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Key words

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Abstract

Background: Psoriasis is a very prevalent systemic chronic inflammatory disease. Major cardiovascular events are the main cause of mortality in these patients which suggests an association between psoriasis and traditional cardiovascular risk factors.

Objective: Identify classic cardiovascular risk factors and metabolic syndrome (MS) in patients with psoriasis, their possible association with its severity and compare it with the non-psoriatic population.

Methods: This is an observational and cross-sectional population study in Lleida (Spain) from a joint hospital / primary care database.

Results: The database comprised 398,701 individuals. There were 6,868 cases registered as psoriasis (1.7%), and 499 of them (7.3%) were classified as moderate-severe psoriasis. Patients with psoriasis had a higher prevalence of traditional cardiovascular risk factors than non-psoriatic population: diabetes mellitus 2 (13.9% vs 7.4%, OR 2.01), dyslipidemia (28.8% vs 17.4%, OR 1.92), arterial hypertension (31.2% vs 19.0%, OR 1.93), obesity (33.7% vs 28.1%, OR 1.30), altered fasting basal glycaemia (21.4% vs 15.1%, OR 1.54), low cholesterol-HDL (38.1% vs 32.3%, OR 1.29), hypertriglyceridemia (45.7% vs 35.2%, OR 1.55) and high waist circumference (75.7% vs 72.3%, OR 1.19). MS was more prevalent in psoriatic patients (28.3% vs 15.1%, OR 2.21) and cardiovascular risk factors were similar between psoriasis severity groups. Psoriatic patients had a higher prevalence of ischemic heart disease (3.3% vs 1.8%, OR 1.87) and vascular-cerebral accidents (1.8% vs 1.2%, OR 1.55). A model for MS showed a significant non-linear relationship with age and sex, and significant differences between patients with and without psoriasis. Conclusion: We found statistically differences in relation to the prevalence of cardiovascular risk factors, MS and major cardiovascular events in psoriatic patients. However, differences were not seen between psoriasis severity groups. Our work reinforces the need for a multidisciplinary approach and close monitoring of cardiovascular risk factors in these patients to prevent a cardiovascular event.

Introduction

Psoriasis is a very prevalent chronic inflammatory disease[1]. In recent years this disease has been associated with several comorbidities, and nowadays, it is considered a

systemic inflammatory disease. Major cardiovascular events are the main cause of mortality in patients with psoriasis[2], which suggests that there are associations between psoriasis and traditional cardiovascular risk factors. It has been described a link between psoriasis and obesity[3], dyslipidemia[4], diabetes mellitus 2 (DM2)[5] and hypertension[6]. This association is probably due to genetic, environmental and immunological factors, such as Th1 and Th17 pathway activation, proinflammatory cytokines and increased oxidative stress. All these factors induce endothelial dysfunction[7,8], which promotes leucocyte adhesion and favor a prothrombotic state[9]. Regarding the metabolic syndrome (MS), a systemic inflammatory and prothrombotic disease, a recent meta-analysis confirmed a strong association between this syndrome and psoriasis (OR 2.14; 95% CI 1.84–2.48)[10]. All this would lead to a higher cardiovascular disease mortality in psoriasis (OR 1.37: 95% CI 1.17-1.60), myocardial infarction (OR 3.04, 95% CI, 0.65-14.35) and stroke (OR 1.59, 95% CI, 1.34-1.89)[11]. This risk seems to be higher in patients with severe psoriasis[12].

Since not all studies confirm a link between psoriasis and cardiovascular risk factors, this topic is still controversial. Furthermore, most studies were conducted in the USA, northern Europe and Asia[10], regions where culture, diet and other risk factors for metabolic and cardiovascular disease are different from the Mediterranean region. We decided to conduct a population study in Lleida, Catalonia, in the Northeast of Spain. Conclusive results of an association between cardiovascular risk factors and psoriasis would reinforce the need for a multidisciplinary assessment of these patients, not only by the dermatologist, as well as a modification of their lifestyle and a strict cardiovascular risk management.

Objectives

1) Obtain the prevalence of MS and classical risk factors: hyperglycemia and DM2, hypercholesterolemia, decreased cholesterol-HDL, hypertriglyceridemia, increased abdominal perimeter and arterial hypertension in patients with psoriasis (subdivided into severity groups) and control population.
2) Calculate the percentage of major cardiovascular events (acute myocardial infarction and stroke) in the psoriasis group and compare it to the non-psoriatic group.
3) Analyze the probability of MS depending on sex, age, psoriasis diagnosis and severity.

Material and methods

This is an observational and cross-sectional population study on electronic records of residents in the province of Lleida, Catalonia, Spain. Databases from Primary Care and the Dermatology department of the Hospital Universitario Arnau de Vilanova de Lleida (the only Dermatology department in the province) were collected in June 2016, provided by the "Unitat de Recerca de l'Institut Català de Salut" of Lleida (UR-ICS-Lleida). From the resulting database, duplications were eliminated and the records with the diagnosis of cutaneous psoriasis (L40) were selected. The UR-ICS-Lleida built the final database, erasing identifiers. The cases were assigned an internal code the UR-ICS-Lleida knows and that allowed to review or to verify the information of each register if it were necessary. This dissociated database (anonymous for researchers) only contained variables relevant to the study. These variables included sex, age, height, weight (to obtain the body mass index), diagnosis of psoriasis, drugs used for the treatment of psoriasis, cardiovascular risk factors such as DM2 (E11), hypertension (I10), hypercholesterolemia (E78.0), decreased HDL (E78.6) and hypertriglyceridemia

(E78.1) and major cardiovascular disease: acute myocardial infarct (I21, I22) and stroke (I63).

Diagnostic criteria of classical cardiovascular risk factors and MS are summarized in tables 1 and 2 and the lack of data in a MS criterion was considered a non-pathological value.

Since BSA and PASI are not usually registered in Primary Care, we defined moderate-severe psoriasis according to the treatment prescribed. This method has been used previously by some authors[13]. Each subject was registered as a moderate-severe psoriatic patient when he or she had been treated with narrowband UVB (NB-UVB), psoralen and ultraviolet A (PUVA), traditional systemic drugs (acitretin, methotrexate or cyclosporine) or biological therapy (infliximab, etanercept, adalimumab, ustekinumab, secukinumab or ixekizumab), defining the rest as mild psoriasis. The study was approved by the "Hospital Arnau de Vilanova de Lleida ethics committee" (CEIC-1655).

The anonymized database was captured and analyzed with SPSS v24.0 software (IBM Corporation, Armonk, NY, USA). Comparisons of proportions and ranges of variables between different groups were performed by Chi-square, Student's *t*-test, or One-Way ANOVA as appropriate. The calculated Odds Ratios compared the occurrence of each cardiovascular risk factor or major cardiovascular event in the presence or absence of psoriasis. The selected p value for considering differences as statistically significant in all analyses was $p < 0.05$.

A model to assess the association between metabolic syndrome and having a psoriasis diagnosis once adjusted by the relationship with age and sex was modeled by multivariable logistic regression model. Non-linear association with age was allowed by using natural cubic splines. The existence of first and second order interactions was also

assessed. Statistical contribution of variables or interaction terms was assessed by likelihood ratio test. Model calibration and discrimination was assessed by Hosmer-Lemeshow test and AUC estimation. A graphic was drawn to facilitate the interpretation of the resulting model (Fig. 1). A second model was fitted with the psoriasis diagnosis graded in three levels: none, mild or moderate/severe (Fig. 2). A significance level of 0.05 and the software R14 were used.

Results

The joint hospital / primary care database collected a total of 398,701 individuals. The mean age was 42.34 years and the percentage of males was 50.7%. We obtained 6,868 patients (1.7% of the population) catalogued as psoriatic (55.3% were males). Male prevalence of psoriasis was 1.9% and in women was 1.6%. There were 499 patients whose psoriasis was classified as moderate-severe (7.27% of patients with psoriasis).

Firstly, prevalence and odds ratio of classical cardiovascular factors was calculated comparing psoriatic and non-psoriatic population (table 3.a). The psoriasis group had a higher prevalence of DM2 (13.9%; OR 2.01, 95% CI: 1.87-2.15, p <0.001); dyslipidemia (28.8%; OR 1.92, 95% CI: 1.82-2.03, p <0.001); arterial hypertension (31.2%; OR 1.93, 95% CI: 1.83-2.03, p <0.001) and obesity (33.7%; OR 1.30, 95% CI: 1.22-1.39, p <0.001). In this first statistical evaluation, the lack of any pathological data was considered as a non-pathological individual according to each criterion.

The occurrence of major cardiovascular events was studied in patients with psoriasis and non-psoriatic population (table 3.b). The history of ischemic heart disease was evidenced in 229 patients with psoriasis (3.3%) (OR 1.87, 95% CI: 1.63-2.13, p <0.001). In relation to vascular-cerebral disease, the proportion was higher in patients

with psoriasis (1.8%) than in the non-psoriatic population (OR 1.55, 95% CI: 1.29-1.86, p <0.001).

In order to demonstrate the accuracy of these data, a further analysis focusing on MS was performed. This evaluation only included individuals who had at least one recorded data (whether pathological or not), and not all the individuals from the psoriasis and non-psoriasis groups. MS was more prevalent in the psoriasis group (28.3% vs 15.1%), with an OR of 2.21 (95% CI: 2.10-2.33, p<0.001). All of the MS criteria were analyzed individually (table 3.c) and were also more prevalent in the psoriasis group. Focusing on major cardiovascular events in patients with MS, a 7.4% of these patients presented an acute coronary event and 4.3% had suffered a vascular-cerebral disease.

Moreover, the prevalence of MS, other classic cardiovascular risk factors and cardiovascular major events were studied depending on psoriasis severity. In this case, the proportion of these diagnoses was not higher in the moderate-severe psoriasis group, and only a tendency was seen between a more severe disease and prevalence of metabolic syndrome(table 4).

The model for metabolic syndrome included the variables sex, age and psoriasis diagnosis. The resulting model showed a significant non-linear relationship with age and only one significant interaction, the one between sex and the non-linear effect of age, modeled by natural cubic splines of 3 degrees of freedom. No significant interaction was obtained with psoriasis diagnosis. Thus, the non-linear association between age and the metabolic syndrome was significantly different for men and women, as shown in figure 1. This figure shows the estimated probability of metabolic syndrome in association with age for the groups defined by the combinations of sex and psoriasis diagnosis. Both models, the one for psoriasis diagnosis and the other one for

psoriasis grade showed good calibration (predicted and observed probabilities were very close to each other) and good discrimination, both with a 0.855 area under the curve.

Figure 1 shows the predicted probability of metabolic syndrome depending on age, sex and psoriasis diagnosis. A non-linear association with age that is dependent on sex was identified. Significant differences in the estimated probability of metabolic syndrome between patients with and without psoriasis already appear around the age of 30 years, showing higher probabilities in patients with psoriasis, men or women. Besides, men with psoriasis diagnosis showed a significantly higher probability of metabolic syndrome than women with psoriasis till the age of almost 70 years, were estimated probabilities became very similar. Women older than around 75 years old showed increasing estimated probabilities of metabolic syndrome, in contrast with men, who showed an inflexion point around that age and a decreasing estimated trend from that age. This inflexion point is common to non-psoriasis patients. The OR of metabolic syndrome for psoriasis vs. non-psoriasis patients (the only variable in the model showing an additive effect) was 1.60, with 95%CI=[1.51, 1.70]. Thus, for example, if we try to estimate the probability of metabolic syndrome for a 52-year-old patient (the median age of patients with psoriasis), the expected probability of metabolic syndrome is 0.16 if a woman without psoriasis, 0.20 if it a man without psoriasis, 0.23 if a women with psoriasis and 0.29 if a man with psoriasis. These differences are increased for older ages, and for a 66-year-old patient these estimates are 0.36, 0.39, 0.47 and 0.51, respectively.

Figure 2 shows the predicted probability of metabolic syndrome depending on age, sex and psoriasis grade of severity, it is, with the partition of the group of patients with a diagnosis of psoriasis into two groups of mild and moderate/severe psoriasis. Although estimated probabilities are higher for the moderate/severe psoriasis group in both, men

and women, their confidence intervals are overlapped. This overlap is consequence of the wide confidence interval obtained from the small number of patients with moderate-severe psoriasis. The OR of metabolic syndrome of mild psoriasis vs. non-psoriasis patients and for moderate/severe psoriasis vs. non-psoriasis (the only variable in the model showing an additive effect) was 1.58, with 95%CI=[1.48, 1.68] and 1.94 with 95%CI=[1.56, 2.39], respectively. No significant differences were observed, independently of patient age, between the probabilities of metabolic syndrome for mild versus moderate/severe psoriasis patients.

Discussion

In our study, statistically significant differences were found in relation to the prevalence of cardiovascular risk factors in patients with psoriasis, presenting a higher frequency of DM2, dyslipidemia, hypertension and obesity. In this first statistical evaluation, the lack of any pathological data was considered as a non-pathological individual according to each criterion. We know individuals with these factors have a higher rate of cardiovascular events such as a heart attack or stroke, which are the main cause of death in patients with psoriasis and this association has already been objectified in multiple studies (table 5). Since it seems to be an association between DM2, dyslipidemia, hypertension, obesity and psoriasis, some authors suggest that there is an early common pathogenesis (involving several adipokines and inflammatory cytokines) both in the cutaneous disease and in the other risk factors[15].

In addition, the proportion of MS in the population with psoriasis was also higher than in the general population and we designed a model which predicted the probability of MS that showed a significant non-linear relationship with age, sex and psoriasis.

Our results were slightly smaller than other similar published studies (table 6), although some other authors did not find this association (25.81% vs 21.02%, p> 0.05)[16]. Our data was obtained from a joint database between hospital and primary care and includes one of the largest series ever published related to psoriasis and cardiovascular risk factors in Mediterranean regions, a factor that is increasingly involved in cardiovascular morbidity and mortality. We believe this makes the sample of individuals more representative of the population and the fact that this evaluation only included individuals who had at least one recorded data, whether pathological or not, may be more reliable. It should be considered that carrying out prevalence studies in different populations with a similar methodology would help us to assess which factors influence in the variability of the results obtained.

Analogously, we obtained a higher prevalence of each MS diagnostic criteria (altered fasting glycemia, altered blood pressure, low HDL, hypertriglyceridemia and altered waist circumference) in psoriasis patients, which reinforces the close association and burden of cardiovascular morbidity in this cutaneous disease.

It would be interesting to investigate in future studies whether there is also a correlation between these parameters and other comorbidities associated with psoriasis such as non-alcoholic fatty liver disease (NAFLD). This entity, which according to some authors is closely linked to obesity and metabolic syndrome, is the most prevalent liver disease[17] and its incidence is increased in patients with psoriasis[18]. Due to the risk of hepatocarcinoma from NAFLD, it would be appropriate to assess whether there is a carcinogenic risk from psoriasis itself or a negative influence of skin lesions on lifestyle.

Moreover and surprisingly, no statistically significant differences were found between a higher severity of psoriasis and a greater association with cardiovascular risk factors,

and there was only a tendency between psoriasis severity and MS prevalence (1.18, 95% CI: 0.97-1.44, p=0.099). Some authors obtained a greater risk of MS in patients with psoriasis than general population (OR 1.91; 95% CI 1.47-2.49)[19]. These authors also classified psoriasis severity depending on their treatment and moderate-severe psoriasis prevalence calculated is similar, so we think that geographical or cultural factors could explain these differences. Curcó et. al. could neither find an association, even though a link between psoriasis severity and diabetes mellitus was described[20].

Focusing on the risk of major cardiovascular risk events in psoriasis, Parisi et. at. did not find this link in a Manchester cohort study (2.59% vs 2.30%)[21], as well as in a recent meta-analysis which neither found an association with cerebrovascular disease (OR 1.1; CI 0.9-1.3). On the contrary, an increased risk of ischemic heart disease in psoriasis patients (OR 1.5; 95% CI 1.2-1.9) was obtained[22]. Our data corroborate the increased risk of suffering a major cardiovascular event in patients with psoriasis, both ischemic heart disease (OR 1.87, 95% CI: 1.63-2.13, p <0.001) and cerebrovascular disease (OR 1.55, 95% CI: 1.29-1.86, p <0.001). The hypothesis that a chronic inflammatory disease such as psoriasis may have an independent role in the pathogenesis of a cardiovascular event is not unreasonable, and many authors have linked systemic inflammatory diseases such as rheumatoid arthritis, systemic lupus erythematosus or inflammatory bowel disease with an increased cardiovascular risk[20,23-25]. More publications should be performed to elucidate this topic.

Limitations

The main limitations of this study are those inherent in a cross-sectional population study, such as the lack of data from some patients. In addition, since it is a study focused on the MS, smoking was not included. Similarly, medications for

cardiovascular risk factors such as anti-diabetic or lipid-lowering drugs were not considered, so there could be patients without a coded diagnosis which would be excluded.

Conclusion

Taking into account the data presented above and the review of previous publications regarding the relation between psoriasis, MS and cardiovascular risk factors, we suggest that our work reinforces the need for close monitoring of cardiovascular risk factors in patients with psoriasis which are often only visited by the dermatologist[2] to prevent a major cardiovascular event. Further studies would help us to discern if psoriasis really acts as an independent factor and it would also be interesting to assess whether an adequate management of the cutaneous disease would help to control other risk factors or reduce its cardiovascular risk in the long term.

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