

Subclinical Atherosclerosis in Psoriatic Arthritis: A Case-Control Study

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ABSTRACT. Objective. To investigate the prevalence of subclinical atherosclerosis among patients with psoriatic arthritis (PsA).

Methods. Forty patients with PsA were enrolled. Controls were matched by age, sex, and atherosclerotic risk factors. All patients and controls underwent duplex scan of the carotid arteries. Carotid intima-media thickness (IMT) was evaluated and the presence of atherosclerotic plaques was recorded. The plaques were graded and carotid plaque index was calculated.

Results. Patients with PsA had a higher IMT (mean \pm standard deviation, 1.04 ± 0.35 mm vs 0.88 ± 0.29 mm in controls; $p = 0.03$), and had a higher carotid plaque index than did matched controls (2.3 ± 2.6 , compared to 1.12 ± 2.09 ; $p = 0.03$). Multivariate analysis demonstrated that PsA status as well as age and triglyceride levels were associated with the presence of carotid plaque. Other traditional risk factors were more prevalent among patients with PsA; however, they were not statistically significant.

Conclusion. Our study demonstrates that patients with PsA may have an increased prevalence of subclinical atherosclerosis. These findings may not be solely attributable to traditional risk factors alone. Special attention and strict control of atherosclerotic risk factors in patients with PsA is warranted. (First Release Mar 15 2008; J Rheumatol 2008;35:877–82)

Key Indexing Terms:

ATHEROSCLEROSIS PSORIASIS PLAQUE INTIMA-MEDIA THICKNESS

Recent studies have demonstrated an increased risk of atherosclerotic cardiovascular disease in patients with various rheumatic diseases such as systemic lupus erythematosus (SLE)^{1,2} and rheumatoid arthritis (RA)^{3,4}. Traditional risk factors for atherosclerosis such as hypertension, hyperlipidemia, or reduced physical activity may partially account for these findings. Medication used to treat rheumatic diseases may also influence the expression of risk factors. Inflammation is a key factor in atherogenesis⁵⁻⁷, via T-helper type 1 lymphocytes that activate macrophages and initiate an inflammatory response by production of proinflammatory cytokines such as interferon, tumor necrosis factor- α (TNF- α), and interleukin 1; this provides an additional mechanism to explain the excess atherosclerosis in these chronic inflammatory diseases.

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Psoriatic arthritis (PsA) is a systemic inflammatory disease⁸. In consideration of the known increased atherosclerosis risk in RA and SLE, it may be hypothesized that atherosclerosis would also be more prevalent among patients with PsA. Yet there are relatively few data regarding the risk and prevalence of atherosclerosis/cardiovascular diseases in patients with PsA. Recently, there have been several reports suggesting an association between psoriasis and atherosclerosis. Ludwig, *et al* reported that coronary artery calcifications as assessed by spiral computed tomography were more prevalent among patients with psoriasis⁹. Another prospective, population-based cohort study in the United Kingdom found an increased incidence of myocardial infarction among patients with psoriasis¹⁰.

High-resolution carotid ultrasonography is used to obtain measurements of the thickness of the intima and media of the carotid arteries. Studies have shown a direct association between increased common carotid artery intima-media thickness (IMT) and the involvement of other arterial beds with atherosclerosis^{11,12}. IMT also serves as a risk factor for myocardial infarction and stroke in asymptomatic adults, independent of traditional cardiovascular risk factors¹³. Thus, determination of carotid IMT using ultrasound techniques provides useful and early information about atherosclerosis in subclinical stages of the disease in individuals at risk.

A case-control study was conducted to investigate the prevalence of subclinical atherosclerosis among patients with PsA.

MATERIALS AND METHODS

Eighty subjects were recruited for the 2 study groups — 40 with PsA and 40 controls. We determined the required sample size to achieve 80% power with $\alpha = 0.05$ by 2-sample t-test for the mean differences.

Forty patients with PsA were enrolled from the Haifa Psoriatic Arthritis Registry. This registry was developed during a previous study and includes patients followed at the Clalit Health Services Lin Medical Center and Zvulun Medical Center as well as the Bnai Zion Medical Center rheumatology outpatient clinic, serving the greater Haifa region in northern Israel.

All patients in the registry fulfilled the Moll and Wright criteria for PsA¹⁴. The diagnosis of psoriasis of skin was ascertained by a dermatologist. Patients were recruited consecutively upon arrival at the rheumatology clinic.

Patients were excluded if they had renal failure with serum creatinine > 1.3 mg/dl, preexisting clinical coronary artery disease with a history of angina pectoris or myocardial infarction, or a history of cerebrovascular accident, transient ischemic attack or peripheral vascular disease.

Forty patients without psoriasis who are members of the Clalit Health Services community clinic in the Sapir Center, Haifa, were recruited to serve as a control group. Patients were individually matched to control subjects based on age (within 5 yrs), sex, and history of hypertension, diabetes mellitus, hypercholesterolemia, and smoking status. Previously noted exclusion criteria were also applied to controls. In addition, patients with inflammatory arthritis of any type or other chronic inflammatory diseases, such as sarcoidosis or inflammatory bowel disease, were excluded from the control group. The study protocol was approved by the local Helsinki committee and informed consent was obtained from all cases and controls.

PsA-related disease factors. All patients were examined and interviewed with the use of a standardized questionnaire. Comprehensive medication histories were obtained through patient interviews and chart review. The same physician performed the examination of joints of all subjects and the count of swollen and tender joints was recorded.

Cardiovascular risk factors. Blood pressure was measured and body mass index (BMI) was calculated. Diabetes mellitus (overnight fasting plasma glucose > 125 mg/dl or antidiabetic drug use), hypertension (systolic blood pressure > 140 mm Hg or diastolic blood pressure > 90 mm Hg or antihypertensive drug use), and hypercholesterolemia [total cholesterol > 200 mg/dl or low density lipoprotein (LDL) > 130 mg/dl or triglyceride (TG) > 200 mg/dl or lipid-lowering drug use] were ascertained by patient report, accompanied by a medical record and medication review. Smoking habits were recorded. Blood samples were taken to measure total cholesterol, LDL cholesterol, high density lipoprotein (HDL) cholesterol, TG, and fasting plasma glucose level. Family history of cardiovascular disease was noted (myocardial infarction before 55 yrs of age in first-degree male relatives or before 65 yrs in female relatives).

Laboratory and radiographic studies. A single blood sample was taken from each participant after completion of the interview and examination on the day of enrollment. This sample served for measurement of all laboratory variables. Erythrocyte sedimentation rate (ESR) was measured using the Westergren technique and C-reactive protein (CRP) measured by enzyme linked immunosorbent assay (normal 0–0.5 mg/dl). Serum interleukin 6 (IL-6), tumor necrosis factor- α , and IL-10 were measured with commercial kits (eBioscience). The extent of the joint structural damage was assessed on radiographic imaging of the hands and feet by 2 rheumatologists who were blinded to the patients' status using the modified Steinbrocker scoring method¹⁵.

Carotid ultrasonography. A single trained sonologist performed all measurements, following the study protocol. An ATL HDI-5000 high-resolution scanner with an L12-5 transducer (Philips Medical Systems) was used. The examining sonologist was blinded to the clinical data. Reproducibility and intraobserver variation were checked by repeat scanning of the subjects on different days. The intraobserver intraclass correlation coefficient for artery IMT was 0.94.

Patients and controls were examined while in a supine position with the neck extended and the chin turned contralateral to the side being examined. The scan included detailed B-mode images of both right and left common

carotid arteries (CCA) as well as the carotid bulb, internal carotid arteries (ICA), and external carotid arteries (ECA) on each side. The maximal IMT of each of these was obtained by averaging the maximal measurements of the near and far walls and on right and left sides. Then a composite maximal IMT was calculated by averaging the CCA, ICA, and ECA measurements.

The images were also examined for the presence of atherosclerotic plaques. A plaque was defined as a distinct area protruding into the vessel lumen, with at least 50% greater thickness than that found in surrounding areas. The plaques were graded according to accepted criteria, as follows. Grade 0: no plaque identified; Grade 1: single small plaque (< 30% of the blood vessel diameter); Grade 2: single medium-size plaque (30%–50% of the blood vessel diameter) or multiple small plaques; Grade 3: large plaque (> 50% of the blood vessel diameter) or multiple plaques with at least 1 that meets the criteria for medium-size plaque. Summation of the plaque grades in each individual provided a "plaque index" — a term used to express the extent of carotid atherosclerosis¹⁶.

Statistical analysis. Continuous data were described as mean and standard deviations (mean \pm SD), and categorical variables as percentages. Comparisons between the 2 categories were by Student t-test (2-tailed) for continuous variables. To analyze categorical data the chi-square test was used.

The ultrasound continuous measure of IMT of the 2 groups was compared by t-test with 90% confidence intervals (CI). The plaque index was used to divide the study population into 2 subgroups: those without plaque (plaque index 0) and those with plaque (plaque index > 0). The prevalence of atherosclerotic plaques was compared utilizing Fisher's exact test.

A linear model was built in the total study population (controls and patients). The dependent variable was carotid IMT and the independent variables were traditional cardiovascular risk factors and the presence of PsA. Then an additional linear model was constructed in the PsA reference group. The dependent variable was the presence of atherosclerotic plaques and the independent (explanatory) variables were duration of arthritis, disease activity score, radiographic activity score, type of arthritis, level of acute-phase reactants (ESR, CRP), and the drugs used to treat the arthritis. The importance of each factor in each model was assessed by F value and p value, with 95% CI. The statistical computation was performed by Procedure GLM SAS 9.13 package (Release 9; SAS, Cary, NC, USA).

RESULTS

Comparison between PsA and controls. Characteristics of the study subjects are shown in Table 1. There were no statistically significant differences in age, sex, and cardiovascular risk factors between the groups, apart from HDL cholesterol level, which was slightly higher in controls. As expected, ESR and CRP were significantly higher among patients with PsA.

Characteristics of patients with PsA. The clinical and radiographic features of patients with PsA are summarized in Table 2. Most of the patients had polyarticular involvement (57.5%), and a significant number had articular erosions on roentgenograms (40%). Moreover, most patients were taking disease-modifying drugs. No patient was treated with systemic medications for skin psoriasis.

Ultrasonographic differences between PsA patients and controls. The overall prevalence of atherosclerosis was higher among the patients than the controls. Patients with PsA exhibited greater carotid IMT than controls, 1.04 ± 0.35 mm versus 0.88 ± 0.29 mm, respectively ($p = 0.03$). In addition, the carotid plaque index was higher among patients (2.3 ± 2.6) compared to controls (1.12 ± 2.09) ($p = 0.03$). The presence of plaque and its severity, as indicated by the plaque index, is

Table 1. Characteristics of patients with PsA and healthy controls.

Characteristic	Patients with PsA, n = 40	Controls, n = 40	p
Age, mean (range), yrs	57.85 (43–76)	57.05 (34–79)	0.72
Females, n (%)	28 (70)	28 (70)	1
Diabetes mellitus, n (%)	5 (12.5)	5 (12.5)	1
Glucose level, mg/dl, mean ± SD	105 ± 40	97 ± 15	0.2
Hypertension, n (%)	19 (47.5)	19 (47.5)	1
Body mass index	28 ± 4	27 ± 3	0.3
Ever smoked cigarettes, n (%)	5 (12.5)	7 (17.5)	0.7
Hypercholesterolemia, n (%)	15 (37.5)	15 (37.5)	0.8
Total cholesterol level, mg/dl, mean ± SD	194 ± 47	211 ± 35	0.07
LDL cholesterol level, mg/dl, mean ± SD	122 ± 34	131 ± 33	0.2
HDL cholesterol level, mg/dl, mean ± SD	46 ± 13	53 ± 12	0.02
Triglyceride level, mg/dl, mean ± SD	155 ± 97	149 ± 57	0.7
Use of statin, n (%)	13 (32.5)	6 (15)	0.11
Family history of cardiovascular disease, n (%)	9 (22.5)	7 (17.5)	0.7
ESR, mm/h, mean ± SD	38 ± 21	18 ± 9	0.04
CRP, mg/dl, mean ± SD	1.13 ± 1.28	0.25 ± 0.05	0.03

HDL: high density lipoprotein; CRP: C-reactive protein; LDL: low density lipoprotein; ESR: erythrocyte sedimentation rate; PsA: psoriatic arthritis.

Table 2. Clinical and radiographic features of patients with PsA.

Feature	
Duration of arthritis, yrs	8.5 ± 7.3
Arthritis mutilans, n (%)	2 (5)
Symmetric polyarthritis, n (%)	23 (57.5)
Oligoarthritis, n (%)	13 (32.5)
Spondyloarthritis, n (%)	2 (5)
ACR joint count, mean ± SD	19 ± 18
Nonsteroidal antiinflammatory drug use, n (%)	23 (57.5)
Prednisone treated, n (%)	5 (12.5)
Methotrexate treated, n (%)	23 (57.5)
Sulfasalazine treated, n (%)	8 (20)
Anti-TNF treated, n (%)	5 (12.5)
Radiographic erosions, n (%)	16 (40)
Imaging damage score ± SD	29 ± 40

PsA: psoriatic arthritis; ACR: American College of Rheumatology; TNF: tumor necrosis factor.

presented in Table 3. There was a significant linear trend of more severe plaques among patients with PsA compared to controls ($p = 0.011$). Using logistic regression to examine the relationship between traditional cardiovascular risk factors as well as disease status and subclinical atherosclerosis in this group, only PsA and age were associated with subclinical atherosclerosis (Table 4).

Correlation between clinical and laboratory features and carotid plaque index and IMT. Table 5 summarizes the correlation between different variables and the carotid plaque index. Univariate correlation analysis showed a strong positive correlation between age and the carotid IMT ($r = 0.57$, $p = 0.0001$) and the carotid plaque index ($r = 0.51$, $p = 0.0006$) in patients with PsA. In addition, a positive correlation was found between the carotid plaque index and TG level ($r =$

Table 3. Frequency of plaque index in patients with PsA and healthy controls.

Plaque Index	Controls	Patients with PsA
0, (%)	24 (60)	12 (30)
1–3, (%)	11 (27.5)	18 (45)
≥ 4, (%)	5 (12.5)	10 (25)

$p = 0.011$.

Table 4. Multivariate regression analysis for intima-media thickness in patients with PsA by ANOVA.

Variable	Mean Square	F	p
PsA	0.035	4.71	0.03
Age	0.0138	18.52	< 0.0002
Diabetes mellitus	0.000009	0.01	0.2
Hypertension	0.000004	0.01	0.9
Hyperlipidemia	0.0009	1.34	0.9
Smoking	0.002	3.84	0.054

0.33 , $p = 0.03$) as well as past prednisone treatment ($r = 0.31$, $p = 0.04$). There was no correlation between the carotid IMT and the carotid plaque index and disease duration or other clinical or radiographic characteristics of arthritis. This was also the case for inflammation markers such as CRP, ESR, TNF, IL-6, or IL-10 levels. Similarly, neither the carotid IMT nor the carotid plaque index were associated with classical risk factors of atherosclerosis such as sex, hypertension, diabetes mellitus, hyperlipidemia, cholesterol, LDL-C and HDL-C levels, and smoking status.

Comparison between patients with and without plaque. In order to further investigate arthritis related variables and their

Table 5. Correlation between study population characteristics and carotid plaque index.

Variable	Correlation Coefficient	P
Age	0.51	0.0006
Past prednisone treatment	0.317	0.04
Duration of arthritis	0.14	0.3
Oligoarthritis	-0.19	0.23
Polyarthritis	0.04	0.8
Spondyloarthritis	0.06	0.7
CRP	-0.2	0.2
ESR	-0.07	0.7
Triglyceride level	0.33	0.03
Hypertension	0.27	0.08
Hyperlipidemia	0.24	0.12

ESR: erythrocyte sedimentation rate; CRP: C-reactive protein.

association with atherosclerosis, we compared patients with and without carotid plaque (Table 6). A trend toward longer disease duration and polyarticular involvement reflected in higher tender and swollen joint count scores and the presence of carotid plaque was noted. However, these differences did not reach statistical significance. There were no differences in radiographic severity or current drug treatment between the groups.

In addition, the levels of TNF- α , IL-6, and IL-10 were compared in patients with and without carotid plaque. There were no significant differences in the cytokine levels between the 2 groups.

Using logistic regression analysis to examine demographic variables and risk factors for cardiovascular disease that were more common in patients with plaque than in those without plaque, only the variables of age and TG level remained in the model. In other words, age and TG levels were associated with subclinical atherosclerosis. Other traditional cardiovascular risk factors were more frequent among patients with atherosclerotic plaques; however, this trend was not statistically significant.

DISCUSSION

Previous studies have reported subclinical vascular disease, as manifested by evidence of increased carotid IMT by high-resolution ultrasound studies, in RA^{3,4,17,18} and SLE^{1,2,19}. Systemic inflammation is an important pathogenic mechanism in both RA and atherosclerosis. Proinflammatory T-helper type 1 cytokines, such as TNF- α and interferon, are important participant in plaque formation as well as endothelial dysfunction²⁰. TNF- α is also a key participant in systemic inflammation and the arthritic process in PsA; and anti-TNF therapy is effective in disease control. These shared pathways support the concept of accelerated atherosclerosis in association with chronic systemic inflammation in diseases such as PsA.

We assessed the prevalence of subclinical atherosclerosis in a case-control study of patients with PsA. Significantly increased prevalence of subclinical atherosclerosis, as expressed by their carotid IMT and carotid plaque index, was documented in patients with PsA.

In contrast to the comprehensive data that exist in regard to the cardiovascular morbidity among patients with SLE and RA, this issue has not been extensively studied in patients with PsA. Han, *et al* reported increased co-occurrence rates of congestive heart failure (RR 1.5) and cardiovascular disease (RR 1.3) as well as of cardiovascular risk factors such as diabetes mellitus type II, hypertension, and hyperlipidemia in patients with PsA²¹. An additional report, which included a PubMed search, revealed an increased cardiovascular morbidity and mortality in patients with spondyloarthropathy including PsA²². Kimhi, *et al*²³ recently reported similar findings of increased prevalence of subclinical atherosclerosis, represented by increased carotid IMT, in patients with PsA. However, in contrast to our study, patients with cardiovascular disease were not excluded from the study. In addition, patients and controls were not matched with cardiovascular risk factors, as in our study. These factors might have influenced the results²³.

Recent studies in patients with RA and SLE have described

Table 6. Differences in disease-associated variables between PsA patients with and without carotid plaque.

Variable	With Plaque, n = 28	Without Plaque, n = 12	p
Duration of arthritis, yrs \pm SD	10.6 \pm 7.6	6 \pm 6	0.07
Oligoarticular pattern, n (%)	7 (25)	6 (50)	0.15
Polyarticular + mutilans pattern, n (%)	20 (71)	5 (41)	0.09
ACR joint count, mean \pm SD	22.5 \pm 20.8	11.5 \pm 10.9	0.09
Radiographic erosions, n (%)	11 (39)	5 (41)	1
Imaging damage score \pm SD	31.2 \pm 14.8	24.2 \pm 37.5	0.4
ESR, mm/h, \pm SD	38.1 \pm 14.8	41.2 \pm 29	0.6
CRP, mg/dl, mean \pm SD	0.93 \pm 0.8	1.66 \pm 2	0.09
Current treatment with methotrexate, n (%)	15 (40)	8 (66)	0.5
Current treatment with sulfasalazine, n (%)	5 (18)	3 (25)	0.6
Current treatment with anti-TNF drug, n (%)	4 (15)	0	0.3

ACR: American College of Rheumatology; CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; TNF: tumor necrosis factor.

a correlation between elevated markers of inflammation, joint activity score, longer disease duration, and atherosclerosis²⁴⁻²⁷. In our study a similar trend to correlation between elevated disease activity (polyarthritis, longer disease duration, and higher joint activity score) and carotid plaque was noted, but did not reach statistical significance. This may be explained by the clinical heterogeneity of patients with PsA in our study. The relatively small cohort size precluded comparison between more clinically homogenous subgroups of patients.

Traditional risk factors such as TG level and age were positively associated with more advanced vascular disease. Other traditional cardiovascular risk factors such as hypertension, hypercholesterolemia, and diabetes mellitus were more prevalent among subjects with atherosclerosis, although they did not reach statistical significance. The small size of the cohort limited the evaluation of traditional risk factors within the patient group.

The mechanisms underlying excess atherosclerosis in various connective tissue disorders are not fully understood. It has been suggested that chronic inflammation may play a key role in inducing accelerated atherosclerosis in general. Elevated inflammation markers such as CRP and fibrinogen have been linked to cardiovascular diseases in populations at large⁵⁻⁷. These markers as well as other indicators of active inflammation were positively correlated with subclinical atherosclerosis in patients with RA and SLE. In our study, CRP and ESR, as well as cytokine levels, were not directly associated with carotid plaque. This may be partly explained by the observation that levels of acute-phase reactants such as CRP and ESR are not reliably elevated in patients with PsA even in the presence of active inflammation²⁸.

Increased clinical cardiovascular morbidity in patients with PsA may also be explained in part by the presence of a pathogenic lipid profile²⁹. This pattern is characterized by a decrease in total HDL-C and an increase in the levels of LDL3 total mass and its cholesterol and TG components, and a tendency for Lp(a) lipoprotein to be increased. The combination of low HDL-C and a high LDL3 is strongly associated with an increased risk of atherosclerosis in population studies³⁰. On multivariate analysis in our study, there was a positive correlation between elevated levels of TG and atherosclerosis in the patients with PsA. We did not, however, assess LDL3 or other complex lipid particles.

Psoriasis is associated with an increased prevalence of traditional cardiovascular risk factors including hypertension and diabetes mellitus^{31,32}. Although these may be responsible for the increased prevalence of atherosclerosis in PsA, there were no significant differences in the distribution of these risk factors between the PsA patients and controls in our study. Therefore, we may hypothesize that additional risk factors probably linked to the immune dysfunction of PsA may have a role in driving the atherosclerotic process. One limitation of our study is that the severity of skin psoriasis was not recorded (i.e., by Psoriasis Activity and Severity Index score).

Several recent studies^{9,10} have demonstrated an increased risk of cardiovascular morbidity and mortality in patients with psoriasis. In addition, it has been shown that the severity of skin involvement correlates with the prevalence of atherosclerotic plaques. We focused on patients with joint manifestations of the disease. Therefore, it cannot be excluded that the skin manifestation may contribute to the high prevalence of atherosclerosis in our group of patients. However, the fact that none of our patients was treated with systemic drugs for their skin disease may indicate a relatively limited involvement of skin in this cohort. Further research is needed to separate the influence of skin versus arthritis involvement on the atherosclerotic process.

Our study demonstrates that patients with PsA may have an increased prevalence of subclinical atherosclerosis. These findings may not be solely attributable to traditional risk factors, but seem to be associated at least in part with alterations in the immune system that are part of the systemic inflammatory mechanism of the primary disease. Strict control of atherosclerotic risk factors in patients with PsA would seem warranted. Further research is needed to characterize the clinical and laboratory features that are associated with and that may also predict arterial vascular wall damage in PsA.

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