Acta Dermatovenerol Croat 2015;23(1):28-35 CLINICAL ARTICLE

Cardiovascular Risk Factors in Patients with Chronic Plaque Psoriasis: A Case-control Study on the Brasov County Population

Marius Irimie[1], Alexandru Oanță[1], Claudia Alexandrina Irimie[2], Lazslo Gyula Fekete[3], Dan Ioan Minea[4], Alina Pascu[5]

[1]Department of Dermatology, Transilvania University, Braşov, Romania; [2]Department of Endocrinology, Transilvania University, Braşov, Romania; [3]Department of Dermatology, University of Medicine and Pharmacy, Târgu Mureş, Romania; [4]Department of Neurology, Transilvania University, Braşov, Romania; [5]Department of Pathophysiology, Transilvania University, Braşov, Romania

Correspondending author:
Marius Irimie, MD, PhD
40, Zizinului Street
Braşov 500414
Romania
marius_irimie2002@yahoo.com

Received: April 6, 2014
Accepted: January 15, 2015

ABSTRACT Many studies have suggested that cardiovascular risk factors seem to be more common in patients with psoriasis than in the general population. In this study we aimed to determine the prevalence of cardiovascular risk factors in patients with chronic plaque psoriasis depending on the severity of disease. We conducted a prospective study in Braşov County (Romania) including 142 patients with chronic plaque psoriasis and disease duration of at least six months and 167 controls without psoriasis. The severity of psoriasis was assessed using the psoriasis area and severity index (PASI) score. Along with a thorough medical history and physical examination, serum lipid profile and fasting plasma glucose tests were carried out. The 10-year Framingham risk score (FRS) for general cardiovascular disease, which includes age, gender, total cholesterol, HDL-cholesterol, systolic blood pressure, smoking status, and diabetes mellitus, was applied. The severity of chronic plaque psoriasis was mild in 32 patients (22.53%) and moderate to severe in 110 patients (77.47%). We found a significant higher prevalence of metabolic syndrome in the patient group compared to controls. Individual components of metabolic syndrome like waist circumference, elevated triglycerides, reduced HDL-C, impaired fasting plasma glucose, and arterial hypertension were also more prevalent in patients than in controls. Mean triglycerides, total cholesterol, LDL-cholesterol and HDL-cholesterol levels were significantly raised in patients with psoriasis when compared to controls. The 10-year FRS was significantly higher in patients with psoriasis than in controls (8.36±5.75 vs. 6.61±4.13; $P<0.001$). FRS was higher in men ($P=0.012$) and in patients older than 50 years ($P=0.008$). According to the severity of psoriasis, FRS increases significantly from mild to moderate-to-severe psoriasis (6.82±4.48 to 8.8±6.71; $P=0.003$). Psoriasis, and especially moderate to severe psoriasis, seems to represent a risk factor for cardiovascular disease. Patients with psoriasis should be risk-assessed for cardiovascular diseases, and comorbidities should be actively managed.

KEY WORDS: psoriasis, cardiovascular risk, diabetes, obesity, dyslipidemia, metabolic syndrome, smoking

Acta Dermatovenerol Croat
2015;23(1):28-35

INTRODUCTION

Psoriasis is one of the most common dermatological diseases, with a prevalence of about 1-3% in the general population (1). In addition to the skin manifestations that affects the physical, social, and psychological aspects of the life of patients with psoriasis, other systemic diseases can also constantly occur in these patients. Comorbidities classically associated with psoriasis are arthritis, digestive inflammatory diseases (Crohn's disease, ulcerative colitis), and depressive psychiatric disorders. In recent years, the list of co-morbidities has expanded to include arterial hypertension (AH), obesity, metabolic syndrome (MS), diabetes mellitus (DM), and dyslipidemia, which are known as traditional risk factors for cardiovascular disease (2-5); but psoriasis itself and the systemic treatment of psoriasis may also stimulate premature atherogenesis, increasing the cardiovascular risk (6). We conducted a prospective observational case-control study to determine the prevalence of cardiovascular risk factors in patients with chronic plaque psoriasis.

PATIENTS AND METHODS

Between June 2012 and December 2013, 142 patients with chronic plaque psoriasis aged between 18 and 82 years, 75 men and 67 women, with a mean age of 49.51±18.26 years and M/F ratio of 1.12 were included in study. Additionally, 167 patients with similar age and gender characteristics as the study group (aged between 18 and 79 years; mean age of 47.87±16.43 years, 88 men and 79 women; sex ratio M/F=1.11) were included in the control group consisting of patients without psoriasis. Patients in both groups were recruited from in- or out-patients from the Dermatology Department of the County Emergency Hospital of Brasov, Romania. For assessment of cardiovascular risk factors according to age, patients of both groups were divided into two categories: under and over 50 years. All the patients with psoriasis underwent clinical and histopathological diagnosis for chronic plaque type psoriasis. The severity of psoriasis was assessed using the psoriasis area and severity index (PASI) score. Psoriasis was considered mild if the PASI score was lower than 10, and moderate-to-severe if PASI was over 10 (7). Data about age at psoriasis onset and previous therapy were also collected.

Exclusion criteria were history of renal or liver failure, hypothyroidism, and systemic therapy for psoriasis or treatment with lipid lowering drugs in the 3 months prior to enrollment in order to eliminate factors influencing the serum lipids levels.

Laboratory investigations along with a thorough medical history and physical examination were carried out to diagnose comorbidities. Blood sampling was performed after an overnight fast to determine serum triglycerides, total cholesterol (TC), high density lipoprotein-cholesterol (HDL-C), low density lipoprotein-cholesterol (LDL-C), and fasting plasma glucose (FPG). Oral glucose tolerance test (OGTT) and determination of glycated hemoglobin A1c were also performed in cases of abnormal levels of fasting blood glucose. Body mass index (BMI) and waist circumference (WC) were calculated in each patient. Diagnosis of obesity was made in patients with BMI ≥30 kg/m2. AH was defined as values of ≥140 mmHg systolic blood pressure and/or ≥90 mmHg diastolic blood pressure, or in cases of documented history of AH when the blood pressure values were normal if case the patient was undergoing an antihypertensive treatment (8). The diagnostic criteria for DM used in this study were: a FPG level of 126 mg/dL (7.0 mmol/L) or higher, or a 2-hour plasma glucose level of 200 mg/dL (11.1 mmol/L) or higher during a 75 g OGTT, or a random plasma glucose of 200 mg/dL (11.1 mmol/L), or glycated hemoglobin A1C ≥6.5% (9). MS was diagnosed by the presence of more than three of the criteria of the International Diabetes Federation (10), i.e. abdominal obesity diagnosed by WC of >94 cm in men and >80 cm in women, plus two of the following criteria: 1) elevated triglycerides ≥150 mg/dl or specific treatment for this lipid abnormality, 2) reduced HDL-C <40 mg/dl in men and <50 mg/dl in women or specific treatment for this lipid abnormality, 3) elevated blood pressure >130/85 mmHg or treatment of previously diagnosed hypertension, and 4) elevated FPG >100 mg/dL or previously diagnosed type 2 DM. Patients classified as smokers were current smokers who smoked a minimum of 15 cigarettes per day for more than 5 years. The 10-year Framingham risk score (FRS) for general cardiovascular disease, which includes age, gender, TC, HDL-C, systolic blood pressure, smoking status, and DM, was applied to patients of both groups. FRS was classified as low (<10% risk), intermediate (10-20% risk) or high risk (>20% risk) (11).

The data were recorded in a database using Microsoft XL and subsequently underwent a descriptive statistical analysis; the test used was the chi-square test. The student's t-test was used to evaluate the differences between groups. The estimated relative risk was calculated using parameter odds ratio (OR). Significance threshold was $P<0.05$.

RESULTS

The severity of chronic plaque psoriasis was mild (mean PASI 8.63±5.43) in 32 patients (22.54%) and

Table 1. Characteristics of study population

Characteristics of study population	Psoriasis n=142	Controls n=167	*P* value
Men/Women	75/67	88/79	NS
Age			
Mean±SD	49.51±18.26	47.87±16.43	NS
<50 years	89 (62.67%)	99 (59.28%)	NS
>50 years	53 (37.33%)	68 (40.72%)	NS
Metabolic syndrome	19 (13.4%)	18 (10.77%)	0.032
Waist circumference (>94 cm in men and >80 cm in women)	55 (38.73%)	61 (36.52%)	0.045
Obesity (BMI≥30 kg/m^2)	41 (28.87%)	39 (23.35%)	0.016
Arterial hypertension (>140/90 mm Hg)	61 (42.3%)	65 (38.9%)	0.032
Triglycerides (≥150 mg/dl)	37 (26.05%)	38 (22.75%)	0.034
Total cholesterol (≥200 mg/dl)	40 (28.17%)	40 (23.95%)	0.026
LDL cholesterol (>100 mg/dl)	43 (30.28%)	42 (25.15%)	0.019
HDL cholesterol(<40 mg/dl in men and <50 mg/dl in women)	27 (19.01%)	31 (18.56%)	0.052
Diabetes mellitus	8 (5.63%)	8 (4.8%)	0.047
Smoking	36 (25.35%)	31 (18.56%)	0.006
10-year FRS			
Mean ± SD	8.36 ± 5.75	6.61± 4.13	<0.001
Low (<10%)	112 (78.87%)	139 (83.23%)	0.020
Intermediate (10–20%)	17 (11.97%)	16 (9.58%)	0.033
High (>20%)	13 (9.15%)	12 (7.18%)	0.035

**P* value <0.05 was considered statistically significant

moderate to severe (mean PASI 17.28±11.86) in 110 patients (77.46%). History of psoriasis ranged from 6 months to 38 years, with a mean of 9.62±6.02 years.

The prevalence rates of cardiovascular risk factors in patients with mild psoriasis, moderate to severe psoriasis, and in controls are presented in Table 1. We found a significant higher prevalence of MS in the patient group, at 13.4% (12.5% and 14.54% in patients with mild and moderate-to-severe psoriasis, respectively) compared to controls 10.77% (OR=1.3; 95% CI: 0.64-2.54, *P*=0.032). Individual components of MS such as WC, elevated triglycerides, reduced HDL-C, impaired FPG, and AH were also more prevalent in cases than in controls (Table 1). We observed a higher prevalence of obesity in patients with psoriasis (28.87%) compared to controls (23.35%) (OR=1.33; 95% CI: 0.79-2.22; *P*=0.016). The prevalence of DM, AH, and smoking was also significantly higher among patients with psoriasis than in controls (OR=1.18, 95% CI: 0.43-3.25, *P*=0.047; OR=1.18; 95% CI: 0.75-1.86, *P*=0.032 and OR=1.5; 95% CI: 0.86-2.56, *P*=0.006, for DM, AH and smoking, respectively).

The mean values of triglycerides, TC, LDL-C, and HDL-C in the patients with mild, moderate to severe psoriasis, and the control group are shown in Table 2. Plasma triglyceride levels in patients with psoriasis were significantly raised compared with those of the controls (163.21±56.72 and 109.47±45.29 mg/dL, respectively) (*P*<0.001). Serum TC levels were significantly increased in the patient group (223.42±142.72 mg/dL) when compared to controls (204.3±82.51 mg/dL) (*P*<0.01). LDL-C levels in the patient group were 118.62±36.79 mg/dL and 104.26±31.86 mg/dL in controls, this difference being statistically significant (*P*<0.05). HDL-C levels among patients with psoriasis were lower compared with those of the controls (44.63±11.39 mg/dL and 52.46±8.65 mg/dL, in patients and controls, respectively) (*P*<0.01).

The 10-years FRS was significantly higher in patients with psoriasis than in controls (8.36±5.75 vs. 6.61±4.13; *P*<0.001) (Table 1). FRS was higher in men (Figure 1) and in patients older than 50 years (Figure 2). According to the severity of psoriasis, FRS increased significantly from mild to moderate-to-se-

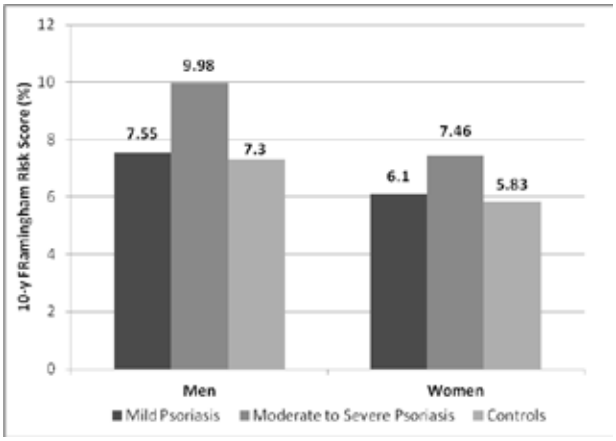

Figure 1. 10-years Framingham Risk Score according to severity of psoriasis and gender

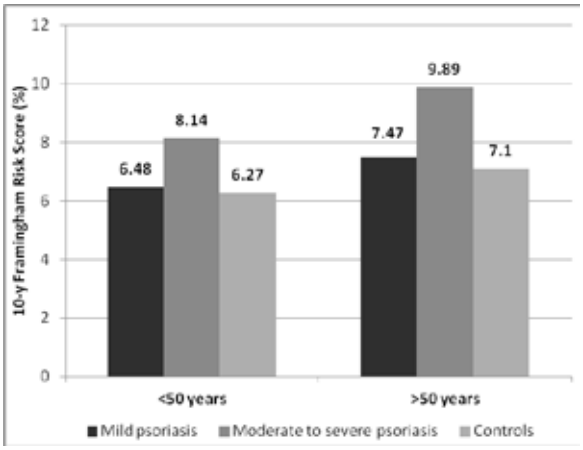

Figure 2. 10-years Framingham Risk Score according to severity of psoriasis and age

vere psoriasis (6.82±4.48 to 8.8±6.71; *P*=0.003). There was no correlation between duration of psoriasis and cardiovascular risk score (OR 1.02, 95% CI: 0.005-0.34; *P*=0.617). Because of the young age of our populations, the majority of patients had a low cardiovascular risk (78.87% and 83.23% for the patients group and controls, respectively; *P*<0.001). However, a higher proportion of patients with psoriasis compared with controls had intermediate and high cardiovascular risk levels (11.97% and 9.15% for the patient group, 9.58% and 7.18% for controls, *P*<0.001) (Table 1).

DISCUSSION

An increasing number of epidemiological studies continues to demonstrate that cardiovascular diseases and their associated risk factors are more common in patients with psoriasis than in the general population (2,12-15). The association between psoriasis and cardiometabolic comorbidities may arise from a genetic predisposition, but may also be the consequence of specific lifestyles including smoking, alcohol consumption, and sedentary habits (16). Biological mechanisms involved in cardiovascular diseases in patients with psoriasis are still largely unknown but their action seems to be multifactorial (6). Recent advances in understanding of the immunopathogenesis and genetics of psoriasis have changed the focus from treating it as a single organ disease confined to skin structures to approaching it as a systemic inflammatory condition (17,18). Systemic inflammation has also been shown to be an independent cardiovascular risk factor (19). Systemic inflammation and hypercoagulability predispose to atherothrombosis and seem to be important features of MS (20-22). One hypothetical mechanism linking psoriasis, MS, and cardiovascular disease centers on chronic Th 1 and Th 17 inflammation (23,24). Pro-inflammatory cytokines such as TNF-α, interleukin-1, and interleukin-6 seem to play a central role (21,25,26). TNF-α induces oxidative stress, which exacerbates pathological processes leading to oxidized LDL-C and dyslipidemia, glucose intolerance, insulin resistance, AH, endothelial dysfunction, and atherogenesis (27,28). Currently, elevated homocysteine levels are also considered an independent risk factor for cardiovascular disease, cerebrovascular disease, and peripheral vascular disease (29,30). Whereas patients with psoriasis seem

Table 2. Comparison of lipid profile between patients with psoriasis and controls (values are expressed as mean±SD)

Parameters	Psoriasis			Controls	*P* value
	Mild n=32	Moderate to severe n=110	Total n=142	n=167	
Triglycerides (mg/dl)	111.78±39.87	169.72±56.47	163.21±56.72	109.47±45.29	<0.001
Total cholesterol (mg/dl)	217.87±38.2	224.69±79.87	223.42±142.72	204.3±82.51	<0.01
LDL-Cholesterol (mg/dl)	104.13±28.92	119.85±34.52	118.62±36.79	104.26±31.86	<0.05
HDL-Cholesterol (mg/dl)	49.8±7.18	44.12±9.16	44.63±11.39	52.46±8.65	<0.01

**P* value <0.05 was considered statistically significant

to have higher homocysteine levels, hyperhomocysteinemia may be considered another aspect that contributes to the increased risk of cardiovascular disease (31,32).

Lifestyle factors such as smoking, alcohol consumption, sedentary lifestyle, and systemic psoriasis therapy may influence cardiovascular risk factors and may have a negative direct impact on these risk factors (33). Patients with psoriasis have a decreased quality of life and increased rates of depression so they tend to smoke and drink more than the general population as well as eat excessively, leading to obesity (34,35). Dyslipidemia is one of the major traditional risk factors for cardiovascular disease. The abnormalities in the lipid profile seen in psoriasis patients, in addition to promoting atherosclerosis, might also lead and maintain the inflammatory reaction in the skin (36). It is still controversial whether changes in lipid profile are primary or secondary to psoriasis or perhaps due to medications such as retinoids, cyclosporine, and methotrexate (37,38), while other medications used for psoriasis as TNF α inhibitors have been found to decrease the risk of cardiovascular disease by reducing the inflammation (39). Thus, in our study we evaluated the lipid profile as a predictor of cardiovascular diseases in patients with psoriasis (without treatment) and we found more prevalent lipid abnormalities in patients with psoriasis compared with the control group. Overall, various studies reported serum TC, HDL-C, and LDL-C levels of psoriatic patient as high, low, or normal (2,40,41), thus these lipid profile abnormalities might be genetically determined rather than acquired (42). However, dietary and socioeconomic factors may also explain their high frequency.

The prevalence of MS in general population is estimated between 15% and 24% (43). Psoriasis patients have an increased prevalence of MS that ranges between 14% and 40%, in some studies being almost double compared to that of the control population (44, 45). Our study revealed an overall prevalence of 13.4% of the MS in patients with psoriasis, prevalence that was correlated with psoriasis severity. Psoriasis is a multigenic disease and predisposition to MS in psoriasis may have a genetic component (46). Several genetic studies showed a significant association between psoriasis and CDKAL1 gene implicated also in DM (47).

Azfar *et al.* (48) found psoriasis as an independent risk factor for type 2 DM, the risk being greatest in patients with severe disease. The appearance of DM in psoriasis patient depends on duration of psoriasis and the severity of the systemic inflammation (49). Overproduction of Th 1 cytokines in psoriasis seems to increase insulin resistance (15). Another factor that may interfere with the development of diabetes in psoriasis is the use of topical corticosteroids for long periods.

A significant association between obesity and psoriasis was noted. Compared with control population, the psoriasis patients in our study had a significant higher prevalence of obesity. The relationship between psoriasis and obesity is thought to be bidirectional with psoriasis increasing the risk of obesity and obesity predisposing patients to psoriasis (50).

Psoriasis has been found to be an independent associated with AH (15). The mechanisms of relationship between psoriasis and AH are not clear established. Elevated plasma renin activity, elevated angiotensin-converting enzyme activity, and elevated endothelin-1 in patients with psoriasis could contribute to poor blood pressure control (51, 52).

Cardiovascular events occur more frequently in patients with severe psoriasis and long disease duration (41). Considering the importance of association of cardiovascular events with psoriasis severity, we assessed cardiovascular risk factors in patients with mild and moderate to severe psoriasis. In the group with mild psoriasis the assessed parameters had mean values close to those of the control group, whereas in patients with moderate to severe psoriasis the frequency of cardiovascular risk factors increased compared with the control group. FRS is a validated tool to predict the absolute risk of cardiovascular events at 10 years in adults by stratifying patients into 3 risk categories: low (<10% risk), intermediate (10% to 20%), and high (>20%) (11). We found that FRS is significant higher in patients with chronic plaque psoriasis than in age and gender matched controls. The risk was higher in patients older than 50 years, in men compared to women, and in patients with moderate to severe psoriasis. Armstrong *et al.* (53) found that mild psoriasis is associated with a significantly increased risk of myocardial infarction (RR 1.29; 95% CI: 1.02-1.63) and stroke (RR 1.12; 95% CI: 1.08-1.16), and severe psoriasis was associated with a significantly increased risk of myocardial infarction (RR 1.70; 95% CI: 1.32-2.18), stroke (RR 1.56; 95% CI: 1.32-1.84), and cardiovascular mortality (RR 1.39; 95% CI: 1.11-1.74). Mehta *et al.* (54) considers that severe psoriasis to confer an additional 6.2% attributable risk on a 10-year incidence of major adverse cardiac events. Psoriasis was also found to be an independent risk factor for mortality (OR 1.86; 95% CI: 1.56-2.21) (55).

The limitations of our study are that it was a descriptive study in which disease and exposure were

measured simultaneously in our study population, and the group of patients with psoriasis represented, in a high proportion, patients with moderate to severe disease who attend our hospital in Brasov (Romania).

CONCLUSION

Psoriasis, especially moderate to severe psoriasis, seems to represent a risk factor for cardiovascular diseases. This could be due to an increased prevalence of traditional cardiovascular risk factors in people with psoriasis, the effect of chronic inflammation in patients with psoriasis, or a combination of both factors. Patients with psoriasis should be risk-assessed for cardiovascular diseases, and comorbidities should be actively managed.

References

1. Langley RG, Krueger GG, Griffiths CE. Psoriasis: epidemiology, clinical features, and quality of life. Ann Rheum Dis 2005;64(suppl):ii18-ii23.
2. Mallbris L, Akre O, Granath F, Yin L, Lindelöf B, Ekbom A, *et al.* Increased risk for cardiovascular mortality in psoriasis inpatients but not in outpatients. Eur J Epidemiol 2004;19:225-30.
3. Mallbris L, Ritchlin CT, Stahle M. Metabolic disorders in patients with psoriasis and psoriatic arthritis. Curr Rheumatol Rep 2006;8:355-63.
4. Robinson D, Bala M, Wu Y, Kimball A. Increased prevalence of cardiovascular risk factors among psoriasis patients – results from two large healthcare databases. J Am Acad Dermatol 2006;54(suppl): AB203.
5. Akcali C, Buyukcelik B, Kirtak N, Inaloz S. Clinical and laboratory parameters associated with metabolic syndrome in Turkish patients with psoriasis. J Int Med Res 2014;42:386-94.
6. Dommasch ED, Troxel AB, Gelfand JM. Major cardiovascular events associated with anti-IL 12/23 agents: a tale of two meta-analyses. J Am Acad Dermatol 2013;68:863-5.
7. Mrowietz U, Kragballe K, Nast A, Reich K. Strategies for improving the quality of care in psoriasis with the use of treatment goals – a report on an implementation meeting. J Eur Acad Dermatol Venereol 2011;25:1-13
8. Mancia G, Fagard R, Narkiewicz K, Redon J, Zanchetti A, Böhm M, *et al.* 2013 ESH/ESC Practice Guidelines for the Management of Arterial Hypertension. Blood Press 2014;23:3-16.
9. *** [Guideline] Diagnosis and classification of diabetes mellitus. Diabetes Care 2010;33 Suppl 1: S62-9.
10. http://www.idf.org/metabolic-syndrome; Accesed April 2, 2014.
11. *** Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III) final report. Circulation 2002;106:3143–421.
12. Shaharyar S, Warraich H, McEvoy JW, Oni E, Ali SS, Karim A, *et al.* Subclinical cardiovascular disease in plaque psoriasis: association or causal link? Atherosclerosis 2014;232:72-8.
13. Asokan N, Prathap P, Rejani P. Severity of psoriasis among adult males is associated with smoking, not with alcohol use. Indian J Dermatol 2014;59:237-40.
14. Lakshmi S, Nath AK, Udayashankar C. Metabolic syndrome in patients with psoriasis: A comparative study. Indian Dermatol Online J 2014;5:132-7.
15. Ni C, Chiu MW. Psoriasis and comorbidities: links and risks. Clin Cosmet Investig Dermatol 2014;7:119-32.
16. Gisondi P, Girolomoni G. Psoriasis and atherothrombotic diseases: disease-specific and non-disease-specific risk factors. Semin Thromb Hemost 2009;35:313-24.
17. Reich K. The concept of psoriasis as a systemic inflammation: implications for disease management. J Eur Acad Dermatol Venereol 2012;26 Suppl 2:3-11.
18. Grozdev I, Korman N, Tsankov N. Psoriasis as a systemic disease. Clin Dermatol 2014;32:343-50.
19. Calamita AB, Calamita Z, Braga JC. Risk factors for cardiovascular disease in psoriasis: relation to inflammation assessed by the severity and duration of illness. Inflamm Allergy Drug Targets 2013;12:385-90.
20. Wang Y, Gao H, Loyd CM, Fu W, Diaconu D, Liu S, *et al.* Chronic skin-specific inflammation promotes vascular inflammation and thrombosis. J Invest Dermatol 2012;132:2067-75.
21. Cohen AD, Dreiher J, Shapiro Y, Vidavsky L, Vardy DA, Davidovici B, *et al.* Psoriasis and diabetes: a population-based cross-sectional study. J Eur Acad Dermatol Venereol 2008;22: 585-9.
22. Pirro M, Stingeni L, Vaudo G, Mannarino MR, Ministrini S, Vonella M, *et al.* Systemic inflammation and imbalance between endothelial injury and

repair in patients with psoriasis are associated with preclinical atherosclerosis. Eur J Prev Cardiol 2014 Jun 6. pii: 2047487314538858. [Epub ahead of print].

23. Langan SM, Seminara NM, Shin DB, Troxel AB, Kimmel SE, Mehta NN, *et al.* Prevalence of metabolic syndrome in patients with psoriasis: a population-based study in the United Kingdom. J Invest Dermatol 2012;132:556-62.
24. Balta I, Balta S, Demirkol S, Celik T, Ekiz O, Cakar M, *et al.* Aortic arterial stiffness is a moderate predictor of cardiovascular disease in patients with psoriasis vulgaris. Angiology. 2014;65:74–78.
25. Buerger C, Richter B, Woth K, Salgo R, Malisiewicz B, Diehl S, *et al.* Interleukin-1β interferes with epidermal homeostasis through induction of insulin resistance: implications for psoriasis pathogenesis. J Invest Dermatol 2012;132:2206-14.
26. Gisondi P, Ferrazzi A, Girolomoni G. Metabolic comorbidities and psoriasis. Acta Dermatovenerol Croat 2010;18:297-304.
27. Alpsoy S, Akyuz A, Erfan G, Akkoyun DC, Topcu B, Guzel S, *et al.* Atherosclerosis, some serum inflammatory markers in psoriasis. G Ital Dermatol Venereol 2014;149:167-75.
28. Mehta NN, Li K, Szapary P, Krueger J, Brodmerkel C. Modulation of cardiometabolic pathways in skin and serum from patients with psoriasis. J Transl Med 2013;11:194
29. El-Khairy L, Ueland PM, Refsum H, Graham IM, Vollset SE; European Concerted Action Project. Plasma total cysteine as a risk factor for vascular disease: The European Concerted Action Project. Circulation 2001;103:2544-9.
30. McDonald I, Connolly M, Tobin AM. A review of psoriasis, a known risk factor for cardiovascular disease and its impact on folate and homocysteine metabolism. J Nutr Metab 2012;2012:965385.
31. Brazzelli V, Grasso V, Formara L, Moggio E, Gamba G, Villani S, *et al.* Homocysteine, vitamin B12 and folic acid levels in psoriatic patients and correlation with disease severity. Int J Immunopathol Pharmacol 2010;23:911-6.
32. Richetta AG, Mattozzi C, Macaluso L, Cantisani C, Giancritopforo S, D'eprio S, *et al.* Homocysteine plasmatic status in patients with psoriasis. Eur J Dermatol 2011;21:621-3.
33. Naldi L, Chatenoud L, Linder D, Belloni Fortina A, Peserico A, Virgili AR, *et al.* Cigarette smoking, body mass index, and stressful life events as risk factors for psoriasis: results from an Italian case-control study. J Investig Dermatol 2005;125:61-7.
34. Choi J, Koo JY. Quality of life issues in psoriasis. J Am Acad Dermatol 2003;49:S57-S61.
35. Esposito M, Saraceno R, Giunta A, Maccarone M, Chimenti S. An Italian study on psoriasis and depression. Dermatology 2006;212:123-7.
36. Dsouza PH, Kuruville M. Dyslipidemia in psoriasis: as a risk for cardiovascular disease. Int J Res Med Sci 2013;1: 53-7.
37. Hugh J, Van Voorhees AS, Nijhawan RI, Bagel J, Lebwohl M, Blauvelt A, *et al.* From the Medical Board of the National Psoriasis Foundation: The risk of cardiovascular disease in individuals with psoriasis and the potential impact of current therapies. J Am Acad Dermatol 2014;70:168-77.
38. Micha R, Imamura F, Wyler von Ballmoos M, Solomon DH, Herman MA, Ridker PM, *et al.* Systematic review and meta-analysis of methotrexate use and risk of cardiovascular disease. Am J Cardiol 2011;108:1362-70.
39. Famenini S, Sako EY, Wu JJ. Effect of treating psoriasis on cardiovascular co-morbidities: focus on TNF inhibitors. Am J Clin Dermatol 2014;15:45-50.
40. Wakkee M, Thio HB, Prens EP, Sijbrands EJ, Neumann HA. Unfavourable cardiovascular risk profiles in untreated and treated psoriasis patients. Atherosclerosis 2007;190:1-9.
41. Uyanik BS, Ariz OE, Gunduz K, Tanulka A, Durkan K. Serum lipids and apolipoproteins in patients with psoriasis. Clin Chem Lab Med 2002;40:65-8.
42. Mallbris L, Granath F, Hamsten A, Stahle M. Psoriasis is associated with lipid abnormalities at the onset of skin disease. J Am Acad Dermatol 2006;54:614-21.
43. Hu G, Qiao Q, Tuomilehto J, Balkan B, Borch-Johnsen K, Pyorala K; DECODE Study Group. Prevalence of the metabolic syndrome and its relation to all-cause and cardiovascular mortality in nondiabetic European men and women. Arch Intern Med 2004;164:1066-76.
44. Armstrong AW, Harskamp CT, Armstrong EJ. Psoriasis and metabolic syndrome: a systematic review and meta-analysis of observational studies. J Am Acad Dermatol 2013;68:654-62.
45. Gisondi P, Tessari G, Conti A, Piaserico S, Schiamchi S, Peserico A, *et al.* Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. Br J Dermatol 2007;157:68-73.
46. Li Y, Begovich AB. Unraveling the genetics of complex diseases: susceptibility genes for rheumatoid arthritis and psoriasis. Semin Immunol 2009;21: 318-27.

47. Wolf N, Quaranta M, Prescott NJ, Allen M, Smith R, Burden AD, *et al.* Psoriasis is associated with pleiotropic susceptibility loci identified in type II diabetes and Crohn disease. J Med Genet 2008;45:114-6.
48. Azfar RS, Seminara NM, Shin DB, Troxel AB, Margolis DJ, Gelfand JM. Increased risk of diabetes mellitus and likelihood of receiving diabetes mellitus treatment in patients with psoriasis. Arch Dermatol 2012;148:995-1000.
49. Neimann AL, Shin DB, Wang X, Margolis DJ, Troxel AB, Gelfand JM. Prevalence of cardiovascular risk factors in patients with psoriasis. J Am Acad Dermatol 2006;55:829-35.
50. Carrascosa JM, Rocamora V, Fernandez-Torres RM, Jimenez-Puya R, Moreno JC, Coll-Puigserver N, *et al.* Obesity and psoriasis: inflammatory nature of obesity, relationship between psoriasis and obesity, and therapeutic implications. Actas Dermosifiliogr 2014;105:31-44.
51. Ena P, Madeddu P, Glorioso N, Cerimele D, Rappelli A. High prevalence of cardiovascular diseases and enhanced activity of the renin-angiotensin system in psoriatic patients. Acta Cardiol 1985;40: 199-205.
52. Armstrong AW, Harskamp CT, Armstrong EJ. The association between psoriasis and hypertension: a systematic review and meta-analysis of observational studies. J Hypertens 2013;31:433-42.
53. Armstrong EJ, Harskamp CT, Armstrong AW. Psoriasis and major adverse cardiovascular events: a systematic review and meta-analysis of observational studies. J Am Heart Assoc 2013;2:e000062.
54. Mehta NN, Yu Y, Pinnelas R, Krishnamoorthy P, Shin DB, Troxel AB, *et al.* Attributable risk estimate of severe psoriasis on major cardiovascular events. Am J Med 2011;124:775.e1–e6.
55. Prodanovich S, Kirsner RS, Kravetz JD, Ma F, Martinez L, Federman DG. Association of psoriasis with coronary artery, cerebrovascular, and peripheral vascular diseases and mortality. Arch Dermatol 2009;145:700-3.