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ORIGINAL ARTICLE

Hypertension is associated with increased age at the onset of psoriasis and a higher body mass index in psoriatic disease

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Abstract

Background and aims High blood pressure (HBP) is a common comorbidity in psoriatic disease. Some studies indicate a higher prevalence of HBP among arthritis patients, in relation to psoriasis alone, within the psoriatic spectrum. Our objective was to study the prevalence of HBP in both types of patients as well as to analyse the factors associated with it.

Methods A cross-sectional observational study of 600 patients with psoriatic disease attended in a multidisciplinary clinic of a reference centre. We first analysed the frequency of this comorbidity and then the factors associated with it using conditional logistic regression. The significant factors in this first model were introduced in a multivariate model using a backward step approach.

Results A total of 144 patients were hypertensive (24%). Of patients with arthritis, 86/290 (29.7%) had HBP, compared with 58/310 (18.7%) with psoriasis (OR 1.7 95%, CI 1.25–2.50, $p = 0.003$). Hypertension was independently associated with higher age at onset of psoriasis (OR 1.04, 95%CI 1.03–1.06, $p < 0.001$) and a higher body mass index (OR 1.13, 95%CI, 1.06–1.22, $p < 0.001$).

Conclusions HBP is more prevalent in patients with arthritis within the spectrum of psoriatic disease. Patients with a higher body mass index and those with later-onset psoriasis are more prone to this comorbidity.

Key Points

- *The factors of psoriatic disease associated with HBP are little known.*
- *HBP is more prevalent in patients with arthritis within the spectrum of psoriatic disease.*
- *In patients with psoriatic disease, for each point of increase in the body mass index, the risk of HBP increases by 13%.*
- *For each year of onset of psoriasis above 40 years, the risk of HBP increases by 4%.*

Keywords Comorbidity · High blood pressure · Psoriasis · Psoriatic arthritis

Introduction

Psoriasis and psoriatic arthritis (PsA) are chronic immune-mediated diseases that affect a substantial proportion of the general population. It has been estimated that up to one-third of patients with psoriasis end up developing inflammatory arthritis. If we estimate that between 2 and 3% of the general population has psoriasis, it can be concluded that the global prevalence of PsA is very close to the prevalence of rheumatoid arthritis (RA) (0.5–1%) [1]. Psoriasis and PsA are the two poles of what we know today as psoriatic disease, a concept coined to emphasise the systemic nature of these entities [2].

Numerous epidemiological and observational studies in recent years have shown an increase in the incidence and prevalence of traditional cardio-vascular risk factors (CVRF) and adverse cardiovascular (CV) events associated with them, both in subjects with psoriasis and with PsA [3]. However, some evidence points to a higher prevalence of these factors among PsA patients compared with those with skin psoriasis [4, 5]. The CV burden may therefore be higher in patients with PsA compared with psoriasis patients that do not have arthritis. The extent of atherosclerosis, measured by imaging modalities, is higher in PsA than in the general population and in

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patients with psoriasis alone [6, 7]. Therefore, the presence of arthritis may indicate an increased, underlying systemic inflammation that may worsen comorbidities and CV outcomes. This finding has led researchers to speculate a close connection between the inflammatory load characteristic of these entities and an increased risk of CV events [3].

High blood pressure (HBP) is a major risk factor for the development of CV disease and, thus, an important modifiable cause of premature morbidity and mortality. A meta-analysis of 24 observational studies found a pooled odds ratio (OR) for the association between psoriasis and HBP to be 1.58 (95%CI 1.42–1.76). The OR for HBP was 1.30 (95%CI 1.15–1.47) for patients with mild psoriasis and 1.49 (95%CI 1.20–1.86) for severe psoriasis [8]. In addition, the likelihood of poorly controlled HBP appears to increase with a more severe skin disease, independent of body mass index (BMI) and other risk factors [9]. However, the prevalence of HBP seems to be significantly greater in PsA patients than in psoriasis patients that do not have arthritis, even after adjusting for conventional CVRF, psoriasis duration and severity, medication history and other comorbid conditions [5]. This finding suggests that the additive burden of a chronic inflammatory joint disease may account for the increased prevalence of HBP seen in PsA compared with psoriasis without arthritis [3, 5].

Over the past 10 years, epidemiologic studies have provided significant advances in our understanding of comorbidities associated with psoriatic disease. However, much work remains in understanding the complex relationship between these conditions 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 the present study, we have analysed the comparative prevalence of HBP in a population of patients with psoriatic disease treated at a referral centre. We have also analysed the factors of the disease associated with this comorbidity.

Patients and methods

This cross-sectional, observational study included all patients who were treated in a multidisciplinary dermatology-rheumatology clinic from a reference hospital between January and December 2016. In total, 290 patients with PsA who met the ClASssification for Psoriatic ARthritis (CASPAR) criteria [10] and 310 patients with psoriasis, without arthritis were included. Patients were assessed according to a standard protocol and regularly evaluated every 3 to 6 months, depending on their disease activity or severity. The work procedures of this clinic have been published previously [11]. Patients were informed about the objectives of the study, and informed consent forms were signed by all participants. This study was conducted following the guidelines for good clinical practice (Helsinki Declaration). The study was approved by the Clinical Research Ethics Committee of Hospital Universitario Central de Asturias (reference no. HUCA 68/16). Patient anonymity and confidentiality of data have been preserved throughout the study.

Study population and study variables

Regarding PsA, we described the disease patterns, both at the beginning of the disease (first 6 months) and during follow-up, according to the following: patients with four or less swollen joints were labelled as having oligoarthritis; those who presented with five or more were tagged under the polyarthritis category. Patients with axial disease (spondylitis) were classified according to the Assessment of SpondyloArthritis International Society (ASAS) criteria for axial spondyloarthritis [12]. 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. Body weight and BMI were also collected. Data regarding skin disease included the main type of psoriasis, the location of lesions, nail disease, the percentage of patients with involvement of three or more body areas and Psoriasis Area and Severity Index (PASI). All cases of psoriasis were confirmed by a dermatologist. 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, erythrocyte sedimentation rate, human leukocyte antigen (HLA)-B*27, HLA-C*06, rheumatoid factor, antinuclear antibodies and C-reactive protein (CRP). Glucocorticoid, Non-Steroidal AntiInflammatory Drugs (NSAID) and conventional as well as biologic Disease-Modifying Anti-Rheumatic Drugs (DMARD) use were also collected.

High blood pressure was defined by the finding of at least two fasting determinations, on different days, of blood pressure values greater than 140/90 mmHg during a 1-month period, the chronic use of antihypertensive treatment or a diagnosis by a nephrologist, cardiologist, internist or family doctor.

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 differences between quantitative variables with normal distribution according to the Kolmogorov-Smirnoff test were analysed by Student's *t* test. Differences between quantitative non-normal variables were studied by non-parametric tests (Mann-Whitney *U* test or Kruskal Wallis *H* test). Pearson's chi-square or Fisher's exact test was used for qualitative variables. The frequency of HBP was compared in both subpopulations. Odds ratio values with a 95%CI were calculated by conditional logistic regression analysis. Initially, a univariate analysis was performed to examine unadjusted associations of HBP with its potential risk factors. Significant variables in the univariate analysis ($p < 0.10$) were then introduced in a multivariate analysis with a backward stepwise approach. The tests were two-tailed with a significance level of 5%. The study was descriptive; thus, the sample size was not determined a priori. Data were analysed using SPSS V19.0 statistical software (IBM Corp. NY, USA).

Results

The cohort was composed of 324 men and 276 women with a mean age of 53 ± 12 years (age range, 22–83) and a mean disease follow-up of 8.2 ± 6.4 years. The study included 290 PsA patients and 310 patients with psoriasis without arthritis. One hundred forty-four of the 600 patients presented HBP (24%). The mean age at onset of psoriasis (39 ± 17 in HBP vs. 26 ± 16 years in non-HBP, $p < 0.01$) and arthritis (49 ± 17 in HBP vs. 41 ± 14 years in non-HBP, $p < 0.01$) was significantly higher in the HBP population. The mean body weight (83 ± 16 in HBP vs. 77 ± 15 kg in non-HBP, $p < 0.01$) and BMI (30.2 ± 4.9 in HBP vs. 27 ± 4.4 in non-HBP, $p < 0.01$) were significantly higher in HBP patients. HBP (29% vs. 18%, OR 1.7, 95%CI 1.25–2.50, $p < 0.01$) and dyslipidaemia (28% vs. 13.5%, OR 2.5, 95 %CI 1.7–3.3, $p < 0.01$) were more common in PsA than in psoriasis alone. However, obesity (36.5% vs. 27.6%, OR 1.5, 95%CI 1.1–2.1, $p < 0.05$) and tobacco use (34.5% vs. 27.2%, OR 1.4, 95 %CI 1.0–2.0, $p < 0.05$) were more prevalent among the psoriasis group than the PsA group. There were more smokers among non-HBP patients (36% vs. 22%, $p < 0.01$). The prevalence of HLA-C*06 was higher among non-HBP (43% vs. 30%, $p < 0.05$). Table 1 represents the clinical characteristics of both subpopulations.

No differences were detected between patients with or without HBP in relation to the duration of illness, HLA-B*27 or consumption of systemic medication (DMARD and/or biologics). The variables significantly associated with HBP in the univariate analysis ($p < 0.10$) were an age at onset of psoriasis above 40 years (OR, 4.1), age at onset of arthritis above 40 years (OR, 2.6), low educational level (OR, 4.9), family history of PsA (OR, 2.9), pustular psoriasis (OR, 3.6), PASI > 10 (OR, 3.4), polyarthritis during follow-up (OR, 1.8), diabetes (OR, 17.2), obesity (OR, 3.9), ex-smokers (OR, 2.2), ischemic heart disease (OR, 4.9), stroke (OR, 8.7) and peripheral vascular disease (OR, 12.2). After correcting for age, sex, duration of disease, arthritis, treatments and other CVRF, multivariate analysis showed that HBP was associated with a higher age at onset of psoriasis (according to a cut-off value of 40 years), where the OR was 1.04 (1.03–1.06, $p < 0.001$) and a higher BMI, where the OR was 1.13 (1.06–1.22, $p < 0.001$).

Discussion

The prevalence of HBP found in this study was similar to that found in other populations of non-inflammatory patients seen in our clinical setting [13]. However, in this study, we have shown a higher prevalence of HBP in patients with PsA compared with patients with psoriasis without arthritis. Our results seem to corroborate previous studies and points to the theory that a higher inflammatory load may contribute to modelling the profile of CVRF in patients with psoriatic disease [3]. The HBP prevalence in our patients with PsA fell within the range of 25% to 49% reported in past PsA studies, thus confirming HBP as the leading CVRF in PsA [3, 5].

When analysing the prevalence of CVRF in psoriatic disease, we verified a differential distribution. Thus, hypertension and dyslipidaemia were more common in patients with arthritis, while other CVRF, such as smoking or obesity, were more prevalent in patients with psoriasis without arthritis. We have also substantiated that HBP was more frequent in patients with significantly higher ages of onset, both for psoriasis and arthritis. In that line, the stratification of psoriatic disease according to the age of onset of symptoms or depending on the presence of arthritis has helped to better define the cardiovascular phenotype of this entity [14, 15]. For example, most classic CVRF tend to occur in subjects with onset of psoriasis or arthritis above 40 years. However, when the age factor is corrected in regression analysis models, psoriasis itself, or arthritis, continue to contribute differentially to the presence of these factors. In fact, a clear association between HBP and arthritis of onset above 40 years and between diabetes and psoriasis, above that age limit, has been recently reported [15]. These findings reinforce the notion that psoriatic disease per se contributes to the increase of CV risk over the age factor and other classic CVRF.

In recent observational studies of patients with PsA, it has been confirmed that HBP, together with other factors more linked to the inflammatory nature of this condition, predicts the development of adverse CV events [13]. Therefore, it is interesting to analyse what factors of psoriatic disease are associated with this comorbidity.

Psoriasis and PsA share striking similarities with other systemic inflammatory diseases, such as rheumatoid arthritis

Table 1 Disease characteristics of both subpopulations

Variable	PsA, $n = 290$	Psoriasis, $n = 310$	p values
Age (year ± SD)	54 ± 12	53 ± 11.5	NS
Age at psoriasis onset (year ± SD)	32 ± 16	31 ± 14.2	NS
Age at arthritis onset (year ± SD)	46 ± 14		
Duration of psoriasis (year ± SD)	21 ± 10	22 ± 11	NS
Duration of arthritis (year ± SD)	11 ± 7.2		
Male gender (*n*, %)	159 (54.8)	164 (52.9)	NS
Education level			
Primary (*n*, %)	145 (50)	148 (47.7)	NS
Secondary (*n*, %)	79 (27.2)	87 (28.1)	NS
Academic (*n*, %)	66 (22.8)	235 (24.2)	NS
Plaque psoriasis (*n*, %)	250 (86.2)	272 (87.7)	NS
Nail disease (*n*, %)*	122 (42.1)	110 (35.5)	NS
Psoriasis in ≥ 3 body areas (*n*, %)	130 (45)	155 (50)	NS
Family history of psoriasis (*n*, %)	130 (45)	136 (44)	NS
Family history of PsA (*n*, %)	44 (15.2)	15 (4.8)	< 0.05
PASI	6.5 ± 4.3	6.8 ± 3.5	NS
Oligoarthritis as onset (*n*, %)	174 (60)		
Polyarthritis as onset (*n*, %)	81 (28)		
Axial disease as onset (*n*, %)	35 (12)		
Oligoarthritis during follow-up (*n*, %)	122 (42.1)		
Polyarthritis during follow-up (*n*, %)	81 (28)		
Axial disease during follow-up (*n*, %)	17 (5.8)		
Mixed pattern during follow-up (*n*, %)	70 (24.1)		
Dactylitis (*n*, %)	87 (30)		
DIP joint disease (*n*, %)	72 (24.8)		
Mutilating arthritis (*n*, %)	5 (1.7)		
Erosive disease (*n*, %)	58 (20)		
HAQ (mean ± SD)	0.74 ± 0.32		
BASDAI (mean ± SD)**	3.64 ± 2.12		
Pain VAS (mean ± SD)	4.09 ± 2.64		
HLA-B*27 (*n*, %)	52 (17.9)		
HLA-C*06 (*n*, %)	112 (38.6)	124 (40)	NS
NSAID (*n*, %)	72 (24.8)	47 (15.2)	NS
Glucocorticoids (*n*, %)	34 (11.7)	15 (4.8)	NS
MTX (*n*, %)*	189 (65.2)	128 (41.3)	< 0.05
Biologics (*n*, %)	128 (44.1)	132 (42.6)	NS

SD, standard deviation; *PsA*, psoriatic arthritis; *PASI*, psoriasis area and severity index; *DIP*, distal interphalangeal joint; *HAQ*, Health Assessment Questionnaire; *BASDAI*, bath ankylosing spondylitis disease activity index; *VAS*, visual analog scale; *NSAID*, non-steroidal anti-inflammatory drugs. *MTX*, methotrexate. *Defined as in the CASPAR criteria. **Only in patients with axial disease

(RA) and atherosclerosis. The typical histological features of the psoriatic plaque, with dermal inflammation and leucocyte infiltration, are similar to those of the atherosclerotic plaque [3]. In atherosclerosis, psoriasis, PsA and RA, the immune system activates an inflammatory cascade, particularly involving T-helper (Th)1, Th17, regulatory T cells and downstream expression of cytokines [3]. Visceral obesity and insulin resistance, which are common findings in psoriatic disease, are characterised by the persistent production of abnormal adipocytokines such as TNF, IL-6, IL-1, leptin and adiponectin. Persistent production of these adipocytokines contributes to the development of a pro-inflammatory state and further a chronic, subclinical vascular inflammation that modulates and results in atherosclerotic processes [3]. The pathophysiologic mechanisms of HBP in patients with psoriatic disease remain unknown, although several biological pathways have been implicated, including overexpression of endothelin I, a potent vasoconstrictor expressed in both

vascular endothelium and keratinocytes, increased oxidative stress and common inflammatory pathways, including key cytokines such as tumour necrosis factor and IL-17 [16, 17]. Upregulation of the renin-angiotensin signalling pathway may also promote the development of more difficult-to-control HBP in patients with psoriatic disease. This hypothesis is supported by the observations of increased expression of the renin gene in lesioned skin of patients with moderate to severe psoriasis compared with matched non-lesioned skin and greater plasma renin activity and increased urinary aldosterone excretion in patients with psoriasis [18]. In relation to this, we have found a positive association between severe forms of psoriasis (PASI > 10 and pustular forms) and polyarticular forms of PsA with this CVRF. However, these associations were only found in the unadjusted univariate model of this study.

When potential confounders were taken into account, only two factors were independently associated with HBP. Thus, we found that for each year of onset of psoriasis above 40 years, the risk of HBP increased by 4%, while for each point of an increase in BMI, this risk increased by 13%. It is obvious that HBP, like other CVRF, is linked to ageing, although the presence of psoriasis would contribute to increasing this risk independently of age. Conversely, weight gain would also contribute to increasing this risk. Ultimately, the increase in CV risk in psoriatic disease, observed in different epidemiological studies of the last decade, is linked not only to the presence of traditional CVRF but also to others partially known and is probably linked to the inflammatory nature of this entity [3, 19].

How can weight gain contribute to the onset of HBP and even contribute to the onset of psoriatic disease? Adipose tissue has ceased to be a mere reservoir of energy and has become a metabolically active tissue with the production, among other substances, of pro-inflammatory cytokines. Visceral obesity and insulin resistance, which are common findings in psoriatic disease, 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. The role of Th17-derived cytokines, in the pathogenesis of obesity and related inflammatory diseases, is increasingly recognised. Supporting the implication of IL-17 in the metabolic syndrome, the levels of IL-17R expression in the liver or muscles have been shown to correlate with insulin resistance, and IL-17 blocking has resulted in the decrease of hepatic inflammation in non-alcoholic steatohepatitis syndrome. These findings demonstrate the close relationships between obesity and inflammation in IL-17-mediated diseases, such as psoriatic disease [3, 19].

Why does arthritis seem to contribute to the risk of HBP above psoriasis alone? It can be speculated in line with the above that in patients with PsA, there are two inflammatory entities (skin and joints) and that this greater inflammatory load could increase the risk of HBP and other elements of the metabolic syndrome. In fact, there are some formal proofs of that [20]. It can also be speculated that patients with PsA tend to receive more NSAIDs and more systemic corticosteroids, which could increase the risk of HBP and other CVRF. However, in our study, it was not clear that NSAIDs or corticosteroids explained a higher frequency of HBP in patients with PsA. Both factors were included in the multivariate model, but were not significant in relation to HBP.

This study has the limitations of a cross-sectional study, so it is difficult to discern the direction of the associations found in it. Further, the relatively small number of subjects for an epidemiological study limits the conclusions that can be drawn. However, this study has not been designed as a controlled epidemiological study to know the prevalence of HBP in our patients, but rather it has been a point-in-time observation of a well-studied cohort of patients with psoriatic disease. Among the strengths of the study is the fact that these patients are periodically evaluated in a rigorous manner and represent practically the entire phenotypic spectrum of both entities.

Cardiometabolic comorbidity is a common companion of psoriasis and PsA. These factors must be evaluated periodically and receive prompt corrective measures. According to the results of this study, clinicians treating psoriatic disease should be rigorous with weight control measures adopted for these patients and be especially alert to the occurrence of HBP in patients whose disease begins after 40 years.

Conclusions

HBP is more common in patients with arthritis within the spectrum of psoriatic disease. Patients with psoriatic disease whose psoriasis has a late onset or those who gain weight should receive special attention to detect and adequately treat HBP.

Compliance with ethical standards

Disclosures None.

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