Hypertension and diabetes significantly enhance the risk of cardiovascular disease in patients with psoriatic arthritis

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Abstract

Objective

New evidence has lightened the linkage between psoriatic arthritis (PsA) and the development of atherosclerosis and cardiovascular disease (CVD). We aimed to describe the prevalence of cardiovascular events and associated risk factors among patients with PsA.

Methods

Retrospective evaluation of medical records from consecutive PsA patients who fulfilled the CASPAR criteria for PsA attending a specialised spondyloarthritis clinic at a single referral centre. CVD was defined based on the occurrence of coronary artery disease (CAD) or cerebrovascular ischaemic disease events.

Results

We evaluated 158 PsA patients, 48.7% females and 51.3% males, aged 53.7±13.9 yrs. Mean PsA duration was 13.7±8.9 yrs and polyarticular subtype affected 66 (42%) patients. According to drug therapy, 85 (54%) were using NSAIDs and 21 (13%) low-dose prednisone; 32 (20%) were on anti-TNF agents, 94 (60%) metothrexate, 18 (11%) leflunomide, 13 (8%) sulfasalazine, 5 (3%) other immunossupressors and 4 (2.5%) were on chloroquine. Over half patients (87, 55%) had arterial hypertension (AH); 51 (32%) had dyslipidaemia (DLP), 38 (29%) hypertriglyceridaemia and 36 (23%) diabetes mellitus (DM). Lipid profile was similar for both genders with mean total cholesterol= 186.5±38.6mg/dl, LDL=112.3±30.6 mg/dl, HDL= 47.89±14.6 and triglycerides= 127.4± 65.6 mg/dl. Of note, 14% PsA patients have had CVD, namely cerebrovascular or coronary heart disease. Sex, age, disease duration, joint involvement subtype, disease activity, CRP and lipid levels were similar among patients with and without CVD. The prevalence of AH (95% vs. 45%, p<0.001), DLP (75% vs. 27.7%, p<0.001) and DM (60% vs. 19%, p<0.001) were significantly greater in PsA patients who have had CVD compared to those without CVD, conferring an odds ratio of 21.0 for AH and of 5.4 for DM.

Conclusion

The high prevalence of CVD in PsA patients is influenced by increased AH and DM. Hence early recognition and specific treatment is mandatory in order to reduce the risk for CVD, avoiding early morbidity and mortality.

Key words

psoriatic arthritis, cardiovascular disease, arterial hypertension, diabetes, risk factor

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Introduction

Psoriatic arthritis (PsA) is an inflammatory musculoskeletal condition associated with skin psoriasis (PsO) and a diversity of clinical manifestations. Articular involvement can be aggressive and destructive, varying from axial and/or peripheral disease which can be monoarticular, oligoarticular, or polyarticular. Nearly half patients display evidence of enthesitis, dactylitis, and/or spondylitis. Cutaneous PsO affects 2% to 4% Caucasians worldwide (1), while the prevalence of PsA in the general population is estimated to be between 0.02% to 0.25% (2) and, according to different studies, 4% to 48% patients with PsO may develop arthritis (2, 3). Actually, lack of a standard case definition, simple laboratory biomarkers, and overlook of diagnosis by dermatologists and general practitioners may contribute to the heterogeneity and paucity of available data to date, resulting in such a wide prevalence range of PsA among patients with skin PsO (2).

Despite not being recognised as a systemic illness until recently, the concept of psoriatic disease is evolving rapidly. Skin PsO is now understood as an inflammatory disorder potentially involving multiple organ domains, associated to release and over-expression of a variety of pro-inflammatory cytokines, such as TNF-α (tumour necrosis factor) and activation of various autorreactive cells including dendritic cells, T lymphocytes and macrophages (4). These alterations are hallmarks of disease activity both in the affected joint and skin. Likewise, the wide clinical spectrum of the psoriatic disease may be a consequence of its complex etiopathogenesis, which involves immune dysregulation triggered by the interaction of genetic and environmental factors.

In cutaneous PsO, comorbidities such as diabetes (5, 6), hypertension (7, 8), dyslipidaemia (9, 10) and obesity have been demonstrated and smoking may also be increased (11); mortality is augmented (12), primarily related to cardiovascular and respiratory disease (13). In a case control study, Mehta *et al.* (14) found that psoriatic patients presented greater frequency of hypertension, hyperlipidaemia, smoking, diabetes (15-19) and higher cardiovascular disease (CVD) mortality. After adjustment for risk factors (age, sex, hyperlipidaemia, hypertension, smoking and diabetes), severe PsO was determined to be an independent risk factor for death due to CVD. Furthermore, CVD in individuals with PsO occurs in early age groups, suggesting acceleration of the development of atherosclerosis in this population (14).

In PsA patients, recent studies have also suggested an increased risk for CVD (20), but results yield conflicting findings. A higher than expected prevalence of metabolic syndrome (21), increased arterial stiffness (22), endothelial dysfunction and acceleration of the atherosclerotic process (23, 24) have been described. However, a definite image of risk and clear guidelines for screening and management of CVD among PsA patients have not been established. Therefore, we sought to investigate the prevalence of CVD and some of its related risk factors in a cohort of PsA patients from a single centre. Correlation with particular PsA clinical characteristics was further considered, in order to delineate a CV risk profile for these patients.

Patients and methods

A transversal retrospective study design was conducted in order to evaluate the prevalence of CVD in a cohort of PsA patients from a single rheumatology centre followed at our university hospital, University of Sao Paulo Medical School, Brazil. CVD was defined based on the occurrence of coronary artery disease (CAD) or cerebrovascular ischaemic disease events (25). The presence of traditional CV risk factors such as diabetes mellitus (DM) dyslipidaemia (DLP) and systemic arterial hypertension (AH) were searched. Smoking, obesity and familiar history of CVD were not analysed due to the fact that these parameters were not regularly recorded on every visit for most patients.

Data from all consecutive patients with PsA according to the CASPAR (26) criteria and regularly followed at our spondyloarthritis clinic were reviewed and last visit clinical registries and

laboratoty tests were gathered. All information including comorbidities was obtained from electronic charts registries containing clinical and laboratory records investigated according to standard care. Clinical disease activity was considered based on BASDAI (27) for patients with axial disease and on DAS28 (28) for peripheral articular involvement. In agreement to the ethical committee from our institution, there was no need for specific ethical approval, since this was an observational study and all data was collected from charts with no specific intervention.

Fasting 12-hour lipid profile, glucose, C-reactive protein (CRP) levels and erythrocyte sedimentation rate (ESR) were determined by routine laboratory methods performed at the central hospital laboratory. Total cholesterol, HDL-cholesterol and LDL-cholesterol were directly measured by colorimetric automated technique and glucose was quantified by enzymatic colorimetric automated methods. CRP was analysed by immunoassay (normal <5mg/L) and ESR by the Westergren ESR automated test (normal <20mm for women and 10mm for men).

Systemic AH was determined in accordance to the criteria established by the JNC VII - The seventh report of the Joint National Committee on Prevention, detection, evaluation and treatment of high blood pressure (29). Characterisation of CAD and cerebrovascular disease were considered as events registered in the charts. DLP was recognised by elevated lipid levels based on national guidelines (30) or by regular use of statins. Hypertriglyceridaemia was defined as a measure over 150mg/dl and low HDL-cholesterol as a value under 50mg/dl for women and 40mg/dl for men. DM was established according to the guidelines of the American Diabetes Association (31).

For statistical comparisons, univariate analysis was performed using the software GraphPad Prism4, adopting level of significance of $p \leq 0.01$.

Results

PsA patients' characteristics

We evaluated 158 consecutive PsA patients, 81 males and 77 females (51.3% *vs*. 48.7%). Their mean age was 53.7±13.9 years, ranging from 22 to 86 years, similar for women (52.6±14.9 years) and men (54.7±12.8 years) (p=0.34). Cutaneous involvement preceded joint manifestations in 52.5% of patients; in 38.6%, skin and joint disease simultaneously emerged and in 8.9%, joint symptoms occurred before skin PsO. Mean length of cutaneous PsO was 18.7±11.1 years (0 to 54 years) and mean articular disease duration was 13.7±8.9 years (1 to 52 years). At the time of articular disease diagnosis, mean age was 39.95±13.59 years (36 to 61 years). Joint involvement manifested as pure axial, peripheral oligoarthritis and peripheral polyarthritis in 12%, 20% and 43% of patients respectively. The combination of axial disease with oligoarthritis was present in 7% and axial disease was associated to polyarthrirtis in 18% of patients. Assessment of PsA clinical activity for peripheral joint involvement revealed mean DAS28 of 3.0±1.6 and for axial disease, mean BASDAI of 2.83±2.29, reflecting low disease activity indexes, though mean CRP level was 9.13±16.25mg/dL (0.1–142.7mg/dl) and mean ESR was 14.34±15.71mm (1-84mm). According to current treatment prescribed in order to achieve disease control, 85 patients (54%) were on non-steroidal anti-inflamatory drugs (NSAIDs) (11 monotherapy, 7.9%), 21 patients (13%) were on glicocorticosteroids (4 monotherapy, 1.98%) and disease-modifying anti-rheumatic drugs (DMARDs) were taken as follows: methotrexate, leflunomide, sulfasalazine and chloroquine by 94 (60%), 18 (11%), 13 (8%) and 4 (2.5%) respectively, while other immunosuppressive agents were needed in further 5 patients (3%). Combination of two DMARDs was prescribed for 13 subjects (8.6%) and 32 (20%) were under the action of anti-TNF biologic agents, either combined with a DMARD in 18 patients (11.9%) or as monotherapy in 14 (9.3%).

Table I. Comparison between PsA patients with and without CVD.

Characteristic	With CVD n=22	Without CVD n=133	*p*-value
Gender (M:F) (n)	14:6	65:68	NS
Age (yrs, mean ± SD)	64.73± 12.45	51.9 ± 13.49	0.0001
PsA duration (yrs, mean ± SD)	14.62± 7.45	13.25 ± 8.98	NS
DM (n)	15	24	<0.0001
DLP (n)	15	36	<0.0001
AH (n)	21	66	<0.0001
Total cholesterol (mg/dl, mean ± SD)	168.85± 23.53	188.88 ± 39.16	0.01
CPR (mg/dl, mean ± SD)	12.4± 18.94	8.74 ± 15.96	NS

PsA patients' profile for CVD risk

Serum lipid profile revealed mean total cholesterol levels = 186.5±38.6mg/dL (range 102–316mg/dl); HDL-cholesterol = 47.9±14.6mg/dL (range 21-116mg/dl); LDL-cholesterol = 112.3±30.6mg/dL (range 45–188mg/dl) and triglycerides = 127.4±65.6mg/dL (range 17–1366mg/dl). Hypertriglyceridaemia was demonstrated in 38 patients (29%) and low HDL-cholesterol in 57 (36%): 33 women (42%) and 24 men (35%). A total of 96 of 158 PsA patients (60.7%) had at least one of the associated comorbidities focused: 87 AH (55%), 51 DLP (32%) and 36 DM (23%). CVD was documented in 14% PsA patients (22/158); 20 of them had AH (95.5%) and 12 had DM (54.5%). The occurrence of CVD (Table I) was significantly associated with the presence of AH (95% *vs*. 45%, p<0.001), DLP (75% *vs*. 27,7%, p<0.001) and DM (60% *vs*. 19%, p<0.001). Patients with CVD were older (64.73±12.45 yrs *vs*. 51.9±13.49 yrs, p=0.0001), whilst the comparison of PsA patients with and without CV events for all other parameters revealed similar gender (14 men and 6 women *vs*. 65 men and 68 women, p=0.095), PsA mean disease duration (14.62±7.45yrs *vs*. 13.25±8.98, p=0.58), PsA clinical subset distribution (0 *vs*. 19 patients, p=0.13 for axial disease and 3 oligoarticular + 12 polyarticular *vs*. 40 oligo + 73 polyarticular, p=0.7 for peripheral

Table II. Therapeutic options.

Medication	With CVD n=22	Without CVD n=133	*p*-value
Glicocorticosteroids	3	21	NS
NSAIDs	8	74	NS
Anti-TNF drugs	4	28	NS
Sulphassalazine	3	9	NS
Methotrexate	7	92	0.0005
Leflunomide	4	14	NS

disease), mean CRP levels (12.4mg/dl ± 18.9 *vs*. 8.74±15.9, p=0.42) and ESR (p=1.0) in the univariate analysis. BASDAI (4.29±2.92 *vs*. 2.63±2.15, p=0.04, not significant for the cut-off of 0.01 adopted) and DAS 28 (3.5±2.3 *vs*. 2.91±1.46, p=0.37) were also similar between the two groups. The distribution of different pharmacological options is shown in Table II. Of note, the odds ratio (OR) conferred by AH on the risk of CVD was 21 (95% CI 2.74–160.86) and by DM was 5.4 (95% CI 2.09–13.94).

Discussion

We demonstrate an elevated prevalence of CVD in a cohort of PsA patients from a single centre and a high prevalence of AH and DM associated to significantly enhanced CV risk conferred by these classical risk factors in PsA.

These increased prevalence of 55%, 23% and 14% documented herein for AH, DM and CVD respectively are higher than those previously demonstrated. In the study of Han *et al*. (32) the prevalence of HA, DM and ischaemic heart disease and cerebrovascular disease were 28.5%, 11.3%, 7.3% and 3.1% respectively among 3066 patients while in a prospective study conducted by Gladman *et al*. (33), a prevalence of 35% of at least one cardiovascular condition, represented by AH, cerebrovascular accident, CAD, or congestive heart failure was reported. Additional concurrent studies have correlated PsA to enhanced risk of AH but neither for DM nor CVD, suggesting that the entire panel is still obscure (34, 35).

In our Brazilian population, the prevalences of AH, DLP and DM of the same bracket of age are 26%, 32% and 7.6% respectively (data from the Ministry of Health available at www.datasus.gov.br). Thereby, although the occurrence of DLP found in our PsA patients was close to the expected, the prevalences of AH and DM were much higher. In addition, the risk of CV events correlated with AH and DM in our PsA patients (OR of 21 and 5.4, respectively) is much higher than the ones described in the worldwide literature. In fact, data from the Framingham study (36) suggest that AH alone doubles the risk of CV events, and in the Mediterranean cohort of the ATTICA study (37), odds ratios conferred by AH and by DM were both 4.53, inferior for DM and considerably lower for AH compared to our findings herein in this study.

When comparing our results with those related to cutaneous psoriasis, we found similar evidence. Data from the UK General Practice Research Database (16) suggests that patients with PsO requiring systemic treatment are at increased risk of myocardial infarction and reduced life expectancy. Patients with more severe PsO are at greater risk and the relative risk for myocardial infarction was higher in the population of younger patients (16). In an observational study, the presence of PsO conferred increased risks for ischaemic heart disease (OR 1.78, 95% CI 1.52–2.11), cerebrovascular disease (OR 1.7, 95% CI 1.33–2.17), peripheral arterial disease (OR 1.98, 95% CI 1.38–2.82) and increased mortality from CVD (19.6% *vs*. 9.9%, p<0.01) (15).

The amount of evidence establishing an association of CVD and PsA is lower, but there seems to be indeed an increased frequency of CV risk factors such as hypertension, insulin resistance, diabetes and dyslipidaemia (31, 38-41). Tam (42) evaluated 102 patients with PsA and found a higher prevalence of hypertension (OR 3.37, 95% CI 1.68–6.72), diabetes (OR 9.27, 95% CI 2.09–41.09) and low HDL (OR 0.16, 95% CI 0.07–41). It is also important to point out that the expressive 14% prevalence of cardiovascular disease documented in our PsA population may be even underestimated due to the fact that subclinical atherosclerotic disease may be even present. Our patients with CVD were older but additional factors may also contribute to this increased CV risk framework in PsA including specific clinical and laboratory manifestations related to the whole systemic inflammatory aspect of the psoriatic disease, such as high CRP levels, disease activity, concomitant use of specific medications, sedentarism, smoking, depression and obesity (15-19). Reviewing medical records, one of the reasons why the use of methotrexate was less frequent in the group with CVD was hepatotoxicity, which may be due to polypharmacy associated with metabolic complications. The impossibility to use this important medication may lead to the trend of higher activity measured present in the CVD group.

Moreover, it is possible that PsA might be associated to a cluster of risk factors for CVD so that clinical and/or pathophysiological interactions may enhance the risk for CVD. Those interactions may be related to common genetic and pathophysiological processes between PsA, PsO, hypertension, diabetes and atherosclerosis.

We must also consider that our study may have some limitations: We used a retrospective design in which information of traditional risk factors was obtained by chart review and routine laboratory analysis performed for regular clinical care. We were not able to obtain information regarding other important risk factors, such as obesity or smoking and this should certainly be searched in prospective studies. Moreover, our patients had long mean disease duration, implying longer periods of medication such as glucocorticoids and NSAIDs which could also have influenced the development of DM and AH allied to an altered metabolic and CV risk profile. A risk of population bias is feasible, since we have analysed a single

tertiary centre, implying that our data could not be extrapolated to general practice; a healthy control group was not evaluated and we compared our findings to local population defined data. The broad confidence interval for the variables demonstrated herein, may be minimised by further longitudinal studies including larger number of patients, consideration of a wider group of variables and more specific tools of evaluation such as Psarc index. Nevertheless, our preliminary findings points out the magnitude of this problem and can certainly be used as an initial guide for further work aiming to actively search for new cardiovascular risk factors in PsA.

In conclusion, the high prevalence of CVD in PsA patients influenced by increased AH and DM indicates that early recognition and specific treatment is mandatory in order to reduce the risk for CVD. Patients with PsA should be properly investigated and preventative measures for CVD must be implemented (42, 43). Interaction between PsA and AH or DM potentiates the global risk for CVD and these modifiable risk factors should be addressed in an effort to reduce the prevalence of CVD. The association of PsA with increased prevalence of hypertension and diabetes, and the CV risk given by these two entities in these individuals is greater than expected for the general population. Therefore, strategies for prevention and treatment of cardiovascular comorbidities should be emphasised in the multidisciplinary approach of PsA management in order to avoid early morbidity and mortality.

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