid profile results (total cholesterol, high-density lipoprotein [HDL], low-density lipoprotein [LDL], and triglycerides) were also noted.

Assessment of brachial artery flow-mediated dilatation

A blinded cardiologist performed the measurement of brachial artery diameters. Calculation of FMD using brachial artery reactivity was performed using 2-dimensional grayscale and color-flow Doppler as well as vascular imaging using an echocardiography device (Vivid 5; GE Healthcare, Inc. Chicago, IL, USA) with a 10-MHz vascular ultrasound probe as previously described.[15] Participants fasted for 8 to 12 hours and all medications were withheld before the study. Par-

ticipants also did not exercise or ingest substances that might affect the FMD, like caffeine or high-fat foods, or use tobacco products before the assessment. After resting in the supine position for 10 minutes in a quiet, air-conditioned room, the brachial artery was prepared for measurements. The brachial artery was scanned longitudinally at 2 to 5 cm above the antecubital crease. This location was marked on the skin and all subsequent measurements were performed at the same location. To calculate the FMD, percent diameter changes were determined as follows: (diameter after reactive hyperemia–baseline diameter)/baseline diameter×100. To avoid confounding effects of arterial compliance and its cyclic changes in dimension, all of the measurements were obtained at the peak of the R-wave of the electrocardiogram. The mean diameter of the brachial artery was determined at baseline and then continuously for up to 5 minutes after reactive hyperemia.[16]

Assessment of carotid intima media thickness

CIMT was also measured by an experienced cardiologist who was blinded to the clinical data of the participants. CIMT is defined as the distance between the media-adventitia interface and the lumen-intima interface. Measurements were performed using a duplex ultrasound system with a 10-MHz scanning frequency in the B-mode, pulsed Doppler mode, and color mode using the Vivid 5 device. CIMT was measured at the far wall of the right and left common carotid arteries, 10 to 20 mm proximal to the carotid bulb. The mean of 5 measurements of each artery was recorded. The reproducibility of the CIMT measurements was examined by conducting another scan 1 week later on 10 patients. In our laboratory, the intra-observer variability is below 10% for CIMT (4.1±1.2%), demonstrating good reproducibility. A search was made of the common, internal, and external carotid arteries for carotid plaques. The presence of carotid plaque was defined as intima–media thickening >1.0 mm. CIMT measurement was always performed in plaque-free regions.

Statistical analysis

Continuous variables were presented as mean±SD or median (minimum-maximum), whereas categorical variables were presented as percentages. The Kolmogorov-Smirnov criterion was used for the assessment of normality. Continuous variables were compared using Student's t-test or the Mann-Whitney U test, and proportions were compared using a chi-square test or Fisher's exact test among patients with PsA vs RA. Comparisons of multiple mean values were performed with the Kruskal–Wallis test or analysis of variance with a post hoc Bonferroni comparison, as appropriate. Categorical variables were compared using a chi-square test or Fisher's exact test with a 3x2 contingency table. When performing correlation analysis, non-normally distributed continuous variables were log10-transformed. Correlation analysis was performed with Pearson's correlation test for parametric variables, and Spearman's correlation test was used for non-parametric variables. Power analysis using published data indicated that this sample size was adequate to detect significant differences in the FMD percentage and CIMT between subjects with PsA compared with healthy controls (α: 0.05; β: 0.2; power: 80%). A p value <0.05 was considered statistically significant. All analyses were performed using SPSS Statistics for Windows, Version 20.0 (IBM Corp., Armonk, NY, USA).

RESULTS

The median duration of PsA was 60 months (range: 8–216 months). Among 30 patients with PsA, only 13 (48.1%) had active disease, 16 (53.3%) had polyarthritis, 12 (40%) had oligoarthritis, 2 (6.7%) had monoarthritis, 9 (30%) had dactylitis, 14 (46.7%) had pitting, 10 (33.3%) had enthesitis, and 14 (46.7%) had nail involvement. In addition, among the PsA patients, 19 (63.3%) patients had peripheral joint involvement, 1 (3.3%) patient had axial involvement, and 10 (33.3%) patients had both peripheral and axial joint involvement. Only 22 of the 30 (73.3%) patients had the diagnosis of psoriasis at the time of PsA diagnosis. The study groups were similar in age, gender, BMI, fasting plasma glucose, serum creatinine, uric acid, total cholesterol, triglycerides, and LDL-cholesterol levels. The duration of disease and DAS-28 values were not significantly different between the PsA and RA groups. All of the patients with PsA and RA were using disease-modifying antirheumatic drug therapy. A total of 23 (76.7%) PsA patients and 5 (16.7%) RA patients were using anti-TNF-alpha treatment (p<0.001). PsA patients had a lower HDL level than the RA patients (p=0.002). Both the CRP and ESR levels were significantly higher in PsA and RA pa-

Table 1. Demographic, clinical, and laboratory parameters of the study groups

	Psoriatic arthritis (n=30)	Rheumatoid arthritis (n=30)	Healthy control (n=30)	p
Age, years	43.8±11.6	44.1±13.7	46.1±12.2	0.740
Female gender, n (%)	24 (80)	24 (80)	24 (80)	NA
Body mass index (kg/m^2)	26.6±2.9	25.4±3.9	25.7±3.9	0.361
Smoking, n (%)	5 (16.7)	7 (23.3)	7 (23.3)	0.767
Duration of disease (months)	60 (8–216)	66 (11–240)	–	0.265
Erytrocyte sedimentasyon rate (mm/h)	21.5 (3–73)	16 (7-79)	6 (1–20)	<0.001[a]
C-reactive protein (mg/dL)	0.35 (0.30–8.30)	0.50 (0.30–6.90)	0.28 (0.10–0.81)	<0.001[a]
Disaese activity score-28	3.52±1.60	3.27±1.26	–	0.168
Anti-TNF treatment, n (%)	23 (76.7)	5 (16.7)	–	<0.001
Duration of anti-TNF treatment (months)	13 (6–72)	12 (6–50)	–	0.985
Total cholesterol (mg/dL)	176.8±43.5	189.5±36.1	190.6±35.8	0.311
Triglycerides (mg/dL)	119 (44–274)	98 (49–212)	113 (51–260)	0.105
LDL cholesterol (mg/dL)	112.6±30.8	101.8±35.2	116.5±24.0	0.157
HDL cholesterol (mg/dL)	49 (25–154)	68.5 (43–160)	58 (33–154)	0.002[b]
Serum creatinine (mg/dL)	0.78±0.18	0.75±0.18	0.76±0.17	0.725
Serum uric acid (mg/dL)	6.7±1.9	6.6±1.3	6.0±1.1	0.392
Fasting plasma glucose (mg/dL)	91±13	86±11	89±10	0.221

Data were shown as mean±SD, median (minimum-maximum), or n (%). P<0.05 for [a]PsA and RA vs healthy controls, [b]PsA vs RA. PsA: Psoriatic arthritis; RA: Rheumatoid arthritis; TNF: Tumor necrosis factor; HDL: High density lipoprotein; LDL: Low density lipoprotein.

tients compared with the healthy controls (p<0.001). The demographic, clinical, and laboratory data of the study groups are presented in Table 1.

The FMD percentage was significantly lower in the PsA and RA patients than in the healthy participants (7.8±3.25 for PsA and 8.25±2.51 for RA vs 11.9±2.8 for healthy controls; p<0.001) (Fig. 1). While both the median right and left CIMT were significantly greater in RA patients compared with the healthy controls (p=0.039 and p=0.002, respectively), there

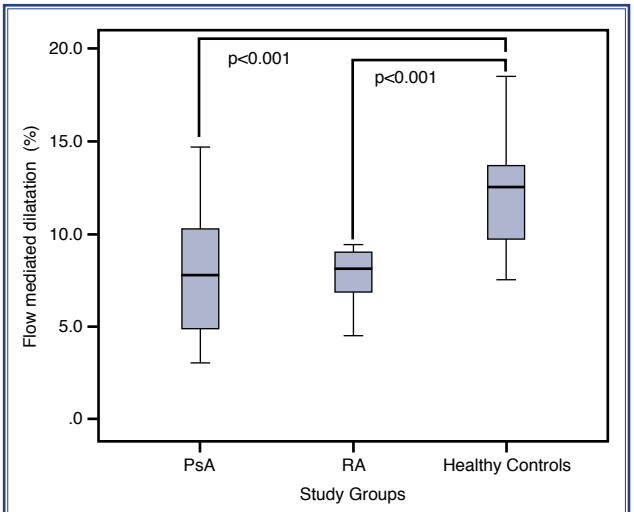

Figure 1. Comparison of flow-mediated dilatation (FMD) percentage between study groups (p<0.001 for psoriatic arthritis [PsA] and rheumatoid arthritis [RA] vs healthy controls).

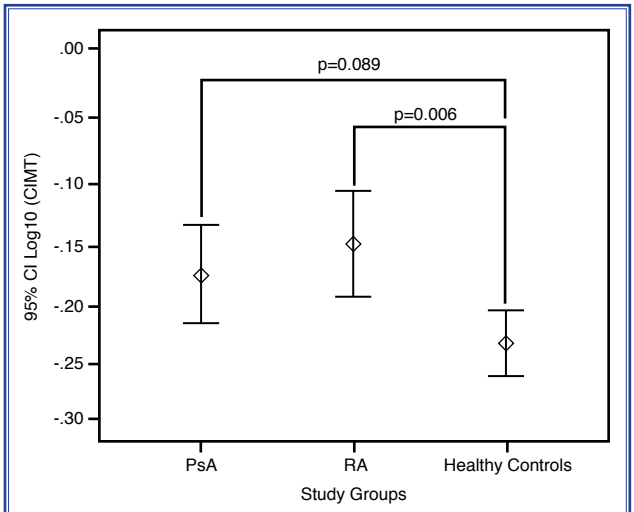

Figure 2. Comparison of log10 (mean carotid intima media thickness [CIMT]) between study groups (p=0.006 for rheumatoid arthritis [RA] vs healthy controls).

Table 2. Comparison of parameters for subclinical atherosclerosis between study groups

	Psoriatic arthritis (n=30)	Rheumatoid arthritis (n=30)	Healthy control (n=30)	p
Flow mediated dilatation (%)	7.88±3.25	8.25±2.51	11.9±2.80	<0.001[a,b]
Left CIMT (mm)	0.65 (0.45–1.30)	0.72 (0.43–1.21)	0.60 (0.38–0.95)	0.002[b]
Right CIMT (mm)	0.64 (0.43–1.38)	0.66 (0.43–1.34)	0.58 (0.43–0.89)	0.039[b]
Mean CIMT (mm)	0.65 (0.48–1.34)	0.73 (0.43–1.28)	0.60 (0.42–0.92)	0.008[b]
Log10 (Mean CIMT)	-0.17±0.11	-0.15±0.11	-0.23±0.75	0.006[b]
Carotid plaque, n (%)	0 (0)	4 (13.3)	0 (0)	0.015[b,c]

Data were shown as mean±SD or median (minimum-maximum).
[a]PsA vs healthy controls, [b]RA vs healthy controls, [c]RA vs PsA.
CIMT: Carotid intima media thickness; Log10 (Mean CIMT): Logarithmic transformation of mean CIMT. PsA: Psoriatic arthritis; RA: Rheumatoid arthritis.

was no difference between the PsA patients and the healthy controls in regard to right and left CIMT (Fig. 2). The mean log10 (CIMT) was also significantly higher in the RA patients than it was in the healthy controls (p=0.006). Carotid plaque was observed in 4 (13.3%) patients with RA, but no carotid plaque was seen in the PsA patients or the healthy controls (Table 2). There was no correlation between the DAS-28 results and FMD (r=0.058; p=0.688) or log10 (CIMT) (r=-0.119; p=0.405). However, there was a significant positive correlation between the duration of PsA and log10 (CIMT) (r=0.283; p=0.033) (Fig. 3; Table 2). In addition, correlation analysis revealed that there was a significantly positive correlation between CRP level and CIMT (r=0.315; p=0.01) and a trend for a positive correlation between ESR and CIMT (r=0.197; p=0.068). There was no significant correlation between FMD and either ESR or CRP. The FMD and CIMT values were similar between patients with wither an active or remission phase disease diagnosis.

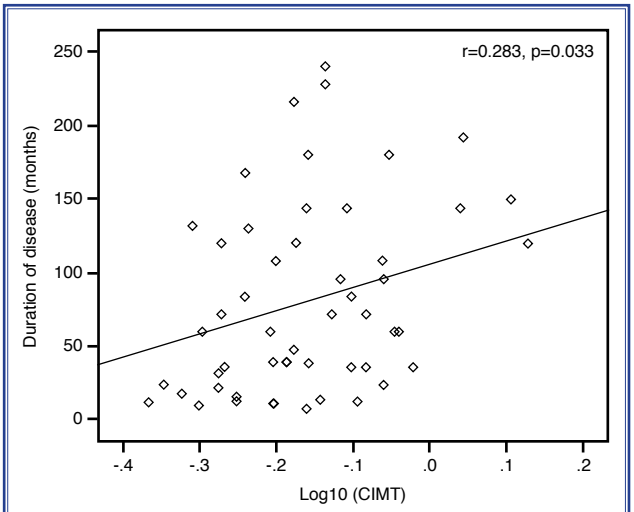

Figure 3. Correlation analysis of log10 (mean carotid intima media thickness [CIMT]) and duration of psoriatic arthritis (PsA) (r=0.283; p=0.033).

DISCUSSION

Our study results indicated that PsA and RA patients demonstrated significantly lower FMD values compared with healthy controls. However, CIMT was only higher in RA patients compared with healthy controls and was similar between PsA patients and healthy controls. Additionally, there was a positive correlation between the duration of disease and log10 (CIMT) values, but no correlation was found between disease activity and parameters of endothelial dysfunction or subclinical atherosclerosis.

PsA is known as one of the most common chronic immune-mediated inflammatory arthropathies.[1] Previous studies have reported that traditional cardiovascular risk factors were more prevalent in PsA, as in other chronic inflammatory rheumatological diseases,[6,17,18] and that CVD and cardiovascular mortality are also significantly increased in these patient groups compared with the general population.[19,20] RA is the prototype and most common form of inflammatory and immune-associated arthritis, and has the greatest impact on cardiovascular outcomes. Therefore, scientific statements have been developed by rheumatology societies for RA patients to reduce cardiovascular risk.[21] It has also been studied and observed that CVD risk is increased in other forms of inflammatory rheumatic diseases like PsA.[10,22–26] However, the increased cardiovascular morbidity and

mortality in patients with PsA cannot entirely be explained by traditional cardiovascular risk factors, and chronic inflammatory status may act as an independent risk factor for CVD in these patients, like RA.[27,28] Therefore, the association between PsA and subclinical atherosclerosis and endothelial dysfunction, proven indicators of CVD, is still a matter of research. In our study, we aimed to assess the presence of endothelial dysfunction and subclinical atherosclerosis in patients with PsA as the primary patient group. We also included patients with RA as the prototype and most common form of chronic inflammatory arthritis associated with CVD as a secondary patient group, as well as a healthy group for comparison.

It is apparent from the literature that atherosclerosis is linked to an inflammatory pathological processes and significantly associated with chronic inflammatory and immune-mediated diseases.[7,29–31] Therefore, chronic inflammatory status and abnormal immune pathways in inflammatory and immune-mediated rheumatological diseases may be directly associated with subclinical and clinical atherosclerosis and adverse CV outcomes. The impact of inflammation and immunity during the atherosclerotic process may be more prominent in the absence of traditional CV risk factors. Thus, we included patients with PsA and RA without a previous history of CVD or traditional CV risk factors and aimed to assess the impact of the rheumatological disease process on endothelial dysfunction and subclinical atherosclerosis. The positive correlation between CRP level and CIMT in our study group supports the hypothesis that the atherosclerotic pathophysiological process is linked to chronic inflammation.

Impaired endothelial dysfunction is a precursor of atherosclerosis and has consistently been associated with increased CV risk.[8] Ultrasonography is used to noninvasively assess endothelial function using the FMD percentage in the brachial artery.[12,16] CIMT, determined by ultrasonography, is a valuable, non-invasive surrogate indicator of clinical CVD and potential adverse outcomes and provides information about the subclinical stage of the atherosclerotic disease.[32,33] In our study, we found that FMD was significantly lower in patients with PsA and RA patients compared with healthy controls. These findings showed that endothelial function was significantly impaired in PsA and RA patients. Furthermore, CIMT was also significantly higher in the patients with RA than in the healthy controls, but there was no significant difference in CIMT between the PsA patients and the controls. Gonzalez-Juanatey et al.[25] reported that the FMD percentage was significantly lower in patients with PsA without CV risk factors or clinically evident CVD compared with healthy controls, indicating endothelial dysfunction in PsA as a potential basis for the association between PsA and atherosclerosis.[34] However, there have been contradictory results regarding the increased risk of subclinical atherosclerosis assessed by CIMT in patients with PsA in case-control studies and meta-analyses.[2,10,11,23,24,35,36] We proposed that the main reason for a non-significant difference in CIMT between PsA and healthy controls was the greater use of anti-TNF-alpha treatment, as a stronger anti-inflammatory agent, compared with the RA patients in our study and other studies.[37,38] Previous studies have shown that anti-TNF-alpha treatment in psoriatic patients reduced CIMT.[38] Patients with PsA without clinically evident CVD or traditional CV risk factors in our study population demonstrated an impaired endothelial functions as a precursor of atherosclerosis, but no difference in CIMT as a marker of subclinical atherosclerosis when compared with healthy controls. Additionally, HDL-cholesterol levels were significantly different between the PsA and RA patients in our study (lower in PsA patients). Although a low level of HDL-cholesterol is significantly linked to atherosclerotic disease and cardiovascular adverse events, the assessment in inflammatory conditions is more complex as a result of a reduction in HDL-cholesterol level as an acute phase reactant and changes in structure.[39] We thought that a pathological inflammatory process, rather than a cholesterol hypothesis (regarding low HDL-cholesterol) may have more importance in the development of atherosclerosis among inflammatory rheumatological diseases.

As a clinical implication of our study results, the CV risk of patients with PsA may be evaluated using indicators of endothelial dysfunction (FMD) and subclinical atherosclerosis (CIMT). As a proposal, such a screening program may help in the early diagnosis of CVD and reducing CV morbidity and mortality.

Our study results should be interpreted with some significant limitations. First, our small, non-randomized parallel group study has no power to show any causality between PsA and subclinical atherosclero-

sis, and the study results cannot be generalized to the whole PsA population due to the absence of traditional CV risk factors. Second, most of our PsA patients were using biological agents, which might impact the measurements of endothelial function and subclinical atherosclerosis. Third, we did not assess the level of homocysteine, vitamin B12 or folate, which have been closely associated with endothelial function and shown to be affected in immune mediated disorders. Finally, approximately half of both the PsA and RA groups were in the active form of their disease, which might impact FMD measurement.

In conclusion, there was an increased risk of impaired endothelial function in the PsA patients without clinically evident CVD or traditional CV risk factors that was similar to RA patients as a prototype for high CV risk. Chronic inflammatory status in the PsA disease process may be the most likely risk factor for the occurrence of early atherosclerotic changes in these patients. However, further randomized controlled studies are needed to understand the causal relationship between PsA, inflammation, immunity, and atherosclerosis. Therefore, it is reasonable to assess patients with PsA with regard to CV risk as well as other system findings.

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