Prevalence and Risk Factors of Atherosclerosis in Patients with Psoriatic Arthritis

Oded Kimhi, MD,* Dan Caspi, MD,† Natan M. Bornstein, MD,‡ Nitsan Maharshak, MD,§ Alexander Gur, M.D.PhD.,¶ Yaron Arbel, MD,§ Doron Comaneshter, PhD,** Daphna Paran, MD,* Irena Wigler, MD,* David Levartovsky, MD,§ Shlomo Berliner, MD,† and Ori Elkayam, MD††

Objectives: To evaluate the extent of subclinical atherosclerosis by measuring the intima-media wall thickness (IMT) of the common carotid artery in patients with psoriatic arthritis (PsA) and to identify vascular risk factors associated with PsA.

Methods: Forty-seven patients with PsA were compared with 100 allegedly healthy subjects. Carotid duplex scanning was used to measure common carotid artery IMT. Traditional risk factors, such as gender, age, body mass index (BMI), hypertension, smoking, and lipids were checked. Assessment of PsA activity included clinical patterns of involvement, degree of severity, duration of morning stiffness, number of tender and swollen joints, degree of pain and fatigue, the Bath Ankylosing Spondylitis Disease Activity Index, the Psoriasis Area and Severity Index, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), and fibrinogen.

Results: The average IMT (mean ± standard deviation) for PsA patients was significantly higher compared with controls (0.76 ± 0.11 versus 0.64 ± 0.27, respectively, P < 0.00001) for the whole group and after adjustment for age, gender, BMI, hypertension, and hyperlipidemia. The PsA subjects had significantly higher levels of hypertension, hyperlipidemia, ESR, CRP, and fibrinogen, and their average IMT significantly correlated with age, BMI, duration of skin and joint disease, spine involvement, ESR, and fibrinogen. IMT did not correlate with the presence of oligo- or polyarthritis but was increased in patients with clinical spinal involvement. IMT was not associated with the degree of severity or the use of different therapies for PsA, including methotrexate or tumor necrosis factor-α-blocking agents.

Conclusions: PsA patients exhibited greater IMT than healthy controls. Increased IMT independently correlated with parameters of disease activity and conventional risk factors of atherosclerosis.

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Increased cardiovascular morbidity and mortality have been observed in several inflammatory rheumatic diseases, including rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE) (1–5). The accelerated development of atherosclerosis in inflammatory disorders may be related to the inflammatory overload as well as to the accumulation of classical risks factors such as hyperlipidemia, smoking, and others (1–5). Psoriatic arthritis (PsA) is a chronic inflammatory joint disease with considerable clinical variation (6). Some evidence suggests an increased mortality risk in PsA patients directly related to circulatory and respiratory causes (7). Markers of disease activity, such as prior use of medications, high erythrocyte sedimentation rate (ESR) at presentation, and evidence of radiological damage are apparently associated with increased cardiovascular mortality (8). Likewise, a 50% increased risk of cardiovascular mortality has been reported in patients with severe psoriasis requiring hospitalization (9). Despite these data, no measures of atherosclerosis have been examined in PsA patients,
and there are few data on the correlation between disease activity and other risk factors.

The carotid arteries are easily accessible to noninvasive study by using ultrasound techniques, which provide accurate measurement of atherosclerosis even in its subclinical stages (10). B-mode ultrasound allows measurement of the intima-media wall thickness (IMT), which is considered to be a sensitive marker of early atherosclerosis (11). Recent data have demonstrated that IMT, a measure of carotid atherosclerosis, is increased in both RA and SLE (12,13).

The aims of the present study were to assess the extent of atherosclerosis by measuring the IMT of the common carotid artery in patients with PsA compared with apparently healthy controls and to evaluate the potential association between IMT and cardiovascular risk factors and/or markers of inflammation in patients with PsA.

PATIENTS AND METHODS

Patients

Patients 18 years of age or older who were diagnosed as having PsA and were being routinely treated at our medical center’s Department of Rheumatology were consecutively invited to participate in this study. All patients who agreed to be part of the study were unselectively recruited and evaluated. They all fulfilled the currently accepted criteria for psoriasis, defined as the presence of typical skin lesions confirmed by a dermatologist, and for PsA, ie, the presence of a rheumatoid factor-negative inflammatory arthritis associated with psoriasis (14). Patients with other joint diseases, such as typical RA, SLE, and gout, were excluded, but not those with a history of cardiovascular events. The first 47 patients to fulfill entry criteria were enrolled in the study after signing an informed consent. The study was approved by the Institutional Ethics Committee.

Controls

One hundred consecutive individuals who were undergoing a routine checkup in the outpatient department of the Tel Aviv Medical Center volunteered to participate in this study. They underwent a complete clinical and physical examination, an evaluation of risk factors for atherosclerosis, as well as routine IMT studies. Individuals with joint disease were excluded. Since the controls were not age-matched to the PsA patient group, a subgroup of 30 age- and gender-matched subjects was formed from the whole group and compared with the study group.

Variable Measurements

Data for this study were derived from an interview, a physical examination, laboratory tests, and carotid ultrasound studies.

Traditional Cardiovascular Risk Factors

The clinic visit included anthropomorphic measurements (height, weight), blood pressure reading, and a venous blood sample after a 14-hour fast. Blood samples were used to measure total cholesterol, low-density lipoprotein cholesterol (LDL-c), high-density lipoprotein cholesterol (HDL-c), triglycerides, glucose and fibrinogen, ESR, and C-reactive protein (CRP) using standard methods at the hospital’s biochemistry laboratory. Hypertension was defined as a systolic blood pressure >140 mm Hg or a diastolic blood pressure >90 mm Hg or the use of antihypertensive agents. Information was collected on age, ethnicity, education, smoking habits, family history of cardiovascular disease, menopausal status, estrogen replacement, and diabetes.

Evaluation of Disease Activity

The duration of morning stiffness was recorded. Pain, fatigue, and patients’ global self-estimation of well-being were evaluated using a 10-point visual analog scale where 0 indicates excellent well-being and 10 indicates feeling extremely unwell. The Bath Ankylosing Spondylitis Disease Activity Index was used to evaluate the degree of axial involvement activity, and the Psoriasis Area and Severity Index (PASI) was used to assess the extent of skin involvement. Physical examination included recording the number of tender and swollen joints, the presence of dactyliitis, as well as the number of permanently deformed joints. Laboratory markers of disease activity included ESR, highly sensitive CRP, and complete blood count.

Evaluation of Disease Severity

The clinical charts of the patients were reviewed for the treatment for PsA. According to the pattern of involvement, the patients were classified into oligoarthritis, polyarthritis, and axial involvement (15). The diagnosis of axial involvement was established on clinical grounds. Patients were asked whether they have suffered from inflammatory back pain (defined as chronic back pain of more than 3 months, improved with physical activity or exercise but not with rest, with morning stiffness of more than 1 hour). The treating physician stratified the patients according to the degree of severity throughout the years of treatment into 3 groups: mild, moderate, and severe.

Intimal-Media Wall Thickness

Carotid artery atherosclerosis was determined by ultrasonographic measurement of the IMT of the common carotid artery between 1 and 3 cm proximal to the carotid artery bifurcation on the left and right sides. IMT was measured at the distal wall of the carotid artery on a 10-mm segment. IMT was defined as the distance from the leading edge of the lumen–intima interface to the leading edge of the media–adventitia interface of the far wall (16) determined by semiautomated computer soft-
ware, by an average of 80 to 100 different samples of the examined segment.

Ultrasoundographic scanning was performed using carotid duplex equipment [128XP/10, Acuson, (Diasonics Ultrasound, Gateway 2D, VST, C20060, Santa Clara, CA, USA)] with a 7-MHz linear array transducer (axial resolution of at least 0.3 mm). The final IMT value represents an average of the IMT results from the left and right sides.

**Statistical Analysis**

Comparisons between the study and control groups regarding demographic (gender, age) and clinical factors (laboratory and imaging results) were performed using t-tests for independent samples, and χ² and Fisher’s exact tests, as applicable. A comparison of group means of all the imaging parameters, adjusted for gender, age, body mass index (BMI), hypertension, smoking, and lipids was performed using a one-way analysis of covariance (ANCOVA) with gender-matched with each patient. Paired t-tests and analysis of variance for independent samples in the study group. Pearson correlation coefficients were used to study the relationship between clinical parameters and the imaging results. The analysis was performed for each group separately and for the entire sample. Pearson partial correlation, controlled for age, was also computed for all parameters.

To perform a paired analysis, one control was age- and gender-matched with each patient. Paired t-tests and the Wilcoxon nonparametric tests were then used to evaluate the differences between the PsA patients and their paired controls with regard to the imaging results.

The duration of psoriatic symptoms (arthritis, skin) was divided into 2 categories: <1 year and ≥1 year. A multiple linear regression analysis was performed on the PsA patients to evaluate the effect of each of the studied parameters (demographics, background diseases, and psoriatic severity) simultaneously on the imaging result (average of IMT scores). The model construction was done in the 2 following ways: (a) the hierarchical regression comprised 3 steps. First, an initial score was computed based on demographic parameters (age, gender, BMI). Second, a score was computed based on the initial score and clinical background factors (diabetes mellitus, hypertension, hyperlipidemia, and CRP). The final score was based on the second model together with psoriatic symptoms and their severity as determined by the PASI, number of tender and swollen joints, duration of arthritis, and duration of (<1 year, ≥1 year) skin disease. (b) A linear regression model using forward and backward stepwise variable selection methods was implanted in the statistical software. Assessment of goodness-of-fit of the models was done using adjusted $R^2$, which computes $R^2$ adjusted for degrees-of-freedom for each model selected (17).

Normality of distribution was assessed using the Kolmogorov–Smirnov test. Since the mean IMT was not normally distributed, we used the reciprocal transformation of parameters to confirm the results.

Statistical significance was set at $P < 0.05$ and the SPSS for Windows software, Version 12.0, was used for the analysis.

**RESULTS**

Table 1 summarizes the demographic and anthropomorphic data of the entire study cohort. The gender distribution for the 2 groups was similar, but the PsA group was significantly older and had a higher mean body weight and BMI. Most of the patients had psoriasis and PsA for years and most had a polyarticular pattern of arthritis (Table 2). The laboratory findings are summarized in Table 3.

**Medications Used by the Patients**

Methotrexate (MTX) was by far the most frequently used medication (by 63% of the patients) at the time of the study. Fifteen patients (34%) were on Cox-1 inhibitors, 12 (25%) on Cox-2 inhibitors, 3 (6%) on corticosteroids, 4 (9%) on anti-tumor necrosis factor-alpha (TNF-α), 4 (9%) on salazopyrine, and 10 (21%) on statins.

**Intimal Medial Thickness**

The average IMT of the PsA patients was significantly higher compared with the controls (0.76 ± 0.11 mm versus 0.64 ± 0.27 mm, $P < 0.00001$). Since the control subjects were significantly younger and presented fewer
Cardiovascular Risk Factors

Traditional risk factors, such as diabetes mellitus, hypercholesterolemia, and hypertriglyceridemia, were found in a significantly higher proportion of patients with PsA (Table 5). When the subgroups of age-matched subjects were compared, however, no significant difference was found in traditional risk factors with the exception of BMI (26.6 ± 5 mm for the patients versus 24 ± 3.5 mm for the controls, P = 0.02).

Laboratory Markers of Disease Activity

As expected, the ESR, CRP, and fibrinogen levels were significantly increased in the PsA group. Forty-one patients had ESR and 42 had CRP levels above the normal range.

Correlation Between IMT and Clinical and Laboratory Parameters in Patients with PsA

A significant positive correlation was found between the average IMT and traditional cardiovascular risk factors, such as age (P < 0.001), BMI (P = 0.01), systolic blood pressure (P = 0.02), and levels of glucose (P = 0.04). We could also show a clear correlation between IMT and characteristics of PsA, such as duration of skin disease (P = 0.0013), spine involvement (P = 0.001), and increased fibrinogen (P = 0.04). No correlation was found between IMT and the use of nonsteroidal anti-inflammatory drugs, MTX, anti-TNF-α therapies, and salazopyrine (Table 6).

Multilinear Regression Analysis in PsA Patients

A multilinear regression analysis using a 2-model construction revealed similar results. There was a significant correlation between the average IMT and the following parameters: age (0.001), gender (0.057), diabetes mellitus (0.02), duration of arthritis (0.02), and severity and duration of skin disease (0.06). No correlation was found between IMT and hypertension, CRP, hyperlipidemia, PASI, or the number of tender and swollen joints.
more severe disease are seen at referral centers (7). Al-
disease severity and mortality, insofar as patients with
conflicting results suggest a possible relationship between
standardized mortality ratio of 1.6. These apparent
(21). On the other hand, inflammation may not be the
platelets appear to contribute to higher cardiovascular risk
inflammation (21). The size, function, and number of
patients with PsA have high numbers of platelets, as a reflection of
inflammation to atherogenicity in this cohort. Patients
in our cohort. This finding questions the contribution of
possibly due to the relatively low levels of CRP observed
relation between IMT and the CRP level in our patients,
fecting arterial elasticity (20). We could not show a cor-
associated with cardiovascular disease (19), probably af-
Chronic inflammatory conditions are increasingly linked
to accelerated atherosclerosis (1–5), but their association
with PsA has not been investigated. Our findings in the
present study demonstrated greater thickness of the com-
mon carotid artery in PsA patients than in healthy con-
trols. This increased IMT correlated with several tested
parameters, such as the duration of skin and joint disease,
spine involvement and levels of fibrinogen, as well as with
conventional risk factors of atherosclerosis, such as age,
BMI, blood pressure, and serum levels of glucose.

Data on mortality in PsA patients are limited. Shbeeb
and coworkers (18) showed that the survival of patients
with PsA was not significantly different from that ob-
served in the general population, while Wong and co-
workers (7) reported an increased death rate with a stan-
Table 5 Multivariate regression analysis for IMT in patients with PsA

<table>
<thead>
<tr>
<th>Parameters</th>
<th>B</th>
<th>95% CI for B</th>
<th>P-value</th>
<th>R² Change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>0.005</td>
<td>0.002 to 0.007</td>
<td>&lt;0.0001</td>
<td>0.400</td>
</tr>
<tr>
<td>Gender (F vs. M)</td>
<td>-0.056</td>
<td>-0.113 to 0.002</td>
<td>0.057</td>
<td>0.065</td>
</tr>
<tr>
<td>BMI</td>
<td>0.004</td>
<td>-0.001 to 0.010</td>
<td>0.101</td>
<td>0.065</td>
</tr>
<tr>
<td>DM (Yes vs. No)</td>
<td>0.115</td>
<td>0.02 to 0.21</td>
<td>0.020</td>
<td>0.038</td>
</tr>
<tr>
<td>Arth Dur (≥12 vs. &lt;12)</td>
<td>-0.077</td>
<td>-0.146 to -0.008</td>
<td>0.029</td>
<td>0.025</td>
</tr>
<tr>
<td>Skin Dur (≥12 vs. &lt;12)</td>
<td>0.062</td>
<td>-0.004 to 0.128</td>
<td>0.065</td>
<td>0.052</td>
</tr>
<tr>
<td>Smoker (Heavy vs. Low)</td>
<td>0.039</td>
<td>-0.028 to 0.105</td>
<td>0.243</td>
<td>0.018</td>
</tr>
<tr>
<td>HTN (Yes vs. No)</td>
<td>0.022</td>
<td>-0.045 to 0.090</td>
<td>0.501</td>
<td>0.004</td>
</tr>
<tr>
<td>CRP</td>
<td>0.001</td>
<td>-0.002 to 0.003</td>
<td>0.674</td>
<td>0.002</td>
</tr>
<tr>
<td>Hyperlipidemia (Yes vs. No)</td>
<td>0.010</td>
<td>-0.051 to 0.071</td>
<td>0.744</td>
<td>0.001</td>
</tr>
<tr>
<td>PASI</td>
<td>0.001</td>
<td>-0.005 to 0.006</td>
<td>0.760</td>
<td>0.001</td>
</tr>
<tr>
<td>Total R²</td>
<td></td>
<td></td>
<td>0.671</td>
<td></td>
</tr>
<tr>
<td>Adj.R²</td>
<td></td>
<td></td>
<td>0.551</td>
<td></td>
</tr>
</tbody>
</table>

BMI = body mass index; DM = diabetes mellitus; Arth Dur = arthritis duration; Skin Dur = duration of skin disease; HTN = hypertension;
CRP = C-reactive protein; PASI = Psoriasis Area and Severity Index.

DISCUSSION

Although all laboratory measures of inflammation were
significantly elevated in our PsA group, only the fibrin-
ogen level seemed to correlate with IMT. Several studies
have shown the importance of fibrinogen as a major car-
diovascular risk factor (22) and its increase as a manifes-
tation of acute phase response in patients with PsA (23).
Besides the contribution of the inflammatory process in
the evolution of atherosclerosis, our patients had signifi-
cant traditional risk factors for atherosclerosis. Increased
incidences of diabetes mellitus and obesity have been re-
ported in psoriatic patients (24). Other possible risk fac-
tors in PsA and psoriasis patients are an atherogenic lipid
profile (25–31) consisting mainly of increased LDL sub-
fractions and decreased HDL levels (25,29). A few reports
describe increased lipoprotein A (25,29) in psoriasis and
PsA patients. The lipid profile in PsA may vary with the
inflammatory activity, decreasing the LDL when the dis-
Table 6 Relationship between the use of medications and mean IMT in PsA patients

<table>
<thead>
<tr>
<th>Drugs</th>
<th>Mean IMT ± SD</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAIDs user</td>
<td>0.80 ± 0.10</td>
<td>0.17</td>
</tr>
<tr>
<td>Non-NSAIDs user</td>
<td>0.75 ± 0.10</td>
<td></td>
</tr>
<tr>
<td>Steroids users</td>
<td>0.73 ± 0.09</td>
<td>0.16</td>
</tr>
<tr>
<td>Non-steroid users</td>
<td>0.76 ± 0.11</td>
<td>0.23</td>
</tr>
<tr>
<td>TNFα blocker users</td>
<td>0.70 ± 0.08</td>
<td>0.23</td>
</tr>
<tr>
<td>Non-TNFα blocker users</td>
<td>0.76 ± 0.11</td>
<td>0.23</td>
</tr>
<tr>
<td>MTX users</td>
<td>0.78 ± 0.10</td>
<td>0.14</td>
</tr>
<tr>
<td>Non-MTX users</td>
<td>0.73 ± 0.01</td>
<td></td>
</tr>
<tr>
<td>SSZ users</td>
<td>0.76 ± 0.10</td>
<td>0.95</td>
</tr>
<tr>
<td>Non-SSZ users</td>
<td>0.76 ± 0.11</td>
<td></td>
</tr>
</tbody>
</table>

NSAIDs = Nonsteroidal anti inflammatory drugs; TNF = tumor necrosis factor; MTX = methotrexate; SSZ = salazopyrine.
ease flares. Thus, it is not clear to what extent the increased cardiovascular mortality in PsA is related to traditional risk factors and to what degree inflammation plays a role as an atherogenic factor.

We found an association between spinal involvement and an increased IMT. Mortality in patients with ankylosing spondylitis is higher than expected (32), with 40% excess of death attributed to circulatory diseases, such as aortic insufficiency, conduction disease disturbances, mitral valve disease (which are not present in PsA), and ischemic heart disease (32). An important question to consider is whether the treatment of PsA affects the risk of atherosclerosis. MTX was the most widely used medication in our patient group (63%, Table 4). Our findings, however, indicated no correlation between MTX treatment and IMT, although we cannot exclude that the small number of patients might have influenced the results. Although prior use of medications in PsA has been associated with increased mortality (7), there are no studies that directly examined the influence of specific medications on atherosclerosis in PsA. Moreover, the results of studies on RA vary: some authors have demonstrated decreased cardiovascular mortality with the use of MTX (33), while others found no correlation between MTX and IMT (20). Interestingly, preliminary studies suggest a protective cardiovascular effect of anti-TNF-α therapies in RA patients (34).

PsA has been considered a benign disease, but recent data have challenged that concept, calling for earlier and more aggressive treatment (6,8). The present findings lend support to the notion that PsA may be associated with an increased cardiovascular risk similar to RA. Further research is needed to clarify the exact correlations between PsA and cardiovascular risk, particularly for the different clinical subclasses of the disease. We are aware that the relatively small number of patients poses a limitation to our current study. The difference in age between the study and control groups, however, was dealt with by statistical analysis.

In conclusion, our cohort of PsA patients exhibited greater IMT of the common carotid artery compared with healthy control subjects, suggesting that, like other inflammatory conditions, PsA is associated with accelerated atherosclerosis. Our data suggest a need for aggressive treatment of the inflammatory process in PsA patients as well as better monitoring of traditional atherosclerotic risk factors to reduce cardiovascular mortality and morbidity.

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REFERENCES