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Atheroma plaque, metabolic syndrome and inflammation in patients with psoriasis

Background: Chronic inflammation plays an important role in the development of cardiovascular risk factors. Although the prevalence of comorbidities and cardiovascular events has been described in patients with psoriasis, few studies have examined subclinical atherosclerosis in psoriasis patients. *Objective:* Our objective was to investigate the prevalence of atheroma plaques in patients with severe psoriasis compared with control subjects and to analyze the association with metabolic syndrome, homocysteine levels and inflammatory parameters. *Patients and Methods:* This case-control study included 133 patients, 72 with psoriasis and 61 controls consecutively admitted to the outpatient clinic in Dermatology Departments (Granada, Spain.) *Results:* Carotid atheroma plaques were observed in 34.7% of the psoriatic patients *versus* 8.2% of the controls (p=0.001) and metabolic syndrome was diagnosed in 40.3% of the psoriatic patients versus 13.1% of the controls (p<0.001). Significantly higher mean values of insulin, aldosterone, homocysteine and acute phase parameters (fibrinogen, D-dimer, C reactive protein and erythrocyte sedimentation rate) were found in psoriatic patients. Binary logistic regression showed a strong association between psoriasis and atheroma plaque and metabolic syndrome after controlling for confounding variables. *Limitations:* The absence of longitudinal quantification of metabolic syndrome parameters and intima-media thickness in psoriatic patients. *Conclusion:* The chronic inflammation and hyperhomocysteinemia found in psoriatic patients may explain the association with atheroma plaque and metabolic syndrome. Cardiovascular screening by metabolic syndrome criteria assessment and carotid ultrasound in psoriasis may be useful to detect individuals at risk and start preventive treatment against the development of cardiovascular disease.

Key words: Psoriasis, atherosclerosis, cardiovascular risk factors, metabolic syndrome, comorbidity

Abbreviations:

ATP-III	Adult Treatment Panel III
BSA	Body Surface Area
BMI	Body mass index
BP	Blood pressure
CI	Confident interval
CRP	C reactive protein
ESR	Erythrocyte sedimentation rate
HDL-C	High density lipoprotein Cholesterol
HOMA-IR	homeostasis model assessment of insulin resistance
IMT	Intima-media thickness
LDL-C	Low density lipoprotein Cholesterol
MS	Metabolic syndrome
OR	Odds ratio
PASI	Psoriasis Area and Severity Index

Psoriasis is a chronic, immune-mediated inflammatory skin disease that affects 2-3% of the general population [1]. Psoriasis involves the innate and acquired immune systems with an imbalance Th1/Th2 in favor of a Th1 pattern. Recent advances in immunopathogenesis and the genetics of psoriasis have shifted the focus from a single organ disease confined to the skin to a systemic inflammatory condition. Similarly to other immune disorders, patients with psoriasis have an increased risk of developing cardiovascular disease and metabolic syndrome [2]. Recent research has shown that chronic and systemic inflammation plays a major role in the development of atherosclerosis [3] and there are striking similarities between the molecular and inflammatory pathways in psoriasis and atherosclerosis [4].

Although the prevalence of comorbidities and cardiovascular events has been described in patients with psoriasis *versus* control populations [5, 6], few studies have examined subclinical atherosclerosis in patients with psoriasis [7, 8]. The end point of these studies was to analyze carotid

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artery intima-media thickness (IMT) in patients without risk factors and also it has been suggested that the carotid artery IMT does not always correlate with atherosclerosis, particularly in relatively young individuals with chronic inflammatory disease [9]. Some authors even found that myocardial infarction was more closely correlated with atheroma plaque than with the intima-media thickness [10].
The relative impact of systemic inflammation related to psoriasis on vascular lesions and cardiovascular risk nonetheless remains poorly understood. The end point of this case-control study was to investigate the prevalence of carotid atheromatosis (atheroma plaque) in patients with severe psoriasis in comparison with control subjects and to analyze the association with metabolic syndrome (MS), homocysteine levels and inflammatory parameters.

Material and methods

Patients and controls

This case-control study included 133 outpatients, 72 with severe psoriasis (PASI and BSA > 10) and 61 controls with other dermatological diseases other than psoriasis (mainly nevi, seborrheic keratosis, actinic keratosis or verruca, as reported in other similar studies [11]) from the Dermatology Department of San Cecilio University Hospital, Granada (Spain). Psoriatic and control groups were enrolled during the same time period. No significant differences were recorded according to sex of patients or controls (p=0.70). Diagnosis of psoriasis was based on clinical findings. Inclusion criteria were: age > 18 years for males and females, presence of plaque or erythrodermic severe psoriasis with PASI and BSA higher than 10, without systemic treatment in the last 2 months and signing of informed consent to study participation. Exclusion criteria were: cutaneous lymphomas or other cancers except for non-melanoma skin cancer. Inclusion criteria for controls were: age > 18 years for males and females and signing of informed consent to study participation. Exclusion criteria for controls were the same as described above and the presence of psoriasis. The study was approved by the Ethics Committee of San Cecilio University Hospital and written informed consent was obtained from all patients and controls, according to Helsinki Declaration.

Clinical and laboratory parameters and Doppler ultrasound examination

The severity of psoriasis was determined by application of the Psoriasis Area Severity Index (PASI) and the Body Surface Area (BSA). The weight, height and abdominal circumference of subjects were measured, and their body mass index (BMI, kg/m^2) was calculated. Systolic and diastolic blood pressure (BP) was measured after a 5-min rest and again 10 min later, recording the mean value. Serum aldosterone, triglycerides, HDL-C, LDL-C, total cholesterol, blood glucose, insulin, D-dimer, fibrinogen, erythrocyte sedimentation rate (ESR), C reactive protein (CRP), homocysteine and folic acid levels were studied in samples drawn between 8 and 9 am after a rest period of ≥ 30 min. The homeostasis model assessment of insulin resistance (HOMA-IR index, μU/mg) was calculated (fasting insulin × fasting glucose/22.5). Data were also gathered on age, sex, personal or family history of early cardiovascular disease (< 55 yrs in father and < 65 yrs in mother), personal history of psoriatic arthritis or nail psoriasis, mean time with psoriasis, alcoholism (> 40 g/day), smoking (> 5 cigarettes/day), sedentarism (physical exercise < 30 min/day), diet (sodium intake) and drug intake (antihypertensives, diuretics, hypocholesterolemics or oral antidiabetics). Prevalence of metabolic syndrome was calculated according to ATP-III criteria; MS was defined by the presence of three of the following [12]: abdominal circumference > 102 cm in males and > 88 cm in females; hypertriglyceridaemia > 150 mg/dL, HDL-cholesterol < 40 mg/dL in males and < 50 mg/dL in females, blood pressure > 130/85 mmHg or blood glucose > 110 mg/dL.
Subjects underwent Doppler ultrasound examination with Acuson Antares equipment (Siemens, Berlin, Germany), using 5-10 MHZ transducer with supra-aortic trunk programme and recording with M mode the presence of atheroma plaques (intima-media thickness > 1.5 cm) in common carotids, carotid bulb and internal and external carotids. The bilateral common carotids were scanned longitudinally to measure the intima-media thickness (IMT). Images were obtained from the distal portion of the common carotid artery, 1 to 2 cm proximal to the carotid bulb recording a mean value in left and right side. The two bright echogenic lines in the arterial wall were identified as the intima and media lines. The IMT was measured as the distance from the main edge of the lumen-intima interface to the media-adventitia interface of the carotids *(figure 1)*. Patients and controls were examined in supine or semi-supine position, with the neck extended and the chin turned contralateral to the side being examined. The Doppler system was also used to detect carotid flow anomalies. All ultrasonographic measurements were obtained by a single radiologist and all images of the carotid arteries were recorded on the hard disk of the ultrasound system for subsequent analysis and evaluated by an independent

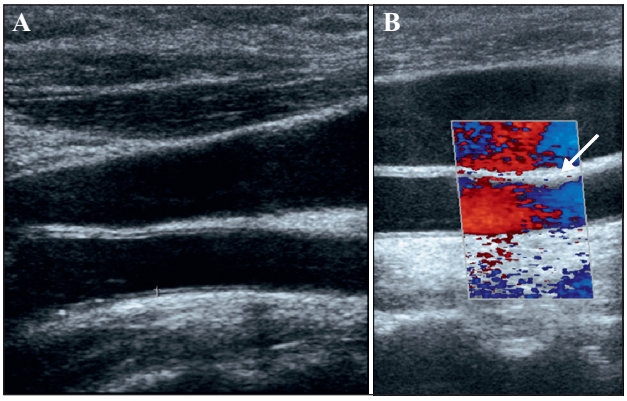

Figure 1. Doppler ultrasound examination.
A) The two bright echogenic lines in the arterial wall were identified as the intima and media lines. The IMT was measured as the distance from the main edge of the lumen-intima interface to the media-adventitia interface of the carotids. **B)** Atheroma plaque in a patient with psoriasis (arrow).

investigator who was unaware of the subjects' clinical status. None of the psoriasis patients or healthy control subjects refused testing.

Statistical analysis

Student's t test was applied to compare mean values of quantitative variables, the Shapiro-Wilk test to examine the normality of their distribution and the Levene test to study the variance. The Mann Whitney U test was used if the variables were not normally distributed. Qualitative variables were analysed with chi-square test or Fisher's exact test if at least one cell had an expected count <5. Correlations among variables were studied by using the Pearson coefficient and binary logistic regression models (Wald method), obtaining estimate-adjusted ORs and their 95% confidence intervals (CI), and were used to measure the association between psoriasis and metabolic syndrome criteria or atheroma plaque in a multivariate analysis. Multiple linear regression analysis was used to predict the independent predictors of IMT. The outcome variable was IMT and the significant predictors in bivariate correlation (age, PASI Score and duration of psoriasis) were included in the model. Standardized coefficient of determination was calculated. Differences were considered significant at $P \leq 0.05$ and nearly significant at $P \leq 0.1$. The SPSS 17.0 programme was used for the data analyses (SPSS, Inc, Chicago, IL).

Results

We studied 72 outpatients (39 male and 33 female) with severe psoriasis (all of them with generalized plaques), all Caucasians. The mean time with psoriasis was 17.64 yrs in the males and 18.72 in the females (p=0.66). The mean PASI value was 19.25 (17.26 *vs* 21.63, p=0.12 for males and females respectively) and BSA was 22.77 (21.86 *vs* 22.87, p=0.97 for males and females respectively). 56.9% of psoriasis patient presented nail psoriasis (56.4% *vs* 57.6%, p=0.91, for males and females) and 34.7% psoriatic arthritis (33.3% *vs* 36.5%, p=0.78 for males and females). Mean age, weight, height, BMI, tobacco, and sedentarism are summarized in *table 1*. No differences in alcohol consumption or diet (sodium intake) were found between groups. The male and female psoriatic groups did not differ in above parameters, while the females showed a lower height (172.87 *vs* 163.60 cm p<0.0001), weight (90.53 *vs* 74.90 kg, p<0.0001) and alcohol consumption (46.2% *vs* 1.2%, p=0.012). No patients or control subjects had previous history of myocardial infarction or cerebrovascular disease.

The control group was formed by 61 outpatients (31 male and 30 female) with other dermatological diseases and without psoriasis. No significant differences were found in antihypertensives (19.4% *vs* 14.7% p=0.31), anticholesterolemics (13.8% *vs* 8.1% p=0.22) or oral antidiabetic intake (12.5% *vs* 6.5% p=0.19) between psoriatic patients and controls respectively. 48.6% of psoriatic patients had a family history of psoriasis *versus* 8.2% of the controls (p<0.0001, OR=10.59 95% CI: 3.80-29.52). 17.4% of the patients with psoriasis presented family history of early cardiovascular disease (<55 yrs in males and <65 yrs in females) *versus* 13.1% of the controls (p=0.32, OR=1.59 95% CI: 0.62-4.11). No significant differences were found in the family histories of early cardiovascular disease between male and female patients with psoriasis (12.8% *vs* 21.2% respectively, p=0.26).

Metabolic syndrome

ATP-III criteria for MS were met by 40.3% of the patients with psoriasis *versus* 13.1% of the controls (p<0.001, OR=4.46 95% CI: 1.85-10.72). The OR for MS was 6.49 (95% CI: 1.68-25.06) for the psoriatic males and 3.25 (95% CI: 1.09-10.62) for the psoriatic females. MS was not significantly more frequent (p=0.88) in the psoriatic males (41%) than in females (39.4%) but was significantly more frequent in the psoriatic patients than in the controls (41% *vs* 9.7% for males, p=0.003 and 39.4% *vs* 16.7% for females p=0.046). Significant differences in MS parameters between psoriatic patients and controls are listed in *table 2*. Male and female psoriatic groups did not significantly differ in the presence of any MS variable or lipid value, with the exception of the abdominal perimeter (p=0.01), LDL-C (p=0.09) and LDL-C/HDL-C (p=0.03), which were higher in the males. Positive significant correlation between MS variables and PASI, BSA and mean time with psoriasis are found in *table 3*. Patients with psoriatic arthritic did not present higher prevalence of MS than patients without psoriatic arthritic (p=0.33). Multivariate studies with binary logistic regression, showed a strong association between

Table 1. Mean (standard deviation, SD) weight, height, age, BMI, mean time with psoriasis, tobacco (%), sedentarism (%) and alcohol consumption (%) in men and women with psoriasis and their respective controls.

	Men		P value	Women		P value
	Psoriasis	Controls		Psoriasis	Controls	
Weight (kg)	90.53 (17.02)	80.25 (11.80)	0.006	74.90 (15.80)	64.66 (13.09)	0.007
Height (cm)	172.87 (9.45)	171.54 (7.40)	0.52	163.60 (7.42)	160.80 (5.21)	0.91
Age (yrs)	46.87 (13.68)	43.54 (12.03)	0.29	45.42 (12.92)	48.43 (8.47)	0.28
BMI (kg/m^2)	30.48 (6.31)	27.25 (3.65)	0.014	28.16 (6.43)	24.95 (4.59)	0.028
Mean time with psoriasis (yrs)	18.64 (10.77)	-	-	18.72 (10.54)	-	-
Tobacco (%)	38.5%	22.6%	0.15	36.4%	10%	0.014
Sedentarism (%)	61.5%	64.5%	0.79	78.8%	60%	0.105
Alcohol (%)	46.2%	29%	0.14	18.2%	10%	0.35

Table 2. Analysis of the ATP-III metabolic syndrome criteria (mean, SD) in men and women with psoriasis and their respective controls. Also LDL-C, total cholesterol, Total Cholesterol/HDL and LDL-C/HDL-C values are listed.

	Men		P value	Women		P value
	Psoriasis	Controls		Psoriasis	Controls	
Abdominal perimeter (cm)	109.28 (16.25)	97.48 (9.6)	0.01	96.66 (12.80)	85.16 (14.37)	0.001
Triglycerides (mg/dL)	130.46 (52.64)	114.16 (57.39)	0.221	43.50 (7.57)	47.07 (8.59)	0.190
HDL-C (mg/dL)	48.82 (13.23)	49.61 (11.24)	0.791	53.33 (15.90)	63.76 (21.91)	0.033
Systolic BP (mmHg)	143.12 (19.67)	123.80 (12.46)	0.0001	139.67 (22.77)	112.0 (12.70)	0.0001
Diastolic BP (mmHg)	87.71 (13.46)	77.03 (9.44)	0.0001	83.45 (11.54)	64.33 (11.04)	0.0001
Blood glucose (mg/dL)	97.56 (26.97)	88.90 (17.17)	0.125	84.15 (13.87)	88.80 (12.20)	0.165
LDL-C (mg/dL)	127.69 (40.08)	117.67 (34.43)	0.273	104.33 (32.39)	112.80 (32.29)	0.304
Total cholesterol(mg/dL)	198.41 (43.91)	186.09 (40.53)	0.232	180.24 (40.98)	191.13 (36.25)	0.148
Total Cholesterol/HDL	4.31 (1.36)	3.95 (1.38)	0.287	3.71 (1.49)	4.71 (6.44)	0.41
LDL-C/HDL-C	2.79 (1.09)	2.50 (1.05)	0.273	2.18 (1.24)	2.87 (4.45)	0.42

Table 3. Correlation (r coefficient and p value, in brackets) between metabolic syndrome variables and PASI, BSA and mean time with psoriasis (N.S.: no significant differences).

	Abdominal perimeter	Triglycerides	HDL-C	Systolic BP	Diastolic BP	Blood glucose
PASI	0.35 (0.0001)	0.19 (0.03)	-0.23 (0.008)	0.36 (0.0001)	0.32 (0.0001)	N.S.
BSA	0.27 (0.002)	0.24 (0.05)	-0.27 (0.02)	0.31 (0.0001)	0.26 (0.002)	0.25 (0.004)
Time with psoriasis	0.33 (0.0001)	N.S.	N.S.	0.42 (0.0001)	0.37 (0.0001)	0.28 (0.001)

psoriatic patients and MS, even after additional adjustment for age, sex, weight, height, tobacco, sedentarism and alcohol consumption (OR=3.45 95% CI: 1.28-9.27, p<0.014, *table 4)*. The MS criteria most frequently recorded in male and female psoriatic groups were abdominal obesity and systolic and diastolic hypertension *(table 5)*.

Carotid atheromatosis

Carotid atheroma plaque was detected in 34.7% of the psoriatic patients *versus* 8.2% of the controls (p=0.001, OR=4.46, 95% CI: 1.85-10.72). It was recorded in 38.5% (OR=9.06 95% CI: 1.81-46.6) of the psoriatic males *versus* 6.5% of male controls (p=0.002) and in 30.3% (OR=3.91, 95% CI: 1.60-15.94) of psoriatic females *versus* 10% of female controls (p=0.047). There was no significant difference in atheroma plaque between male and female psoriatic patients (38.5% *vs* 30.3%, P=0.60). In the group of patients with psoriasis, 45.3% of the plaques were described as fibro-adipose (hyper-hypoechoic) and the remainder as calcified (hyperechogenic). Carotid blood flow abnormalities were detected in only two male patients. The odds ratio for atheroma plaque in patients with psoriasis and metabolic syndrome was 3.53 (95% CI: 1.28-9.76, p=0.013). Patients with atheroma plaque had significantly higher mean abdominal circumference (104.06 *vs* 96.16 cm, p=0.017), hypertriglyceridemia (137.66 *vs* 106.98 mg/dL, p=0.04), systolic BP (146.23 *vs* 126.23 mmHg, P=0.0001) and diastolic BP (87.73 *vs* 76.32 mmHg, p=0.0001). Patients with psoriatic arthritis did not present higher prevalence of atheroma plaques than patients without psoriatic arthritis (p=0.86). Binary logistic regression showed a strong association between psoriatic patients and atheroma plaque, even after additional adjustment for age, sex, weight, height, metabolic syndrome, tobacco, sedentarism and alcohol consumption (OR=7.32 95% CI: 2.00-26.84, p<0.003, *table 6)*.

Patients with psoriasis presented significantly higher carotid intima-media thickness (0.72 *vs* 0.64 mm, p=0.013 for right IMT and 0.72 *vs* 0.65 mm, p=0.042 for left IMT for patients and controls, respectively). There was a positive significant correlation between left and right IMT (r=0.86, p<0.0001). Patients with atheroma plaques presented significantly higher IMT (p=0.003). Males with psoriasis presented significantly higher mean IMT than females with psoriasis (0.77 *vs* 0.67 mm, p=0.049). PASI was positively correlated with right IMT (r=0.19, p=0.029)

Table 4. Binary logistic regression model for metabolic syndrome. The presence of psoriasis and weight were independent factors associated with MS.

Variable	OR	95%CI	P-value
Psoriasis (*vs* control)	3.45	1.28-9.27	0.014
Male sex (*vs* female)	1.58	0.49-5.06	0.44
Age (per year)	1.01	0.96-1.05	0.58
Weight (per kg)	1.05	1.01-1.08	0.01
Height (per m)	0.95	0.89-1.01	0.16
Tobacco	1.56	0.58-4.17	0.37
Sedentarism	0.54	0.19-1.49	0.23
Alcohol consumption	0.79	0.27-2.31	0.67

Table 5. Prevalence of metabolic syndrome criteria (%) in men and women with psoriasis and their respectively controls.

	Men		P value	Women		P value
	Psoriasis	Controls		Psoriasis	Controls	
Abdominal perimeter	61.5%	29%	0.07	75.8%	40%	0.004
Triglycerides	43.6%	22.%	0.066	27.3%	16.7%	0.31
HDL-C	33.3%	22.6%	0.32	30.3%	16.7%	0.20
Systolic BP	66.7%	6.5%	0.0001	60.6%	6.7%	0.0001
Diastolic BP	59%	16.1%	0.0001	42.4%	1.8%	0.0001
Glucose levels	15.4%	9.7%	0.47	3%	10%	0.25

and left IMT (r=0.19, p=0.032). Systolic BP was positively correlated with right (r=0.33, p=0.005) and left IMT (r=0.33, p=0.005). Mean time with psoriasis correlated with right (r=0.22, p=0.009) and left IMT (r=0.25, p=0.003), also age of the patients correlated with right (r=0.58, p=0.0001) and left IMT (r=0.63, p=0.0001). Multiple linear regression analysis showed that age and PASI predicted 0.42 (model R^2) of IMT changes (standardized β for age: 0.62, p=0.0001 and standardized β for PASI: 0.14, p=0.032).

Hormonal study

Patients with psoriasis presented significantly higher mean values of insulin (12.91 *vs* 9.61 μU/mL, p=0.037), aldosterone (267.58 *vs* 205.78 pg/mL, p=0.048) and homocysteine (15.43 *vs* 11.87 μmol/l, p=0.038) for patients and controls, respectively. No significant differences were found in folic acid (11.16 *vs* 10.43 ng/mL, p=0.43), or HOMA-IR index (5.31 *vs* 4.25 μU/mg, p=0.22). Hyperinsulinemia, defined as an insulin level >10.0 μU/mL, was significantly higher in psoriatic patients than in controls (68.1% *vs* 27.9%, p=0.0001, OR=5.51, 95CI%: 2.61-11.64). Psoriatic males and females did not differ in mean values of these hormones (data not shown). Patients with metabolic syndrome presented significantly higher insulin levels than patients without MS (16.45 *vs* 9.48 μU/mL p=0.004). Patients with atheroma plaque presented significantly higher insulin values *versus* those without (14.79 *vs* 10.41 μU/mL p=0.019). There was a significant correlation between insulin levels and all the MS parameters: abdominal obesity (r=0.29, p=0.001), triglycerides (r=0.33, p=0.0001), HDL-C (r=-0.34, p=0.0001), systolic BP (0.23, p=0.04), diastolic BP (0.30, p=0.001), blood glucose (r=0.34, p=0.0001) and aldosterone (r=0.52, p=0.0001). PASI correlated positively with insulin (r=0.23, p=0.008), homocysteine (r=0.34, p=0.02) and negatively with folic acid (r=-0.26, p=0.03).

Table 6. Binary logistic regression model for atheroma plaque. The presence of psoriasis, age and metabolic syndrome were independent factors associated with atheroma plaque.

Variable	OR	95%CI	P-value
Psoriasis (vs control)	7.32	2.00-26.84	0.003
Male sex (vs female)	0.77	0.19-3.05	0.71
Age (per year)	1.11	1.05-1.18	0.0001
Metabolic syndrome	6.83	2.07-22.47	0.002
Weight (per kg)	1.94	0.92-1.98	0.26
Height (per m)	1.08	0.70-1.17	0.35
Tobacco	1.22	0.38-3.88	0.730
Sedentarism	1.29	0.40-4.16	0.667
Alcohol consumption	0.81	0.23-2.81	0.749

Acute phase reactants

Table 7 shows the mean fibrinogen, D-dimer, ESR and CRP values in the study groups. Elevated levels of CRP, fibrinogen and D-dimer were noted in male patients with psoriasis and elevation of all the parameters in females with psoriasis. Female psoriatic patients presented significantly higher values of all these parameters than male psoriatic patients: CRP (1.14 *vs* 0.31 mg/dL p=0.025), ESR (26.7 *vs*7.21 mm/h p=0.0001), fibrinogen (416 *vs* 343.5 mg/dL p=0.005) and D-dimer (236.5 *vs* 131.8 ng/mL, p=0.03). Fibrinogen (383.9 *vs* 319.8 mg/dL P=0.002), D-dimer (233.6 *vs* 109.1 ng/mL, P=0.006), ESR (19.5 *vs* 11.1 mm/h, P=0.04) and CRP (1.04 *vs* 0.22 mg/dL, P=0.016) values were significantly higher in patients with MS than in those without. CPR values (0.93 *vs* 0.31 mg/dL, p=0.007), fibrinogen (372.4 *vs* 327.22 mg/dL p=0.03) and D-dimer (218.6 *vs* 121.3 ng/mL p=0.05) were significantly higher in patients with atheroma plaque than in those without. Elevated CRP values were positively correlated with abdominal obesity (r=0.19, p=0.026), triglycerides (r=0.17, p=0.04), systolic BP (r=0.21, p=0.018) and negatively with HDL-C (r= -0.29, p=0.001). Fibrinogen was positively correlated with abdominal obesity (r=0.26, P=0.003), triglycerides (r=0.19, p=0.027), systolic BP (r=0.24, p=0.007) and diastolic BP (r=0.25, p=0.004). D-dimer was positively correlated with abdominal obesity (r=0.23, p=0.009), triglycerides (r=0.21, p=0.016) and systolic BP (r=0.33, p=0.0001), diastolic BP (r=0.20, p=0.021) and negatively with HDL-C (r=-0.33, p=0.0001). PASI and BSA were positively correlated with all acute phase parameters (p=0.0001). Right and left IMT correlated positively with CRP (r=0.23, p=0.014). Insulin was positively correlated with CRP (r=0.57, p<0.0001) and ESR (r=0.41, p<0.0001).

Discussion

The results of this study confirm the association between severe psoriasis and a higher cardiovascular risk in both male and female groups. We found a higher prevalence of

Table 7. Mean (SD) of CRP, fibrinogen, D-dimer, ESR in men and women with psoriasis and their respectively controls.

	Men		p value	Women		p value
	Psoriasis	Controls		Psoriasis	Controls	
CRP (mg/dL)	0.316 (0.2)	0.125 (0.1)	0.002	1.14 (0.8)	0.16 (0.1)	0.009
Fibrinogen (mg/dL)	343.58 (61.1)	274.17 (83.6)	0.0001	416 (126.3)	303.3 (73.9)	0.0001
D-Dimer (ng/mL)	131.83 (84.1)	94.31 (33.2)	0.018	236.5 (55.4)	100.7 (39.4)	0.005
ESR (mm/hour)	7.77 (4.4)	7.21 (3.5)	0.56	26.7 (13.8)	12.5 (8.7)	0.03

subclinical carotid atheromatosis (atheroma plaques) and MS (ATP-III criteria) in patients with psoriasis than in control subjects. Binary logistic regression showed a strong association between psoriasis and atheroma plaque and metabolic syndrome after controlling for confounding variables. The prevalence of these cardiovascular risk factors differs slightly between male and female patients with psoriasis.

Metabolic syndrome

Many studies have demonstrated an increased risk for all the components of metabolic syndrome among patients with psoriasis, based on huge computerized medical databases and this may be problematic due to information bias regarding documentation of the diagnosis of psoriasis and its comorbidities [13]. A recent study showed that only 57% of patients with a registered diagnosis of psoriasis in the computerized medical records had a true diagnosis of psoriasis [14] and most computerized medical records do not compel the physician to input data regarding some parameters such as obesity, body mass index or smoking habits.

We found a higher prevalence of MS in patients with psoriasis than in their respective control groups. Few studies have analyzed the prevalence of MS not based on computerized medical databases [11, 15]. Comparison of published prevalence for different populations is difficult if different diagnostic criteria are used. Studies have reported a MS prevalence of 7.5-20% in the general population [16], within the range observed in our controls.

The importance of metabolic syndrome is that it may confer a cardiovascular risk higher than the individual components, subjects who met ATP-III MS criteria had a 2.59-fold greater likelihood (OR=2.59) of a cardiovascular event in the next 10 yrs [17]. In our study, patients with MS had a 3.5-fold higher risk (OR=3.5, 95% CI: 1.2 - 9.7) of the presence of atheroma plaque. A higher mortality risk for arterial and venous thrombosis and a higher risk of myocardial infarction, especially in young patients with severe psoriasis, has been described [18].

In the present study, a higher mean BMI and abdominal circumference were found in psoriatic patients than in controls. This indicates that psoriatic patients undergo an abdominal redistribution of fat, which is considered an important cardiovascular risk factor and was associated in our study with higher insulin resistance, a key element in the MS. We did not find differences between cases and controls regarding mean levels of blood glucose or lipid levels. In contrast to our findings, others studies showed that diabetes mellitus type 2 and an atherogenic lipid profile ocurred significantly more frequently in patients with psoriasis than in controls [15, 19]. Despite the fact that the association with hypertension has not been completely supported by all of the current literature [1], we found that patients with psoriasis presented higher mean levels of systolic and diastolic BP.

Carotid atheromatosis

We found a significantly higher prevalence of carotid atheromatosis in the male and female psoriatic patients than in controls. The prevalence of atheroma plaque as a marker of subclinical atherosclerosis has not been properly studied in patients with psoriasis. Most studies directly analyse cardiovascular events, e.g., myocardial infarction [20, 21], with the potential bias of only considering those who survive heart disease. The presence of the majority of parameters that constitute MS were positively related to the presence of atheroma plaque in this study. Only two reports analyzed the prevalence of carotid atheroma plaque and IMT in patients with psoriasis, excluding patients with risk factors, without finding significant differences [7, 8]. Impaired endothelial function and increased IMT of the carotid arteries in psoriatic arthritis have also been reported [22]. In this study psoriasis was associated with atheroma plaque even after controlling for confounding parameters and metabolic syndrome in a multivariate analysis. IMT was also significantly higher in patients with psoriasis and correlated with psoriasis activity (PASI) and age in multiple linear regression analysis. So, older patients with severe psoriasis need frequent follow-up to reduce cardiovascular morbidity.

Detection of subclinical atherosclerosis and identification of patients at risk for developing atherosclerosis are important for the prevention of cardiovascular disease. Systemic inflammation has been associated with the development of atherosclerosis, which suggests that psoriatic patients may have a higher risk for cardiovascular disease, also metabolic syndrome parameters and treatments may contribute to the development of atherosclerosis in these patients. Both diseases share common inflammatory cytokine profiles, locally and systemically [23]. The metabolic aspects of chronic Th-1 and Th-17 inflammation in psoriasis have the potential to impact other conditions, such as risk factors and atherosclerosis but inflammatory cytokines and hormones produced in conditions such as obesity, insulin resistance or atherosclerosis may also promote a pro-inflammatory state.

Hormonal study

Patients with psoriasis presented significantly higher insulin levels and hyperinsulinemia, defined as an insulin

level >10.0 μU/mL, was significantly higher in psoriatic patients than in controls. However, the HOMA-IR index did not show differences between the groups, maybe because glucose levels were very similar in patients and in controls. Given that a proportion of patients with psoriasis are obese and abdominal obesity is strongly associated with the development of metabolic syndrome, the relationship between psoriasis and insulin resistance is not unexpected. No differences in blood glucose were found, presumably because of the number of patients involved in the study, but hyperinsulinemia may reflect a trend to develop glucose intolerance in the future. Also, insulin levels correlated positively with all the metabolic syndrome parameters, aldosterone and PASI. Aldosterone, a mineralocorticoid hormone classically involved in sodium balance regulation and hypertension [24], is increased in patients with metabolic syndrome [25-28] associated with insulin resistance, as found in the present study.

Patients with psoriasis presented significantly higher levels of plasma homocysteine without differences in folic acid. Homocysteine correlated positively with psoriasis activity (r=0.34, p=0.02), inflammation (CRP, r=0.29, p=0.01) and mean IMT (r=0.28, p=0.036). Clinical and epidemiological studies have provided strong evidence that plasma homocysteine is an independent risk factor for atherosclerotic diseases including coronary artery disease, stroke and peripheral vascular disease [29]. There have been several studies that investigated homocysteine levels in psoriasis patients with different results. Reduced plasma folate levels in patients with psoriasis, which results from reduced absorption from the gut or increased vitamin utilization in the skin, have been one of several explanations for this hyperhomocysteinemia found in patients with psoriasis [30-33]. In the present case, folic acid correlated negatively with PASI, but no significant differences were found between patients and controls. The mechanisms of hyperhomocysteinemia for the development of atherothrombosis are endothelial injury, increased platelet turnover, enhanced platelet activation with increased thromboxane synthesis, oxidative modification of low-density lipoproteins and endothelial-leucocyte interactions [34]. Dietary supplementation with folic acid and vitamins B6 and B12 appears to be a reasonable and safe therapeutic option in these patients [30].

Acute phase reactants

Mean CRP, fibrinogen, D-dimer and ESR (only in females) values were significantly higher in psoriatic patients *versus* their controls, and these parameters were related to MS and carotid atheromatosis. PASI, BSA and IMT were positively correlated with all acute phase parameters. Chronic inflammation was found to play an important role in the development of insulin resistance, endothelial dysfunction and cardiovascular disease [35] and other studies report that plasma acute-phase protein levels (C-reactive protein or fibrinogen) were significantly elevated in patients with psoriasis compared with healthy controls [36]. The Th-1 and Th-17 pro-inflammatory situation underlying psoriasis, and shown by higher mean values of acute phase reactants, may have a potential impact in other conditions, such as obesity, diabetes, thrombosis, or atherosclerosis.

Although case-control studies can show a possible selection bias, the distribution of the potentially confounding factors as age, sex, tobacco use, sedentarism and drug intake were homogeneous in the two groups. In the present study, the binary logistic regression model showed a higher risk for MS and atheroma plaque in patients with psoriasis, after controlling for multiple confounding factors. Also, case-control studies do not allow the directionality of the association to be ascertained, so more prospective studies with larger numbers of patients are required to analyze the pathogenic mechanisms underlying the increase in cardiovascular risk in patients with psoriasis.

In conclusion, the results obtained indicate an association between psoriasis in males and females and the cardiovascular risk factors of MS and carotid atheromatosis. Our data show that the presence of psoriasis was an independent risk factor for subclinical atherosclerosis (atheroma plaque and higher IMT) and metabolic syndrome, possibly due to chronic inflammation and hyperhomocysteinemia. Cardiovascular screening by MS criteria assessment and carotid ultrasound in males or females with psoriasis may be useful to detect individuals at risk and start preventive treatment against the development of cardiovascular disease. ■

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