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ORIGINAL ARTICLE

Prevalence and type II diabetes-associated factors in psoriatic arthritis

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Abstract

Diabetes is a common cardiovascular risk factor in psoriatic arthritis (PsA). Although the prevalence of diabetes is high, the factors associated with it in PsA are poorly understood. We aimed to analyse the prevalence of type II diabetes and diabetes-associated factors in a hospital-based population with PsA. This cross-sectional study included 340 consecutive patients attended in a tertiary care hospital. The prevalence of diabetes was compared to that of 600 outpatients without inflammatory conditions. To analyse diabetes-associated factors, odds ratio (OR) values were calculated by conditional logistic regression analysis. Significant variables in the univariate analysis were then introduced in a multivariate analysis with a backward stepwise approach. Diabetes was more prevalent among PsA patients (13.8 vs. 5%, OR 2.8, 95% CI: 1.7–4.3, $p < 0.0001$). Diabetes-associated factors in the univariate analysis ($p < 0.05$) were the following: an age of onset of psoriasis > 40 years, an age of onset of arthritis > 40 years, a low educational level, family history of psoriasis, pustular psoriasis, high number of swollen joints during follow-up, hypertension, dyslipidemia, obesity, and cardiovascular events. After controlling for several confounders, diabetes was significantly associated with late-onset psoriasis (OR 8.2, 95% CI: 1.9–12.4, $p = 0.002$) and hypertension (OR 7.5, 95% CI: 1.5–13.3, $p = 0.008$). Diabetes risk should be carefully evaluated in patients with PsA whose psoriasis begins after 40 years.

Keywords Cardiovascular risk · Diabetes · Late-onset disease · Psoriasis · Psoriatic arthritis

Introduction

Psoriatic arthritis (PsA) is a chronic inflammatory musculoskeletal disease, usually seronegative for rheumatoid factor, associated with psoriasis, with a prevalence of 0.02–0.42% in the general population and 13.8–30% among patients with psoriasis [1]. Psoriatic arthritis is a heterogeneous condition with articular and extra-articular manifestations including a combination of peripheral arthritis, spondylitis, enthesitis, dactylitis and skin/nail disease.

Cutaneous psoriasis and PsA are the most important poles of what we now know as psoriatic disease. It is a systemic entity that goes beyond the skin and joints to encompass other aspects such as osteoporosis, ocular inflammation, intestinal inflammation, liver disease and, above all, cardiovascular comorbidity [2].

One of the most important discoveries in the recent history of psoriatic disease is that these patients also exhibit an increased prevalence of traditional cardiovascular risk factors (CVRF) including hypertension, diabetes, obesity and dyslipidemia, when compared to the general population [2–5]. With regard to diabetes, this factor shows a higher incidence and prevalence in patients with psoriasis and PsA with respect to the general population [2–5]. Type II diabetes has been observed in 12 to 18.6% of patients with PsA [2]. This finding may be partially explained by increased obesity and unhealthy lifestyles, and may possibly be related to insulin resistance associated with PsA inflammation [2, 3].

As PsA may be viewed as a 'disease within a disease', it may be difficult to ascertain which CVRF may be attributable to psoriasis and which to PsA. For example, it has been estimated that the presence of joint disease increases the risk of hypertension when compared to psoriasis alone [6]. A recent meta-analysis regarding the risk of diabetes in psoriatic disease showed that patients with PsA had higher diabetes risk as compared to psoriasis alone [7]. This risk seems to be related to age

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at disease onset [8]. However, the connections between psoriatic disease and the risk of diabetes are not completely known.

Optimal care of the patient with PsA means not only treating the skin and joint disease but also identifying comorbidities and making sure that these comorbidities are appropriately addressed. Epidemiologic studies have provided significant advances in our understanding of comorbidities associated with psoriatic disease over the past 10 years [2]. However, little is known about how to address comorbidities in order to improve outcomes and enhance care. Much work remains in understanding the complex relationship between PsA and cardiometabolic comorbidities. In this sense, it is of paramount importance to analyse what factors of the disease may be associated with the presence of these comorbidities, and whether the therapeutic interventions aimed at improving the inflammation of the disease have some positive influence on them.

In this work, we have analysed the prevalence of diabetes and those PsA-related factors that were significantly associated with its presence. This type of study could provide key information to help improve the overall health of these patients.

Methods

This retrospective cross-sectional study included 340 consecutive patients treated at a single university hospital who fulfilled the ClASsification for Psoriatic ARthritis (CASPAR) criteria for PsA [9]. These patients were attended according to a standard protocol in a monographic PsA clinic within our rheumatology department. Patients of this cohort were regularly evaluated every 3 to 6 months depending on disease activity or severity. All demographic, clinical, laboratory, therapeutic and radiographic variables were collected in a standardised manner as depicted below. Patients were informed about the objectives of the study, and consent informed sheets were signed by all participants. This study was conducted following the rules of good clinical practice (Helsinki Declaration). An institutional ethics committee approved the final version of this study. Patient anonymity and confidentiality of data have been preserved at all times.

Study population and study variables

The cohort was composed by 190 men and 150 women with a mean age of 55 ± 13 years. The description of joint patterns was made on the basis of the dominant pattern observed in the last 5 years previous to study entry. Patients with four or less swollen joints were labelled as oligoarthritis; those who presented five or more were tagged under the polyarthritis category. Patients with axial disease were classified according to the Assessment of SpondyloArthritis international Society (ASAS) criteria for axial spondyloarthritis [10]. Patients were stratified in early- and late-onset disease according to a cut-off point of 40 years.

Family history of psoriasis and PsA was collected. Educational levels were assessed and classified under three categories according to the achieved degree: primary, secondary (high school) and university studies. Data regarding skin disease included the main type of psoriasis, location of lesions, nail disease and percentage of patients with the involvement of three or more body areas. All cases of psoriasis were confirmed by a dermatologist. The onset patterns of arthritis were based on the main articular phenotype during the first 6 months of disease evolution. Pelvic, lumbar and cervical lateral x-rays were included in the radiographic study to assess spinal involvement. X-rays of the affected areas during follow-up were also obtained. Laboratory data included the following routine tests: blood and urine biochemistry, blood count, ESR, HLA-B*27, HLA-C*06, rheumatoid factor, antinuclear antibodies and C-reactive protein. Glucocorticoid, NSAID and conventional as well as biologic disease-modifying antirheumatic drug (DMARD) use was also collected.

Definition of cardiovascular risk factors

- Diabetes mellitus (DM): defined by analytical findings during monitoring of glucose elevation of more than 126 mg/dl on two fasting determinations, chronic treatment with antidiabetic or insulin, or diagnosed by an endocrinologist. Type I diabetes patients were not included in this study.
- High blood pressure (hypertension): defined as finding at least two determinations on different days of blood pressure greater than 140/90 mmHg during follow-up, chronic use of antihypertensive treatment or diagnosis by a medical specialist.
- Dyslipidemia: defined as the ongoing finding of cholesterol figures above 200 mg/dl or triglyceride figures above 150 mg/dl during follow-up, chronic treatment with lipid-lowering drugs or diagnosis by medical specialist.
- Obesity: defined as the presence of a body mass index (BMI) equal or greater than 30 kg/m^2, whereas overweight is defined as a BMI between 25 and 29.9 kg/m^2.
- Smoking habit: we consider active smokers to be all daily smoker patients at the time of the study (irrespective of the number of cigarettes); those patients with a past smoking habit (at least 5 years), but who were not active smokers at the time of the study, are regarded as former smokers.

Definition of cardiovascular outcomes

- Ischemic heart disease: defined as at least one cardiac event such as acute MI or stable or unstable angina diagnosed by a medical specialist.

- Cerebrovascular disease: any transient or permanent event as a result of a disorder of cerebral circulation, either ischemic or haemorrhagic, diagnosed by a medical specialist.
- Peripheral vascular disease: defined as the presence of at least one episode of peripheral arterial ischemic disease diagnosed by a medical specialist.

Statistical analysis

A descriptive statistical analysis of all the variables was performed, including central tendency and dispersion measures for continuous variables, and absolute and relative frequencies for categorical variables. The Student *t* test, Mann-Whitney *U* test or Kruskal-Wallis *H* test was used to compare quantitative variables, and Pearson's chi-square or Fisher's exact tests were used for qualitative variables. The frequency of CVRF was compared to that of 600 non-inflammatory outpatients matched by age (± 3 years) and sex (1:1) with the study population. The non-inflammatory population was mostly composed of osteoarthritis, soft tissue rheumatism, chronic non-inflammatory back pain, fibromyalgia and patients with skin non-inflammatory conditions. Odds ratio (OR) values with its 95% CI were calculated by conditional logistic regression analysis. Initially, a univariate analysis was performed to examine unadjusted associations of diabetes and CV events with its potential risk factors. Significant variables in the univariate analysis were then introduced in a multivariate analysis with a backward stepwise approach. Tests were two-tailed with a significance level of 5%. Data were analysed using SPSS V19.0 statistical software.

Results

This series included 190 men (56%) and 150 women (44%), with an average age of 55 ± 13 years. The average age of onset of psoriasis was 33 ± 17 years, while the average age of onset of arthritis was 45 ± 14 years. The majority of patients suffered from common or plaque psoriasis (86.7%). Nail psoriasis was detected in 142 patients (41.8%). One hundred fifty patients presented with psoriasis in three or more body areas. Forty-six percent had a family history of psoriasis, while 15% had a family history of PsA. The most common form of PsA was the mono-oligoarticular form (41.5%), while 20% of this series had erosive disease. Twenty percent of patients were HLA-B*27 positive, and 38% expressed the HLA-C*06 allele. Table 1 shows the main clinical demographic characteristics of this series.

The statistically significant differences between genders after the Bonferroni correction were as follows: nail disease (males 48% vs. females 33.3%, $p = 0.010$), psoriasis in gluteal/inguinal folds (males 30.5% vs. females 18.7%, $p = 0.020$), PsA of axial onset (males 14.7% vs. females 8%, $p = 0.049$), diabetes (males 10.5% vs. females 18%, $p = 0.046$), obesity (males 28.9% vs. females 44%, $p = 0.010$) and ex-smokers (males 31.6% vs. females 18.7%, $p = 0.015$). Although there were differences in the distribution of certain CVRF between men and women, the distribution of CV events did not differ between genders.

The frequency of traditional CVRF was as follows: diabetes 13.8%, hypertension 36%, dyslipidemia 31%, obesity 35%, overweight 24.1%, smokers 26% and former smokers 26%. Compared with the control population, patients in this

Table 1 Disease characteristics of the study population

Variable	N: 340 (%)
Age (yr ± SD)	55 ± 13
Age at psoriasis onset (yr ± SD)	33 ± 17
Age at arthritis onset (yr ±SD)	45 ± 14
Duration of psoriasis (yr ± SD)	21 ± 11
Duration of arthritis (yr ± SD)	11 ± 6.3
Men (n, %)	190 (55.9)
Women (n, %)	150 (44.1)
Education level:	
Primary (n, %)	180 (52.9)
Secondary (n, %)	85 (25)
Academic (n, %)	75 (22.1)
Plaque psoriasis (n, %)	295 (86.7)
Onychopathy (n, %)	142 (41.8)
Psoriasis in ≥ 3 body areas (n, %)	150 (44.1)
Family history of psoriasis (n, %)	156 (46)
Family history of PsA (n, %)	51 (15)
Mono/oligoarthritis as onset (n, %)	207 (61)
Polyarthritis as onset (n, %)	93 (27.4)
Axial disease as onset (n, %)	40 (11.8)
Mono/oligoarthritis during evolution (n, %)	141 (41.5)
Polyarthritis during evolution (n, %)	95 (28)
Axial disease during evolution (n, %)	20 (5.9)
Concomitance of axial plus peripheral arthritis (n, %)	80 (23.5)
Dactylitis (n, %)	93 (27.4)
DIP joint disease (n, %)	74 (21.8)
Mutilating arthritis (n, %)	5 (1.5)
Erosive disease (n, %)	68 (20)
HLA-B*27 (n, %)	68 (20)
HLA-C*06 (n, %)	129 (38)
NSAIDs (n, %)	85 (25)
Glucocorticoids (n, %)	40 (11.7)
MTX (n, %)	221 (65)
Biologics (n, %)	146 (43)

yr years; *SD* standard deviation; *N*, *n* numbers; *DIP* distal interphalangeal; *NSAIDs* non-steroidal anti-inflammatory drugs; *MTX* methotrexate

study had higher frequencies of hypertension (36 vs. 23%, OR 2.4, 95% CI: 1.6–2.7, $p < 0.0001$), diabetes (13.8 vs. 5%, OR 2.8, 95% CI: 1.7–4.3, $p < 0.0001$), obesity (35 vs. 22%, OR 2.1, 95% CI: 1.5–2.8, $p < 0.0001$) and tobacco use (26 vs. 21%, OR 1.4, 95% CI: 1.0–1.8, $p < 0.05$).

Of the 340 patients, 32 subjects (9.4%) presented 41 CV events: 15 events of ischemic heart disease, 15 cerebrovascular disease events and 11 events of ischemic peripheral vascular disease. When analysing the events separately, an age at onset of psoriasis > 40 years (OR 4.1, 95% CI: 1.04–16.2, $p < 0.05$) and dyslipidemia (OR 5.8, 95% CI: 1.5–22.8, $p < 0.05$) were independently associated with coronary events in the multivariate analysis. Hypertension was an independent predictor of stroke (OR 8.0, 95% CI: 1.7–38.1, $p < 0.05$). In the analysis of peripheral arterial disease, the associations with the presence of dactylitis and hypertension were significant, but due to the small number of events, the regression model did not converge and ORs could not be calculated. When analysing all CV events together, an age of onset of psoriasis > 40 years (OR 3.4, 95% CI: 1.1–10.0, $p < 0.05$), a polyarticular evolution (OR 2.9, 95% CI: 1.1–8.0, $p < 0.05$), hypertension (OR 5.3, 95% CI: 1.6–17.6, $p < 0.01$) and dyslipidemia (OR 2.6, 95% CI: 1.0–7.2, $p < 0.05$) behaved as independent associations for CV events in multivariate analysis.

The factors that were associated with the presence of diabetes in the univariate analysis were as follows: an age of onset of psoriasis > 40 years ($p < 0.0001$), an age of onset of arthritis > 40 years ($p = 0.0090$), a low educational level ($p = 0.0010$), family history of psoriasis ($p = 0.0250$), pustular psoriasis ($p = 0.0060$), a high number of swollen joints during follow-up ($p = 0.0200$), hypertension ($p = 0.0001$), dyslipidemia ($p = 0.0010$), obesity ($p = 0.0090$) and CV events ($p = 0.0010$). After controlling for age, sex, disease duration and other confounders, diabetes was significantly associated with late-onset psoriasis (OR 8.2, 95% CI: 1.9–12.4, $p = 0.0020$) and hypertension (OR 7.5, 95% CI: 1.5–13.3, $p = 0.0080$). Table 2 shows the univariate and multivariate risk models for diabetes in this study.

Discussion

In this hospital-based series, we have corroborated a higher rate of diabetes in PsA compared to a population without PsA matched by age and sex. We found that a late-onset age of psoriasis (together with hypertension) was independently associated with the risk of diabetes. The higher frequency of diabetes in our population confirms similar findings reported by other authors in recent years [2–5].

Since the seminal publication by Henseler and Christophers in which psoriasis was divided between type I (before 40 years old) and type II (beginning after that age), the age at disease onset of psoriatic disease has become an adequate element of stratification, which has contributed to a better understanding of this entity [8, 11]. We have shown that late-onset psoriasis is independently associated with the risk of type 2 diabetes. Diabetes is an essential component of the metabolic syndrome. In that sense, Caso et al. have recently found that in patients with PsA and active psoriasis, the prevalence of metabolic syndrome is clearly higher when compared to the same risk in patients with PsA *sine* psoriasis [12]. Therefore, these data reinforce the strength of our findings.

Other classic CVRF were more frequent in our patients with PsA than in those without this condition. These findings are therefore in line with other data from the literature that finds a higher prevalence of metabolic syndrome components in patients with psoriatic disease [2–5]. In addition, we have been able to confirm that the development of CV events in this

Table 2 Univariate and multivariate risk models for diabetes in this study

Variable	Univariate model OR (95% CI)	*p* value	Multivariate model OR (95% CI)	*p* value
Psoriasis onset > 40 yr	9.4 (3.2–7.5)	0.0001	OR 8.2 (1.9–12.4)	0.002
Arthritis onset > 40 yr	4.01 (1.3–12.2)	0.009		
Low educational level	6.5 (1.8–23.1)	0.001		
Pustular psoriasis	5.5 (1.4–21.2)	0.006		
Family history of psoriasis	2.9 (1.1–7.4)	0.025		
Polyarticular evolution	2.7 (1.1–6.2)	0.020		
Mixed pattern	2.8 (0.93–8.6)	0.058		
Hypertension	17.2 (5.6–23.1)	0.0001	7.5 (1.5–13.3)	0.008
Dyslipidemia	4.1 (1.7–9.8)	0.001		
Obesity	3.6 (1.3–9.9)	0.009		
CHD	11.0 (2.7–24.3)	0.0001		
Cerebrovascular disease	18.6 (4.3–30.6)	0.0001		
Peripheral arterial disease	8.0 (1.5–32.3)	0.004		

yr years, *CHD* coronary heart disease

population is due to the conjunction of traditional risk factors together with others more linked to the inflammatory nature of the disease. Recent studies have found that 30 to 50% of patients with PsA with atherosclerosis do not have these traditional CV risk factors [2, 13]. Therefore, it seems clear that the global CV risk in psoriatic disease depends on factors that go beyond the classical risk factors, and our study is in line with this. For example, although women in this study had higher rates of diabetes and obesity, the rate of adverse cardiovascular events was similar between sexes, which again points to other factors, unrelated to traditional risk factors, in the genesis of such events.

The non-association between diabetes and CV events in our population is unexpected since diabetes is a known risk factor in this regard. Due to the retrospective nature of this study, we may have overlooked other important factors linked to diabetes and global CV risk such as CRP or other atherogenic risk biomarkers, which were not specifically addressed. However, in line with our results, data from the CARMA study (a multicentre prospective project aimed at studying the CV comorbidity of inflammatory rheumatic diseases in Spain) showed that hypertension and hypercholesterolemia were significantly associated with CV disease in all inflammatory groups. However, diabetes and CV events were found to be significantly associated only in rheumatoid arthritis and not in the other conditions, including PsA. [4].

It is not entirely clear why patients with psoriatic disease tend to have a higher frequency of CVRF such as diabetes. Excessive weight gain can provoke hypertension, type 2 diabetes, atherosclerosis and hyperlipidemia, which define the metabolic syndrome, but only half of obese patients with a body mass index from 30 to 50 kg/m^2 are metabolically unhealthy [14–17]. Furthermore, metabolic syndrome can transiently occur in lean individuals during infection, where increased secretion of TNF, IL-6 and IL-1 by macrophages induces a temporary insulin-resistant state [14–17]. While transient inflammation-mediated insulin resistance can be helpful, permanent inflammation makes it become chronic; conversely, chronic inflammation of adipose tissue with the infiltration of macrophages and T cells leads to insulin resistance and eventually type 2 diabetes mellitus in obese individuals. Visceral obesity and insulin resistance are characterised by the persistent production of abnormal adipocytokines such as TNF, IL-6, IL-1, leptin and adiponectin, which contribute to the development of a pro-inflammatory state and further a chronic, subclinical vascular inflammation that modulates and results in atherosclerotic processes [14–17]. Moreover, the arthritic process itself can severely limit the mobility of these subjects, making them more prone to a sedentary lifestyle and obesity, thus closing a loop that promotes a pro-inflammatory and pro-diabetic state. In fact, one of the factors that we found associated with diabetes was a polyarticular form of PsA, although this association was not maintained in the multivariate analysis. However, we did find a clear association between a high number of inflamed joints (five or more) and CV outcomes.

To date, no prospective studies have specifically examined the effect of aggressive PsA treatment on the risk of CV events. Prior studies investigating the hypothesis that CV risk can be attenuated by decreasing inflammation through the use of DMARD therapy have produced conflicting results [18, 19]. In fact, we did not find any difference between exposure to drugs and CV risk factors or CV events (data not shown).

Finally, this study has certain limitations such as its retrospective and cross-sectional nature, the relatively small number of patients for an epidemiological study and the fact of dealing with a single-centre series (inclusion bias). It is important to consider that the fact of working with an arbitrary cut-off point in 40 years involves, in the majority of cases that we are studying, two normally distributed populations with two overlapped tails; i.e. patients with type I psoriasis will fall into the distribution curve of type II and vice versa, although we see that as patients move away from that age point, they keep conforming more homogeneous groups from the clinical and CV standpoint [20].

In summary, we have found a high prevalence of diabetes in this population of patients with PsA. We have highlighted the importance of the disease factors linked to this CVRF and we have identified which factors of the disease are linked to CV events. The concept of a common pathogenic mechanism for atherosclerosis and systemic rheumatic diseases has resulted in the increasing importance of a multidisciplinary integrated approach to optimise screening and therapy for patients with PsA and its comorbidities, with active coordination between different specialists (rheumatologists, cardiologists, dermatologists and endocrinologists) as well as primary care colleagues [21]. This comprehensive multidisciplinary view should be the basis for a better global prognosis of the disease and its complications.

Conclusions

Diabetes, as well as other components of the metabolic syndrome, is a common finding in PsA. The comprehensive management of these patients must necessarily include an estimate of CV risk. According to the results of this study, this estimate is particularly relevant in subjects whose cutaneous disease debuts after 40 years of age.

Compliance with ethical standards

Disclosures None.

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