Coronary Flow Reserve and Asymmetric Dimethylarginine Levels: New Measurements for Identifying Subclinical Atherosclerosis in Patients with Psoriatic Arthritis

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ABSTRACT. ***Objective.*** To identify the presence of subclinical atherosclerosis in patients with psoriatic arthritis (PsA) and healthy controls using intima-media thickness (IMT), coronary flow reserve (CFR), and the plasma concentration of asymmetric dimethylarginine (ADMA), to evaluate the correlations among ADMA, IMT, and CFR.

Methods. The study involved 22 patients who fulfilled the ClASsification of Psoriatic ARthritis study group criteria for PsA and a cohort of 35 healthy controls with no history or current signs of coronary artery disease (CAD). Common carotid IMT was measured using high-resolution B-mode ultrasonography. Dipyridamole transthoracic stress echocardiography was used to evaluate CFR. Blood samples were obtained to assess ADMA levels. The clinical manifestations were recorded. All patients were treated with disease-modifying antirheumatic drug, but none had received any biological or steroid therapy.

Results. Plasma ADMA levels were significantly higher in the patients with PsA (0.71 ± 0.07 μmol/l vs 0.48 ± 0.07 μmol/l; p = 0.00) and CFR was significantly reduced in that group (2.86 ± 0.70 vs 3.3 ± 0.43; p < 0.01) compared to controls. Common carotid IMT was greater in the patients with PsA, but the difference was not significant (0.64 ± 0.26 mm vs 0.62 ± 0.5 mm; p = 0.65). There was a significant correlation between CFR and plasma ADMA levels in the PsA group (R = 0.28; p < 0.01), but no correlation between plasma ADMA levels and IMT (R = 0.02; p = 0.32), Disease Activity Score 28 (p = 0.52), or Psoriasis Area and Severity Index (p = 0.98).

Conclusion. Our patients with PsA showed a profile of subclinical atherosclerosis. ADMA may be a useful marker of endothelial dysfunction in PsA. (First Release June 1 2011; J Rheumatol 2011;38: 1661–4; doi:10.3899/jrheum.100893)

Key Indexing Terms:
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Both psoriatic arthritis (PsA) and psoriasis are associated with an increased cardiovascular (CV) mortality and morbidity[1,2,3], probably correlated to disease activity. Traditional CV risk factors are more common in patients with PsA than in controls[4]. Kimhi, *et al*[5] found greater intima-media thickness (IMT) of the common carotid artery wall in patients with PsA than in controls, a finding that was correlated with both disease features and conventional risk factors for atherosclerosis. Gonzalez-Juanatey, *et al*[6,7] found that patients with PsA without conventional CV risk factors or clinically evident CV disease had endothelial dysfunction and a higher prevalence of increased carotid artery IMT than matched controls.

Plasma asymmetric dimethylarginine (ADMA), a major endogenous inhibitor of nitric oxide synthase, is a risk factor for the endothelial dysfunction associated with enhanced atherosclerosis[8]. It predicts CV risk, and increased levels have been found in patients with diseases associated with atherosclerosis[9]. We have found that plasma ADMA levels are significantly increased in patients with early rheumatoid arthritis

(ERA)[10]. ADMA levels also impair coronary flow reserve (CFR), a diagnostic marker for coronary artery disease (CAD) in patients with ERA who have not been diagnosed with CAD[10]. In addition, we have shown that CFR is reduced in patients with longstanding RA who have no clinical evidence of heart disease[11].

Our aim was to assess the presence of subclinical atherosclerosis in patients with PsA on the basis of IMT, CFR, and ADMA levels. The secondary endpoint was to evaluate the correlation between ADMA levels and CFR.

MATERIALS AND METHODS

Patients. The study involved 22 unselected consecutive outpatients satisfying the ClASsification of Psoriatic ARthritis study group criteria for PsA[12], with no clinical history or signs of CAD or other cardiac diseases. They were all receiving nonsteroidal antiinflammatory drugs (NSAID) and disease-modifying antirheumatic drugs but none had received any biological agent, steroid therapy, or selective cyclooxygenase-2 inhibitors.

Sixty consecutive individuals undergoing a routine examination at the outpatient department of a cardiology unit volunteered to participate as controls. They underwent a complete clinical and physical examination, an assessment for risk factors for atherosclerosis, and routine CV studies. Thirty-five subjects with no past or current signs of CAD and no significant traditional risk factors were recruited.

Pain, fatigue, patients' global health assessment score using a 100 mm visual analog scale, and duration of morning stiffness were collected. The physical examination included tender and swollen joint counts, the presence of dactylitis, and the number of permanently deformed joints. All subjects underwent radiography of hands and wrists. Peripheral joint involvement was assessed using the 28-joint Disease Activity Score (DAS28), axial involvement by means of the Bath Ankylosing Spondylitis Disease Activity Index, and psoriasis by means of the Psoriasis Area and Severity Index (PASI).

Laboratory analyses. The laboratory markers of disease activity included erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) and complete blood counts. Serum total cholesterol, triglyceride, and high-density lipoprotein (HDL) cholesterol levels were determined using an autoanalyzer. Low-density lipoprotein (LDL) cholesterol was calculated by means of the Friedewald formula. Other standard clinical laboratory tests were performed under fasting conditions on the same day. The mean glomerular filtration rate was calculated using the Cockcroft-Gault formula. Plasma ADMA concentrations were determined using the high pressure liquid chromatography method described by Teerlink, with modifications.

CV assessment. All the patients underwent CV risk profiling that included arterial blood pressure, standard echocardiogram, conventional and stress transthoracic echocardographic examinations with CFR measurement, and carotid ultrasound evaluation. The transthoracic Doppler-derived CFR and common carotid IMT data were collected and analyzed by 2 independent echocardiographers not involved in patient care.

Transthoracic echocardiography was performed using a commercial ultrasound unit (Sonos 5500, Philips Medical Systems, Andover, MA, USA) equipped with 1.3–2.6 MHz (S3) transducer capability and a 3.5–7 MHz broadband high-frequency transthoracic transducer (S8) with second harmonics. Left ventricular diameters and wall thicknesses were measured using the 2-D targeted M-mode echocardiographic trace as recommended by the American Society of Echocardiography.

Carotid artery ultrasound was performed using a Sonos 5500 with a 7–11 MHz linear array transducer. The carotid arteries were scanned in the transverse and longitudinal planes with the patient lying supine, neck extended, and chin turned contralaterally to the examined side. Common carotid artery IMT was measured 1 cm distally to the carotid bifurcation in the posterior wall, over the right and left carotid arteries. IMT was defined as the distance between the leading edges of the lumen interfaces and the media-adventitia interface of the far wall. The results of 3 measurements were averaged.

Statistical analysis. Quantitative variables were expressed as mean values and SD, and Student t-test was used to test statistically significant differences between the grouped means. The associations between the quantitative variables were studied by means of correlation analysis, and those between the qualitative variables by means of contingency tables. Statistical significance was tested using the chi-squared or Fisher's exact test in the case of 2×2 tables. A 2-tailed p value < 0.05 was considered statistically significant.

RESULTS

Table 1 shows the characteristics of the patients with PsA and healthy controls. Most of the patients had peripheral polyarthritis, and 6 (27.2%) had predominant axial involvement. All patients were being treated with nonselective NSAID and the majority were taking methotrexate (MTX) at a mean dose of 12.5 mg/week (range 10–1).

The patients with PsA had significantly higher CRP and ESR values than the healthy controls ($p < 0.01$ for both), but there were no significant differences in heart rate or blood pressure at rest or during dipyridamole infusion. Patients with PsA had plasma ADMA levels significantly higher (0.71 ± 0.07 μmol/l vs 0.48 ± 0.07 μmol/l; $p = 0.00$; Figure 1) and CFR significantly lower (2.86 ± 0.70 vs 3.3 ± 0.43; $p < 0.01$) than controls. A CFR value < 2 was observed in 10/22 patients with PsA, while it was observed in 4/35 healthy controls.

Table 1. Baseline characteristics of the study population compared to controls. Mean values ± SD are indicated unless otherwise specified.

Characteristics	Controls, n = 35	Patients with PsA, n = 22
Women, n (%)	16 (45.7)	10 (45.4)
Age, yrs	55.36 ± 12.97	54.9 ± 12.97
Body mass index, kg/m^2	26.1 ± 3.03	27.6 ± 4.56
Nonsmokers, %	100	98
Systolic blood pressure, mm Hg	128.8 ± 8.93	133.6 ± 6.93
Diastolic blood pressure, mm Hg	82.8 ± 4.8	84.7 ± 4.6
Disease duration, yrs	—	5.73 ± 4.07
DAS28 (score)	—	5.97 ± 0.70
Tender joint count		9.86 ± 2.85
Swollen joint count		7.82 ± 2.44
PASI	—	17.9 ± 12.4
Total cholesterol, mg/dl	176.3 ± 10.6	197.14 ± 24.2
LDL cholesterol, mg/dl	—	109.91 ± 11.0
HDL cholesterol, mg/dl	—	44.6 ± 8.7
Triglycerides, mg/dl	153.7 ± 38.5	175.5 ± 42.29
Glycemia, mg/dl	87.6 ± 5.6	100.2 ± 29.35
Homocysteinemia, μmol/l	10 ± 4.0	11 ± 6.0
Uricemia	4.42 ± 1.07	5.02 ± 0.9
C-reactive protein	0.189 ± 0.08	15.9 ± 17.2*
Erythrocyte sedimentation rate, mm/h	4.9 ± 2.4	36.5 ± 19.3*
Intima-media thickness, mm	0.62 ± 0.52	0.64 ± 0.26
Coronary flow reserve	3.3 ± 0.43	2.86 ± 0.70*
ADMA, μmol/l	0.48 ± 0.07	0.71 ± 0.07*

* $p < 0.01$. PsA: psoriatic arthritis; DAS28: Disease Activity Score 28 joints; PASI: Psoriasis Area and Severity Index; LDL: low-density lipoprotein; HDL: high-density lipoprotein; ADMA: asymmetric dimethylarginine.

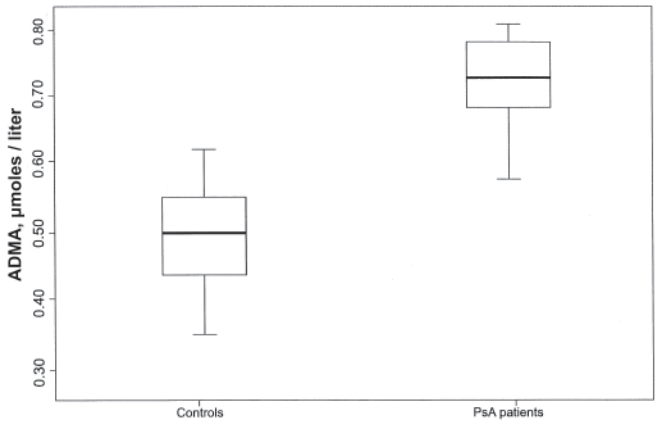

Figure 1. Value of asymmetric dimethylarginine (ADMA) in patients compared to controls. PsA: psoriatic arthritis.

Common carotid IMT was increased in the patients with PsA, but the between-group difference was not significant (0.64 ± 0.26 mm vs 0.62 ± 0.5 mm; p = 0.65). Standard 2-D echocardiography at baseline showed that the patients with PsA had normal left ventricular wall thickness, size, mass, and systolic function.

There was a significant correlation between plasma ADMA levels and CFR in the PsA group (r = 0.28; p < 0.01; Figure 2), but no correlation between plasma ADMA levels and IMT (R = 0.02; p = 0.32), DAS28 (p = 0.52), or PASI (p = 0.98).

DISCUSSION

PsA and psoriasis, like RA, are associated with a higher rate of CV mortality[1,2,3] and a number of studies have shown that patients with PsA have a high prevalence of subclinical atherosclerosis, regardless of traditional risk factors[4,5].

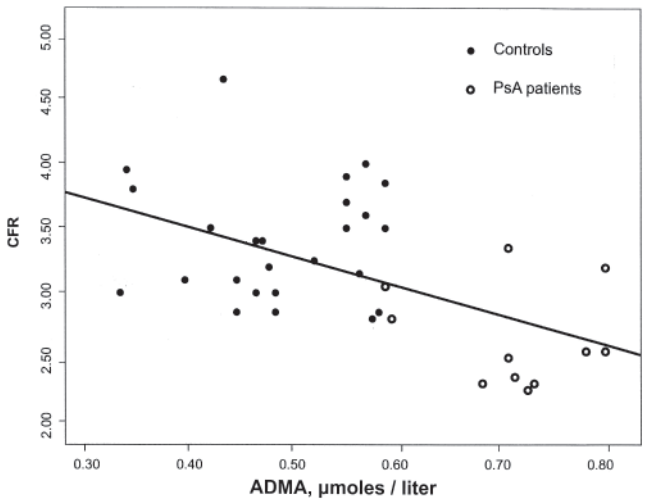

Figure 2. Correlation between plasma asymmetric dimethylarginine (ADMA) levels and coronary flow reserve (CFR) in patients with psoriatic arthritis (PsA). $R^2 = 0.284$.

Our patients with PsA who did not have any signs and risk factors of CV disease had significantly higher plasma ADMA levels than the healthy controls. This finding may be indicative of progressive subclinical atherosclerosis, exactly as in patients with ERA[10]. ADMA has recently been recognized as a major endogenous inhibitor of all 3 isoforms of nitric oxidate (NO) synthase, and it is known that high plasma ADMA levels can impair NO generation and promote the progression of atherosclerosis[13]. The subclinical CV involvement in these patients with PsA seemed to be unrelated to the conditions usually associated with high plasma ADMA levels, which were exclusion criteria in our study.

Psoriatic patients and patients with PsA have a higher incidence of diabetes mellitus and obesity, and an atherogenic lipid profile[4]. As there was no significant difference in the presence of any of these risk factors for atherosclerosis between our patients with PsA and the controls, ADMA could be an independent indicator of subclinical atherosclerosis in PsA. However, although the median blood glucose, cholesterol, and blood pressure levels of the study group were in the normal range, they were higher than the levels of the control group and this could have affected the results.

Further, all the patients were treated concomitantly with NSAID, which have a known increased CV risk, and this could have had an effect on the ADMA levels.

We also found that CFR was significantly reduced in the patients with PsA. CFR is a highly sensitive (> 90%) diagnostic marker of CAD and a CFR < 2 accurately predicts the presence of severe coronary stenosis (i.e., > 70% coronary narrowing). Transthoracic Doppler-derived CFR has been used to identify patients with known or suspected CAD, and its prognostic value has also been confirmed in various cardiovascular settings[11].

The significant correlation between the reduced CFR and increased ADMA levels in our patients with PsA may be indicative of endothelial dysfunction and impaired coronary microcirculation. Patients with PsA seem to have higher common carotid artery IMT values than healthy controls. We also found this, but the difference was not statistically significant. This may have been because of the relatively small number of patients, but it could also indicate that CFR, a functional measurement, is a more sensitive marker of subclinical atherosclerosis than IMT[14,15].

Most of the patients were taking MTX. The possible effect of this therapy, if any, on the results of our study could have been in the direction of a lesser endothelial dysfunction because of the antiinflammatory effect of MTX and the resulting improvement in physical function and mobility. In RA it has been shown that an increase in exercise levels can reduce the risk of CV disease[16].

Our patients had a high mean DAS28 score, which indicates active disease. As there was no correlation between DAS28 and ADMA, disease activity was not directly responsible for the increased ADMA values. Our study confirms that

active PsA is a risk factor for CV disease. Patients with PsA should be screened for subclinical forms of the disease and its risk factors, and treated accordingly. In these patients, ADMA levels and CFR seem to be useful markers of endothelial dysfunction and early subclinical atherosclerosis. Further studies are required to define more precise algorithms for the assessment and management of CV disease in patients with PsA.

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