

High Prevalence of Metabolic Syndrome and of Insulin Resistance in Psoriatic Arthritis Is Associated with the Severity of Underlying Disease

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ABSTRACT. Objective. To investigate the prevalence of metabolic syndrome (MetS) and of insulin resistance (IR) in an ethnically homogeneous cohort of established psoriatic arthritis (PsA), and to identify clinical associations of MetS and IR in patients with PsA.

Methods. A cohort of 283 patients with PsA all meeting Classification for Psoriatic Arthritis (CASPAR) criteria was included. All underwent detailed skin and rheumatologic assessments, along with cardiovascular risk factor evaluation. IR was defined as an elevated homeostasis model assessment (HOMA-IR) value of > 2.5 . Severe PsA was defined as the presence of 1 or more of the PsA-related radiographic damage features (peripheral joint erosions, osteolysis, sacroiliitis), and PsA requiring tumor necrosis factor inhibitor therapy.

Results. The demographic and clinical characteristics of the cohort were mean age 54.6 ± 12 years, 52% female, mean PsA duration 19 ± 9 years. MetS was present in 44% of the studied patients ($n = 283$). On multiple regression analysis, a significant association of MetS was noted with more severe PsA (OR 4.47, $p < 0.001$), higher smoking pack-years (OR 1.03, $p = 0.02$), and worse EQ-5D scores (OR 1.28, $p = 0.02$). Data on IR were available for 263 patients, and among them, the mean HOMA-IR was 1.43 ± 1.09 . Forty-one patients (16%) had IR. On multiple regression analysis, a significant association of IR was noted with more severe PsA (OR 3.49, $p = 0.03$), later psoriasis age of onset (OR 1.07, $p = 0.001$), and higher body mass index (OR 1.22, $p < 0.001$).

Conclusion. Among patients with PsA, MetS and IR are highly prevalent, and are independently associated with the severity of underlying PsA. (First Release June 15 2014; J Rheumatol 2014; 41:1357–65; doi:10.3899/jrheum.140021)

Key Indexing Terms:

PREVALENCE
INSULIN RESISTANCE

PSORIATIC ARTHRITIS

METABOLIC SYNDROME
SEVERE DISEASE

Psoriatic arthritis (PsA) is a progressive immune-mediated musculoskeletal disease with involvement of synovial, enthesal, and axial structures. There are varied reports of its prevalence among patients with psoriasis (PsO)¹. Since the discovery of biologic drugs and their wide use among patients with PsA, we have witnessed a significant improvement not only in the management of arthritic symptoms, but also in the overall quality of life. This has provided rheumatologists with an opportunity to focus on other measures that might improve patients' longterm outlook.

There has been a growing interest in the identification of cardiovascular (CV) disease risks in PsO and PsA, with much of the initial data and pathogenetic explanations extrapolated from the rheumatoid arthritis (RA) literature.

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Mortality studies have shown increased CV mortality in RA, and the evidence suggests that the same is likely to be true in PsA². Research has also shown that diseases of the CV system are the leading causes of death in patients with PsA³, accounting for 20–56%^{4,5} of all deaths among these patients. There is plentiful evidence from large observational cohorts, both retrospective and prospective, and also by using different imaging techniques, to demonstrate that both PsO and PsA are associated with heightened CV risk^{6,7,8,9,10,11,12}.

Metabolic syndrome (MetS) is a cluster of 5 classic CV risk factors. Under current guidelines, revised in 2005 by the US National Heart, Lung, and Blood Institute (NHLBI) and the American Heart Association (AHA), MetS is diagnosed when a patient has at least 3 of the following 5 conditions: fasting glucose ≥ 100 mg/dl, or receiving drug therapy for hyperglycemia; blood pressure $\geq 130/85$ mmHg, or receiving drug therapy for hypertension (HTN); triglycerides ≥ 150 mg/dl, or receiving drug therapy for hypertriglyceridemia; high-density lipoprotein cholesterol (HDL-C) < 40 mg/dl in men or < 50 mg/dl in women, or receiving drug therapy for reduced HDL-C; and for whites, waist circumference ≥ 40 inches (≥ 102 cm) in men or ≥ 35

inches (≥ 88 cm) in women¹³. Studies have estimated that the prevalence of MetS in the Western population is 15–24%^{14,15}. MetS is a well-recognized risk factor for coronary artery diseases, and as a group, may confer a CV risk higher than the individual components. It has been shown that men with MetS are almost 3 times more likely to die of coronary artery disease after adjustment for conventional CV risk factors¹⁶. Interestingly, it has been shown that MetS is associated with a state of chronic, low-grade inflammation^{17,18}.

PsO is a very common inflammatory skin disease that is now increasingly recognized as a chronic systemic inflammatory disorder. MetS and its components are highly prevalent in PsO compared to healthy controls, ranging from 30–40%^{19,20,21}. A recent metaanalysis has confirmed similar results²². Moreover, there is substantial evidence regarding high prevalence of traditional and nontraditional adverse CV risks in patients with PsO^{6,7,10,11}. In relation to PsA, data are incomplete and inconsistent regarding the prevalence of MetS^{23,24,25,26,27}. The prevalence of some of the individual components of MetS such as obesity^{12,28}, HTN^{8,12,29}, and dyslipidemia^{8,12,29,30} has been established. It has been postulated that insulin resistance (IR) explains the increased CV comorbidity associated with systemic inflammatory conditions such as PsO and other immune-mediated inflammatory diseases³¹. IR in turn causes endothelial cell dysfunction, leading to atherosclerosis and finally to end-organ damage with stroke or myocardial infarction. IR can be calculated, based on a single blood test, using a simple formula. A degree of IR is expected in most of the patients with MetS, but it is not clear whether IR is the cause of the MetS or a by-product of a generalized metabolic derangement.

In PsA, there is a coexistence of skin and of musculoskeletal inflammation. We hypothesized, therefore, that there might be a greater burden of MetS and IR in PsA, and consequently of CV diseases because of a greater inflammatory load. The objectives of our study were (1) to investigate the prevalence of MetS and of IR in an ethnically homogeneous cross-sectional cohort of established PsA; and (2) to identify clinical associations of MetS and of IR by examining likely contributing features including underlying patient characteristics, lifestyle factors, and severity of psoriatic disease.

MATERIALS AND METHODS

Patients. All patients attending rheumatology clinics at St. Vincent's University Hospital, Dublin, with a confirmed diagnosis of PsA as per the internationally agreed CASPAR criteria (CIASsification of Psoriatic Arthritis Criteria) were identified. Among them, a consecutive cohort of 283 white patients with a disease duration > 10 years was invited for this cross-sectional evaluation. Histories were obtained of diabetes, HTN, hypercholesterolemia, overt CV disease (including myocardial infarction, angina, stroke, and transient ischemic attack), malignant neoplastic disease, and drug use. These patients were assessed between 2011 and 2012.

Clinical risk factor evaluation. The clinical variables studied were sex, smoking habits, body mass index (BMI), waist and hip circumference, blood pressure (BP), units of alcohol intake per week, smoking habits, and fasting venous blood samples for glucose, lipid profile, and insulin. The homeostasis model assessment for IR (HOMA-IR) was calculated using this formula: fasting insulin (mIU/l) \times fasting glucose (mmol/l)/22.5. IR was defined as an elevated HOMA-IR value of > 2.5 , based on the original HOMA research³². Other risk factors included in the analysis were family history of PsO and PsA, different clinical types of PsO, psoriatic nail disease, duration of PsO and PsA, and PsO and PsA age of onset. Usually, 2 types of PsO, types I and II, can be distinguished. Type I PsO begins at a young age (≤ 40 yrs), has a stronger family history, and is associated with certain HLA types. About 65% of people with PsO have Type I PsO. Type II PsO occurs in those > 40 years old; family history of PsO in such cases is weak or absent and it is generally not associated with HLA antigens. Patients were labeled as hypertensive if they were already taking medication for HTN, or if an elevated BP reading (130/85, as per the definition of MetS¹³) was recorded on 2 separate outpatient visits of ≥ 6 weeks but ≤ 6 months apart. Education status was stratified by whether participants completed secondary education (high school).

Evaluation of disease activity and severity. Following informed consent, patients underwent a detailed skin and rheumatologic assessment including disease activity measures. Because the majority of the cohort was in clinical remission at the time of assessment, we made 2 documentations of all reversible clinical features at different timepoints. These documentations included the clinical variables collected at the time of current assessment, e.g., current skin scores, current inflammatory markers, current tender and swollen joints; and through extensive medical record review, the patient's maximum skin and joints disease activity scores ever documented, e.g., maximum skin scores, maximum inflammatory markers ever raised during a flare of PsA, and maximum tender and swollen joints.

The extent and severity of skin PsO was assessed by the Psoriasis Area and Severity Index (PASI), the most widely used tool for the measurement of severity and extent of PsO. We also measured body surface area as a further estimate of the extent of skin disease. For PsA, physical examination included recording the number of tender and swollen joints using the 68 tender/66 swollen joint count, the presence of dactylitis, the presence of enthesitis, and the number of permanently deformed joints. Clinically deformed joints were defined as the presence of fixed deformities, flail joints, fused joints, and surgically replaced joints^{33,34}. Laboratory assessments included rheumatoid factor, anticyclic citrullinated peptide antibodies, erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP). Patient-reported outcome measures (PROM) were also recorded, e.g., Health Assessment Questionnaire (HAQ), Dermatology Life Quality Index, Bristol Rheumatoid Arthritis Fatigue Numeric Rating Scale, and EQ-5D. Finally, radiographs were obtained for all patients of involved joints along with hands, feet, and sacroiliac joints at the time of assessment. We used radiographic evidence of sacroiliitis to define axial disease because it is less subjective and more reproducible, and has relatively better interassessor agreement. We defined the criteria for identifying sacroiliitis if \geq grade 2 radiographic changes were present (unilateral or bilateral), and it was noted that all these patients had either backache or a history of it. Hand and foot radiographs were assessed for the presence/absence of peripheral joint erosions or osteolysis. All these radiographs were assessed by a consultant musculoskeletal radiologist (EH).

Apart from the data on fasting insulin, which were available for 263 patients, there were no missing data in this cohort ($n = 283$), because patients were assessed in a dedicated research clinic where all the clinical, laboratory, and radiographic details were collected. In relation to the patients with the missing information on fasting insulin, these patients were not different from the remaining study population ($p \geq 0.05$).

According to our pretest hypothesis, we wished to investigate whether MetS was associated with the severity of PsA. Because there has been no agreed-upon definition of severe PsA, we tested 3 models. In model 1, only those patients with PsA who required tumor necrosis factor inhibitor

(TNFi) therapy for their arthritis were included. However, because 60% of the study patients were using TNFi, to avoid confounding by indication, 2 additional definitions or models of severe PsA were used. In model 2, severe PsA was defined as having 1 or more of the PsA-related radiographic damage features — peripheral joint erosions, osteolysis, or sacroiliitis. Finally, in model 3 of severe PsA, only those patients who had both the PsA-related radiographic damage and required a TNFi for their arthritis were included. In other words, model 3 combined the features of models 1 and 2, and possibly included patients with the most severe PsA among all 3 models. The study was approved by the local Medical Research Ethics committee.

Statistical analysis. Statistical analysis was performed using SPSS software, version 17. Significance was defined as $p < 0.05$ (2-tailed). A chi-square statistic was used to investigate the distribution of categorical variables, and continuous variables were analyzed using the Student's t-test, but they were not categorized. We applied OR and associated CI to measure association between different variables. Three different models of severe PsA were examined as described. The association of different clinical variables with the diagnosis of MetS or of IR was determined using univariate and multivariate logistic regressions. The factors associated with MetS or with IR on univariate analysis with significance at the 0.25 level were entered into a multivariate model. The model was then reduced by

backward elimination until the remaining effects were significant at the 0.05 level. Estimates of regression coefficients were obtained from this final model.

RESULTS

A total of 283 patients with PsA (mean age 54.6 ± 12 yrs; 52% female; mean PsA duration 19 ± 9 yrs; 25% with sacroiliitis; 44.5% with radiographic peripheral joint erosions; 8% with arthritis mutilans; 60% of patients requiring TNFi for PsA, mean maximum PASI of 5.7 ± 5.2 , mean current PASI 2.1) attended for detailed assessments. Forty-four percent (44%, $n = 124$) of this cohort was diagnosed with MetS according to revised 2005 AHA/NHLBI guidelines. Figure 1A shows the frequency of the 5 individual components of MetS among the entire cohort. Very high prevalence of these typical CV disease risk factors was noted, in particular elevated BP (74%), elevated waist circumference (56%), and elevated triglycerides (43.5%). We also noted that 50% of these newly

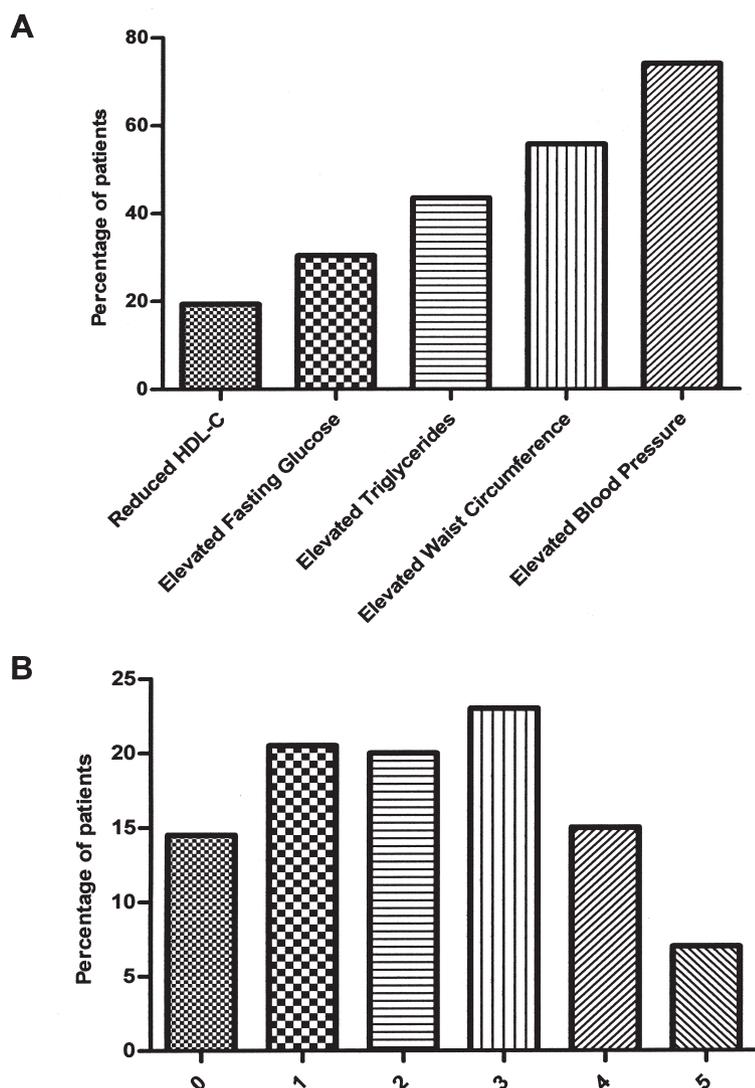


Figure 1. A. The frequency of different features of metabolic syndrome (MetS) among our psoriatic arthritis cohort ($n = 283$). HDL-C: high-density lipoprotein cholesterol. B. Clustering of 5 different components of MetS among the entire cohort ($n = 283$).

diagnosed patients with MetS had clustering of ≥ 4 of MetS risk factors (Figure 1B). Of the whole cohort, about 10% (9.5%, $n = 27$) of patients had known personal history of ischemic CV disease, and 67% of those patients had MetS ($p = 0.01$). Importantly, patients with MetS were noted to have more IR compared to those who did not have MetS (29% vs 7%, respectively, $p < 0.001$).

About one-quarter (20.5%) of the cohort did not complete secondary school education, and these patients had high prevalence of MetS (57%, $p = 0.024$). On univariate analysis (Table 1), patients with MetS had more type II PsO ($p = 0.007$), later PsO and PsA age of onset ($p <$

0.001 and 0.006, respectively), shorter time from PsO to arthritis development ($p = 0.050$), higher HAQ scores ($p = 0.08$), higher fatigue scores ($p = 0.056$), worse EQ-5D scores ($p = 0.01$), higher number of smoking pack-years ($p = 0.056$), and more prevalent severe psoriatic disease ($p = 0.025$). No significant association was noted with duration of PsA, inflammatory markers, and units of alcohol consumed. On multiple stepwise regression analysis (Table 2), a significant association was noted of MetS with more severe PsA (model 3; OR 4.47, $p < 0.001$), higher smoking pack-years (OR 1.03, $p = 0.02$) and worse EQ-5D (OR 1.28, $p = 0.02$). Interestingly, we noted that when we added IR to

Table 1. Descriptive characteristics of PsA patients with and without metabolic syndrome (MetS; $n = 283$). Data are percent unless otherwise indicated.

Characteristics	PsA Patients with MetS, $n = 124$	PsA Patients without MetS, $n = 159$	p
Sex, male	50.8	54	0.58
Age, yrs \pm SD	57.8 \pm 11	52 \pm 12	< 0.001
Smoking			0.76
Never	53	57	
Former smoker	34.7	32.7	
Current	12	10	
Smoking pack-yrs, \pm SD	22.4 \pm 25	15 \pm 12	0.049
Alcohol intake, units/week, \pm SD	8.15 \pm 9	7.5 \pm 7.3	0.53
Education status			
\leq Primary school	27	16	0.02
Duration of PsA, yrs, \pm SD	18.7 \pm 8.7	20 \pm 9.9	0.20
Family history of PsO	59.7	65.4	0.32
Family history of PsA	14.5	18.9	0.33
PsO age of onset, yrs \pm SD	31 \pm 14	24 \pm 13	< 0.001
PsA age of onset, yrs \pm SD	37 \pm 13	33 \pm 13	0.006
Time from PsO to PsA development, yrs \pm SD	5.8 \pm 11	8.4 \pm 10	0.050
Type II psoriasis	24	12	0.007
PASI* maximum, score \pm SD	6.03 \pm 5.4	5.3 \pm 5	0.25
BSA* maximum, score \pm SD	10.8 \pm 13	8.6 \pm 8.3	0.09
PASI* current, score \pm SD	2.2 \pm 2.8	2.0 \pm 2.6	0.61
Nail disease	76	82	0.22
Oligoarthritis	4.8	9.4	0.14
Erosions	46	42	0.43
Sacroiliitis	27	23	0.39
Deformed joints	70	60.4	0.08
PsO requiring TNFi	14.5	9	0.13
PsA requiring TNFi	63	58.5	0.45
Osteolysis	15.7	13	0.50
Arthritis mutilans	8	8	0.97
CRP – current, mg/l \pm SD	3.37 \pm 3.00	3.08 \pm 3.33	0.46
ESR – maximum, mm/h \pm SD	32.6 \pm 26.8	29.5 \pm 21.5	0.27
Severe disease (radiographic PsA damage* along with PsA requiring TNFi)	55.6	26.4	< 0.001
Insulin resistance	29.3	4.7	< 0.001
BRAF, score \pm SD	14.8 \pm 5.5	13.8 \pm 4.8	0.10
HAQ, score \pm SD	0.64 \pm 0.5	0.52 \pm 0.5	0.07
DLQI, score \pm SD	2.6 \pm 3.9	2.6 \pm 4	0.98
EQ-5D, score \pm SD	7.5 \pm 1.8	7.01 \pm 1.8	0.01

* Radiographic abnormalities of peripheral joint erosions, osteolysis, sacroiliitis. P values in boldface are statistically significant. BSA: body surface area; PASI: Psoriasis Area and Severity Index; BRAF: Bristol Rheumatoid Arthritis Fatigue Numeric Rating Scale; HAQ: Health Assessment Questionnaire; DLQI: Dermatology Life Quality Index; TNFi: tumor necrosis factor inhibitor; PsA: psoriatic arthritis; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PsO: psoriasis.

Table 2. Univariate and multivariate (adjusted simultaneously for variables shown) associations of different clinical variables with the development of metabolic syndrome in patients with psoriatic arthritis (PsA; n = 283). Results presented in the order of OR (95% CI) p value. OR are per-unit increase.

Variable	Univariate Analysis	Multivariate Regression Using Model 1 Definition of Severe PsA (adjusted* OR)	Multivariate Regression Using Model 2 Definition of Severe PsA (adjusted* OR)	Multivariate Regression Using Model 3 Definition of Severe PsA (adjusted* OR)
Age	1.04 (1.02–1.06), < 0.001			
Sex	1.14 (0.71–1.82), 0.58			
PsA duration	0.99 (0.95–1.00), 0.20			
Smoking pack-yrs, per unit pack-yr smoked	1.02 (0.99–1.04), 0.056	1.02 (1.00–1.05), 0.03	1.02 (1.00–1.05), 0.052	1.03 (1.00–1.06), 0.02
Low education status	1.94 (1.08–3.48), 0.02			
Type II PsO	2.35 (1.25–4.42), 0.008			
PASI max	1.02 (0.98–1.07), 0.25			
PsO age of onset	1.03 (1.01–1.05), < 0.001			
PsA age of onset	1.02 (1.00–1.04), 0.006			
Time from PsO to arthritis development	0.97 (0.95–1.00), 0.052			
Deformed joints	1.54 (0.93–2.54), 0.08			
HAQ	1.45 (0.96–2.20), 0.07			
EQ-5D	1.16 (1.02–1.32), 0.19		1.22 (1.00–1.05), 0.050	1.28 (1.03–1.59), 0.025
BRAF	1.03 (0.99–1.08), 0.11			
Model 1 of severe PsA (defined as PsA requiring TNFi)	1.20 (0.74–1.94), 0.45	2.36 (1.03–5.41), 0.04		
Model 2 of severe PsA (defined as the patients with PsA radiographic damage**)	1.05 (0.66–1.69), 0.81			
Model 3 of severe PsA (radiographic PsA damage** along with PsA requiring TNFi)	3.49 (2.12–5.76), < 0.001			4.47 (1.96–10.16), < 0.001

* These variables were included in the full regression model: age, sex, PsA duration, smoking pack-years, low education status, type II PsO, PsO and PsA age of onset, time from PsO to arthritis development, deformed joints, HAQ scores, EQ-5D scores, BRAF scores, and PASI maximum scores.

** Radiographic abnormalities of peripheral joint erosions, osteolysis, and sacroiliitis. PASI: Psoriasis Area and Severity Index; BRAF: Bristol Rheumatoid Arthritis Fatigue Numeric Rating Scale; HAQ: Health Assessment Questionnaire; TNFi: tumor necrosis factor inhibitor; PsO: psoriasis.

the multiple regression model along with all the variables shown in Table 2, the severe PsA (model 3) remained significantly associated with MetS (OR 3.14, $p = 0.008$).

The mean HOMA-IR among 263 patients was 1.43 ± 1.09 . Forty-one patients (16%) had IR. Compared to patients with no IR, PsA patients with IR (Table 3) were older ($p = 0.01$), had more smoking pack-years ($p = 0.09$), greater BMI ($p = 0.001$), later PsO and PsA age of onset ($p < 0.001$, $p = 0.009$, respectively), shorter time from PsO to arthritis development ($p = 0.01$), worse HAQ scores ($p = 0.08$), more MetS ($p < 0.001$), and more severe PsA ($p = 0.008$). In this cohort, although trending toward significance, we did not observe an association of IR with the maximum PASI. On multiple regression analysis, a significant association of IR was noted with more severe PsA (OR 3.49, $p = 0.03$), older PsO age of onset (OR 1.07, $p = 0.001$), and higher BMI (OR 1.22, $p < 0.001$), even after adjusting for the presence of MetS (Table 4).

DISCUSSION

Since its first description in late 1980s, there has been ongoing debate about the clinical usefulness of MetS. The supporters of MetS suggest a synergistic effect of multiple

adverse CV risk factors, and that this syndrome may help to focus the attention of both clinicians and patients on a number of relatively minor clinical abnormalities that add up to a significant CV risk³⁵. Critics, however, argue that its precise role in the prediction of future CV events has not yet been defined^{36,37}. Nevertheless, MetS is increasingly recognized as a useful clinical tool for guiding risk assessments and promoting lifestyle interventions³⁸. Likewise, IR has been an area of increasing interest, with possible effects of IR on a wide array of disease spectrums. Insulin resistance, MetS, and atherosclerotic events may well share a common inflammatory basis, and it has been postulated that it is persistent, low-grade systemic inflammation such as might occur in the joints or in the adipose tissue of patients with PsA that leads to impaired insulin action³⁹.

In our cohort of consecutive patients with PsA, we found that 44% (111 out of 283) and 16% (41 out of 263) of patients had metabolic syndrome and IR, respectively. The results of our study are important in a number of ways. First, we confirm a high prevalence of MetS and of IR in patients with PsA. MetS features include risk factors known to be associated with adverse CV outcomes. Even more alarming was the finding that about 50% of these newly diagnosed

Table 3. Descriptive characteristics of patients with PsA (psoriatic arthritis), with and without insulin resistance (IR; n = 263). Data are percent unless otherwise indicated.

Characteristics	PsA Patients with IR, n = 41	PsA Patients without IR, n = 222	p
Sex, male	54	46	0.36
Age, yrs, \pm SD	59 \pm 12	53.6 \pm 12	0.01
Smoking			0.26
Never	46	58.5	
Former smoker	44	31	
Current	10	10	
Smoking pack-yrs, \pm SD	28.7 \pm 35	15.5 \pm 12.6	0.09
Alcohol intake, units/week, \pm SD	9 \pm 9	7.6 \pm 8	0.24
BMI, \pm SD	33 \pm 5	28 \pm 5	< 0.001
Education status			0.22
\leq Primary school	29	22	
Duration of PsA, yrs, \pm SD	18.7 \pm 8	19 \pm 9.6	0.66
Family history of PsO	58.5	64	0.47
Family history of PsA	16.6	17	0.94
PsO age of onset, yrs \pm SD	35.5 \pm 15	25.5 \pm 13	< 0.001
PsA age of onset, yrs \pm SD	39.8 \pm 13	34 \pm 12.5	0.009
Time from PsO to PsA development, yrs \pm SD	4 \pm 7.7	8 \pm 11	0.01
Type II PsO	34	13	0.001
PASI maximum, score \pm SD	6 \pm 5.4	5 \pm 4.8	0.25
BSA maximum, score \pm SD	10 \pm 12	8 \pm 7	0.27
PASI current, score \pm SD	2.2 \pm 2.9	1.6 \pm 1.8	0.21
Nail disease	80	79	0.86
Oligoarthritis	5	7	0.58
Erosions	51	46	0.53
Sacroiliitis	27	26	0.87
Osteolysis	19.5	14	0.35
Arthritis mutilans	12	7	0.27
Deformed joints	71	65	0.53
PsO requiring TNFi	17	11	0.25
PsA requiring TNFi	73	59	0.08
Severe disease (radiographic PsA damage* along with PsA requiring TNFi)	58.5	36	0.008
MetS	83	37	< 0.001
CRP, current, mg/dl, \pm SD	3.3 \pm 2.8	3.1 \pm 3.2	0.73
ESR, maximum, mm/h, \pm SD	36.7 \pm 26	29.6 \pm 23	0.08
BRAF, score \pm SD	14.5 \pm 4.8	14 \pm 5	0.72
HAQ, score \pm SD	0.71 \pm 0.59	0.54 \pm 0.56	0.08
DLQI, score \pm SD	3.6 \pm 5.6	2.3 \pm 3.4	0.18
EQ-5D, score \pm SD	7.6 \pm 1.7	7.1 \pm 1.8	0.11

* Radiographic abnormalities of peripheral joint erosions, osteolysis, and sacroiliitis. BSA: body surface area; PASI: psoriasis area and severity index; BRAF: Bristol Rheumatoid Arthritis Fatigue Numeric Rating Scale; HAQ: Health Assessment Questionnaire; DLQI: Dermatology Life Quality Index; TNFi: tumor necrosis factor inhibitor; ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; PsO: psoriasis; BMI: body mass index.

patients with MetS had a combination of 4 or 5 of these risk features. These results are in agreement with the published literature of relatively small studies reporting a prevalence of MetS in PsA of 27-58%^{23,24,25,26}. Regarding IR, a study of 203 patients with PsA has found a mean HOMA-IR value of 0.97 \pm 0.63, but in our cohort, the value of HOMA-IR was higher at 1.43 \pm 1.09²⁶.

Second, we have shown that severe inflammatory musculoskeletal disease is significantly linked to the presence of

MetS not only on univariate analysis but also after adjusting for IR, severity of skin PsO, and the usual confounders. There is very limited information regarding this. For example, in patients with PsO, it has been shown that patients with more severe skin disease are at a greater risk of having MetS compared to those with milder PsO^{22,40}. In PsA, a study has shown that severe PsO correlates with the diagnosis of MetS²⁶.

Third, we have shown that severe PsA is significantly

Table 4. Univariate and multivariate (adjusted simultaneously for variables shown) associations of different clinical variables with the development of insulin resistance in patients with psoriatic arthritis (PsA; n = 263).

Variable	Univariate Analysis	Multivariate Regression Using Model 1 Definition of Severe PsA (adjusted* OR)	Multivariate Regression Using Model 2 Definition of Severe PsA (adjusted* OR)	Multivariate Regression Using Model 3 Definition of Severe PsA (adjusted* OR)
Age	1.03 (1.008–1.06), 0.01	1.11 (1.04–1.18), 0.001		
Sex	1.36 (0.69–2.65), 0.36			
PsA duration	0.99 (0.95–1.02), 0.66			
Smoking pack-yrs/unit pack-yr smoked	1.02 (1.004–1.05), 0.02			
BMI	1.16 (1.09–1.23), < 0.001	1.24 (1.09–1.40), 0.001	1.22 (1.09–1.36), < 0.001	1.22 (1.09–1.37), < 0.001
Low education status	1.58 (0.75–3.3), 0.22			
Type II psoriasis	3.31(1.56–7.03), 0.002			
PASI max	1.01 (0.78–1.07), 0.39			
PsO age of onset	1.04 (1.02–1.07), < 0.001		1.06 (1.02–1.10), 0.001	1.07 (1.02–1.11), 0.001
PsA age of onset	1.03 (1.00–1.06), 0.01			
Time from PsO to arthritis development	0.95 (0.92–0.99), 0.01	0.93 (0.86–0.99), 0.037		
CRP, maximum	1.008 (0.99–1.01), 0.14			
Deformed joints	1.25 (0.60–2.60), 0.53			
HAQ	1.62 (0.93–2.82), 0.08			
EQ-5D	1.15 (0.96–1.38), 0.11			
MetS	8.2 (3.5–19.5), < 0.001			
Model 1 of severe PsA (defined as PsA requiring TNFi)	1.89 (0.90–3.97), 0.09	9.51 (1.56–58), 0.01		
Model 2 of severe PsA (defined as the patients with PsA radiographic damage**)	1.01 (0.51–1.97), 0.97			
Model 3 of severe PsA (radiographic PsA damage** along with PsA requiring TNFi)	2.45 (1.24–4.84), 0.009			3.49 (1.08–11.2), 0.03

Results presented in the order of OR (95% CI) p value. * These variables were included in the full regression model: age, sex, PsA duration, smoking pack-years, BMI, low education status, type II PsO, PsO and PsA age of onset, time from PsO to arthritis development, CRP maximum, deformed joints, HAQ scores, EQ-5D scores, and PASI maximum scores. ** Radiographic abnormalities of peripheral joint erosions, osteolysis, and sacroiliitis. PASI: Psoriasis Area and Severity Index; BRAF: Bristol Rheumatoid Arthritis Fatigue Numeric Rating Scale; HAQ: Health Assessment Questionnaire; DLQI: Dermatology Life Quality Index; TNFi: tumor necrosis factor inhibitor; CRP: C-reactive protein; PsO: psoriasis; BMI: body mass index; MetS: metabolic syndrome.

associated with the presence of IR, even after adjusting for MetS, severe PsO, and other confounders shown in Table 4. Although there have been some limited data in PsA regarding the IR link with inflammatory markers (high-sensitivity CRP) and the use of TNFi^{26,30}, the association of PsA disease-related endpoints such as joint damage with IR have not been studied in detail. Our findings are novel and support our pretest hypothesis that the risk of MetS and of IR increases with the severity of underlying PsA, probably reflecting the increasing burden of inflammation. However, there was a statistically nonsignificant trend toward higher PASI maximum and higher PsO body surface area with MetS and IR, which suggests that in PsA, possibly the higher burden of inflammatory arthritis or the combination of severe psoriatic disease features play major roles in the development of MetS and/or IR. Because it is possible that the insignificant association of the severity of skin PsO with MetS and IR noted in our study is due to the underrepresentation of patients with moderate to severe skin

PsO (PASI > 10), we have analyzed such patients separately to assess whether PsO affects IR. Only 24.7% (n = 70) of the cohort had moderate to severe PsO (PASI > 10). For those patients, no significant association of PsO severity with MetS was noted on univariate analysis [OR 1.33 (0.76–2.31), p = 0.31] and with IR [OR 1.06 (0.50–2.25), p = 0.87]. Further, our study shows that MetS and IR are independently associated with the severity of PsA. This remains largely speculative, but one plausible explanation lies in the clinical definition of MetS, which is quite broad. There can be considerable variation in the components of MetS among different individuals, and critics have questioned its definition and concept. It is important to recognize that MetS is not a discrete entity but rather a syndrome with multiple pertinent pathogenetic mechanisms¹³.

In RA, it has been shown that methotrexate (MTX) use, but not other disease-modifying antirheumatic drugs or glucocorticoids, is associated with a significantly reduced chance of having MetS⁴¹. Our study, however, shows that in

PsA, MTX usage is not associated with a reduced risk of having MetS ($p = 0.52$). Rather, we found that a significant number of patients with MetS used oral corticosteroids compared to PsA patients without MetS (52% vs 40%, $p = 0.04$). This likely reflects the severity of underlying PsA, because the association of corticosteroids with the diagnosis of MetS and IR was lost in multiple regression analysis.

In recent years, there has been increased recognition that severe PsO is a chronic systemic inflammatory disorder. Increased inflammatory burden, which becomes even more pronounced with concomitant PsA, leads to IR with resultant endothelial cell dysfunction and atherosclerosis. This may result in myocardial infarction and stroke when atherosclerosis affects coronary, carotid, or cerebral arteries³¹. In patients with PsA, markers of disease activity as reflected by a high ESR at presentation and evidence of radiological damage are associated with an increased CV mortality⁴². Tam, *et al* have recently shown that inflammation in PsA contributes not only to traditional CV risk factors (higher BMI, HTN, diabetes, increased waist circumference, and insulin resistance), but also likely causes increased thrombotic tendency³⁰. In the same study, the authors conclude that a shared inflammatory pathway exists between PsA and obesity, HTN, dyslipidemia, and IR.

The strengths of our study are (1) we included a wide range of demographic details, clinical features, PROM, and most disease activity indices, not only for PsA but also for PsO, which allowed us to investigate the predictors of MetS and IR, and also to explore more effectively the effect of inflammatory skin and/or musculoskeletal disease on MetS and IR; (2) to minimize the selection bias, we have attempted to recruit all consecutive patients; (3) to standardize the study procedures, all patients were reviewed by a single, trained rheumatologist; (4) because ethnic variation in MetS susceptibility has been described⁴³, we performed our study in a relatively homogeneous Irish population (both parents of every studied patient were Irish); and (5) to our knowledge, our study is the largest to date that has attempted to identify in great detail the clinical associations of MetS and IR.

We acknowledge some limitations to our study. For example, there is a risk of selection bias because this was not a population-based study; selecting the maximal level of disease activity measures can also potentially introduce a bias, because patients with longer duration of followup have more observations recorded and are thus more likely to have higher scores; the PsA severity classification needs further validation; the prevalence of MetS was examined in 1 cross-sectional assessment, which is not the ideal study design to investigate the predictors of MetS and IR; nonetheless, this still provides useful information worthy of testing in further prospective studies. We did not investigate other risk factors such as postmenopausal status, low household income, high carbohydrate diet, and physical

inactivity, all of which can potentially confound these results.

Our study confirms the high prevalence of MetS and IR in patients with PsA. Because CV diseases are the leading cause of mortality in patients with PsA, the observed clustering of typical adverse CV risk factors should serve as a basis for guiding risk assessment and management. Our study also provides the first detailed evidence that MetS and IR are independently associated with a more severe PsA phenotype, an observation that can also help inform risk stratification.

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