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Inflammatory markers predict insulin sensitivity in active rheumatoid arthritis but not in psoriatic arthritis

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SUMMARY

Whether the insulin resistance commonly observed in patients with inflammatory arthritis is a disease-specific feature and/or is limited to a disease phase (*i.e.*, it occurs only during phases of high disease activity) is unknown.

Fifty-three rheumatoid arthritis (RA) and 44 psoriatic arthritis (PsA) patients were recruited consecutively along with 194 controls matched for age, sex and body mass index for a case-control study. All underwent an oral glucose tolerance test, the results of which were analysed to derive the following indexes: homeostatic model of insulin resistance (HOMA-IR), insulin sensitivity index (ISI) and early insulin sensitivity index (EISI). These data were related to anthropometric, clinical and laboratory findings.

Metabolic parameters of patients and controls were similar. Neither inflammatory markers nor disease activity scores were related to glucose metabolism for the generality of RA and PsA patients; however, by restricting the analysis to the subset of RA patients with residual disease activity, an association emerged between erythrocyte sedimentation rate, on the one hand, and fasting insulin (β=0.46, p=0.047) and HOMA-IR (β=0.44, p=0.02), on the other. Moreover, C-reactive protein (CRP) levels were associated with plasma glucose and insulin levels measured 120 min after the glucose load (β=0.91, p=0.0003 and β=0.77, p=0.0006, respectively); ISI and EISI were predicted by CRP (β=-0.79, p=0.0006; β=-0.80, p=0.0001, respectively). The same did not hold true for PsA patients.

The association between systemic inflammation and insulin resistance indexes is a feature of RA with residual disease activity, not a universal feature of inflammatory arthritides.

Key words: *Insulin sensitivity; Insulin resistance; Rheumatoid arthritis; Psoriatic arthritis; Oral glucose tolerance test.*

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INTRODUCTION

Comorbidities, including diabetes, have become a hot topic in the management of inflammatory arthritis (1). In this regard, an association has been reported between inflammation and insulin resistance in rheumatoid arthritis (RA) and psoriatic arthritis (PsA) (2, 3). Since insulin resistance is one of the major drivers of cardiovascular diseases, which in turn are responsible for a significant morbidity and mortality burden among patients with inflammatory arthritis (4), this proposed association may have important clinical implications. First and foremost, it would support the hypothesis that better disease control may extend its benefits on cardiovascular health. Indeed, both classical and biological disease modifying anti-rheumatic drugs (DMARDs) improve insulin sensitivity (5, 6), confirming that activation of inflammatory pathways may impair insulin action. The mechanisms linking insulin resistance and inflammatory arthritis are debated, however, and very limited data on insulin

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resistance dynamically investigated by an oral glucose tolerance test (OGTT) exist (7). Moreover, there is a paucity of data comparing glucose metabolism in RA *vs* PsA (8). With the present study, we aim to fill these gaps.

MATERIALS AND METHODS

In the present case-control study, cases were consecutively recruited at an immune-rheumatology clinic of an academic hospital, between November 2014 and June 2015. Inclusion criteria were: age >18, diagnosis of either RA (according to ACR/Eular classification criteria 2010 (9)) or PsA (according to CASPAR criteria (10)). Patients were excluded if previously diagnosed as diabetics. The study was conducted according to the principles of the Helsinki Declaration.
The following data were collected:

• Demographic and clinical characteristics: age, sex, active anti-rheumatic treatment, steroid treatment, cumulative dose of steroids administered in the preceding 3 and 12 months, comorbidities. The Disease Activity Score (DAS28), the Clinical Disease Activity Index (CDAI) and the Simplified Disease Activity Index (SDAI) were used to assess disease activity in RA; patients affected by PsA were classified as achieving minimal disease activity when 5 of the 7 following criteria were met: tender joint count ≤1; swollen joint count ≤1; Psoriasis Activity and Severity Index ≤1 or body surface area ≤3%; patient pain visual analogue score (VAS) ≤15; patient global disease activity VAS ≤20; health assessment questionnaire ≤0.5; tender entheseal points ≤1 (11).

• Anthropometric data: weight (to the nearest 0.1 kg) and height (to the nearest cm) were measured with the patient wearing only light underwear; body mass index (BMI) was calculated according to the formula weight (kg)/height (m)^2, and interpreted according to WHO classification (http://www.euro.who.int/en/health-topics/disease-prevention/nutrition/a-healthy-lifestyle/body-mass-index-bmi). Waist circumference was measured halfway between the costal edge and the crista.

• Laboratory data: erythrocyte sedimentation rate (ESR) was measured by the Westergren method (VES-Matic Cube 200", DIESSE Diagnostica senese, Siena, Italy); C-Reactive Protein (CRP) was dosed by immunoturbidimetric analysis (Advia 1800 chemistry system, Siemens healthcare and diagnostics, Leverkusen, Germany). All patients underwent a standard OGTT: following at least 12 hours of fasting, 75 grams of glucose were administered after a first, baseline, blood sampling. A second sample was taken after 2 hours. Plasma glucose was measured by the hexokinase-reaction (Advia 1800 chemistry system, Siemens healthcare and diagnostics, Leverkusen, Germany), while insulin plasma concentration was determined by immunometric sandwich chemiluminescence (Advia Centaur, Siemens healthcare and diagnostics, Leverkusen, Germany). The results of the OGTT were interpreted according to ADA recommendations (12), as follows: normal fasting plasma glucose (FPG) if <100 mg/dl (5.6 mmol/l); impaired FPG (IFG) if FPG was 100–125 mg/dl (6.9 mmol/l); impaired glucose tolerance (IGT) if 2-h post-OGTT plasma glucose was 140–199 mg/dl (7.8-11.0 mmol/l); T2DM if FPG was ≥126 mg/dl (≥7 mmol/l) on two days apart, or if 2-h post-OGTT plasma glucose (2hPG) was ≥200 mg/dl (≥11.1 mmol/l). Glycated haemoglobin (HbA1c) was simultaneously measured by a chromatographic assay (Variant Biorad, Hercules, California, USA). HbA1c values of 5.7 and 6.5% were considered as thresholds for normal glucose metabolism and T2DM, respectively.
Finally, the following insulin sensitivity and resistance indices were derived:

– Insulin resistance was calculated by the homeostatic model of insulin resistance (HOMA-IR) as fasting insulin (FPI, μU/m) × [FPG (mmol/l)/22.5] (13);
– Insulin sensitivity index (ISI) (14) as 2/[FPG+2hPG)/178 × (FPI+2hPI)/46.94 + 1];
– Early Insulin Sensitivity Index (EISI) (15): EISI = 0.156 – 0.0000459 × 2hPI – 0.000321 × FPI – 0.00541 × 2hPG.

For each patient, two sex and age (+/- 2.5 years) matched controls were selected

from a metabolic diseases clinic of the same academic hospital. Controls were also matched for presence/absence of arterial hypertension and belonged to the same World Health Organization BMI category of cases.

Data were recorded in a database and analysed using the statistical software package MedCalc v. 9.3.8.0 (MedCalc Software, Broekstraat 52, 9030, Mariakerke, Belgium). A significant departure from normal distribution was verified by the D'Agostino-Pearson test for continuous variables; accordingly, the measures of centrality and dispersion of data chosen were median and interquartile range [IQR]. Continuous variables of interest in groups (controls, RA and PsA) were compared by the Kruskal-Wallis (K-W) test. The distribution of categorical variables was compared between groups by Pearson's χ^2. The existence of an association between potential predictors of glucose metabolism and blood glucose parameters was investigated by univariate analysis; the corresponding putative predictors of glucose metabolism were then used to build multivariate models of prediction. The significance level chosen for each test was 0.05 (two-tails).

RESULTS

The study population included 53 consecutive patients with RA, 44 with PsA and 194 controls matched for age, sex and BMI.

Demographic features, metabolic and disease-related parameters are reported in Table I. We found no significant differences comparing metabolic parameters of patients and controls (see Table I for details).

We then performed a univariate analysis on RA patients, to search for predictors (age, BMI, WC, ESR, CRP, daily prednisone dose, disease duration, disease activity, DAS28, CDAI, SDAI) of FPG, 2hPG, FPI, 2hPI, Hb1Ac alteration and of

Table I - Demographic, metabolic and disease related features of the population.

	Controls (194)	Rheumatoid Arthritis (53)	Psoriatic Arthritis (44)	Anova (K-W)* or χ^2 (pearson)$
Age (years)	56 [48-64]	57 [50-67]	54 [48-60]	p=0.025*
Sex (M/F)	58/136	9/44	20/24	p=0.010$
BMI (kg/m^2)	26.9 [23.8-31.1]	26.8 [23.3-31.4]	27.7 [24.3-32.5]	p=0.259*
WC (cm)	90 [80-101]	87 [75-98]	90 [81-102]	p=0.241*
FPG (mmol/l)	5.19 [4.89-5.67]	5.06 [4.72-5.61]	5.22 [4.94-5.72]	p=0.279*
2hPG (mmol/l)	5.97 [5.11-7.61]	5.61 [5.00-6.83]	6.14 [4.94-7.67]	p=0.355*
FPI (pmol/l)	71.8 [47.6-105.4]	81.6 [52.0-114.0]	76.5 [50.5-114.8]	p=0.510*
2hPI (pmol/l)	405.6 [258.4-808.3]	456.1 [258.4-719.5]	324.8 [159.5-739.7]	p=0.359*
HOMA-IR	2.25 [1.52-3.60]	2.53 [1.70-3.59]	2.53 [1.69-3.87]	p=0.696*
HbA1c	5.6 [5.4-5.9]	5.6 [5.3-6.0]	5.5 [5.3-5.8]	p=0.440*
ISI	0.74 [0.45-1.02]	0.76 [0.53-1.03]	0.89 [0.46-1.17]	p=0.475*
EISI	0.08 [0.04-0.10]	0.08 [0.06-0.10]	0.08 [0.05-0.10]	p=0.955*
ADA categories (NGT/IFG/IGT/IFG-IGT/diabetes)	118/12/32/20/12	35/1/9/4/4	27/2/7/5/3	p=0.971$
Prednisone use (y/n)	0/194	33/20	3/41	p=0.0001$
Median daily dose (mg)	0.00 [0.00-0.00]	1.46 [0.47-3.50]	0.00 [0.00-0.00]	p<0.0001*
Disease activity (active/remission)	n.a.	18/33	13/31	p=0.838$
Disease duration (months)	n.a.	26 [19-60]	29 [21-58]	p=0.505$

BMI, Body mass index; WC, Waist circumference; FPG, Fasting plasma glucose; 2hPG, 2-h post-OGTT plasma glucose; FPI, Fasting plasma insulin; 2hPI, 2-h post-OGTT plasma insulin; HOMA-IR, homeostatic model of insulin resistance; HbA1c, glycated hemoglobin; ISI, insulin sensitivity index; EISI, early insulin sensitivity index; NGT, normal glucose tolerance; IFG, impaired fasting glucose; IGT, impaired glucose tolerance.

Table II - Predictors of glucose metabolism in RA: univariate analysis, associations with clinical and lab data.

	Rheumatoid Arthritis in remission (DAS28 < 2.6)							Rheumatoid Arthritis with residual activity (DAS28 ≥ 2.6)						
	Age (years)	BMI	WC (cm)	ESR (mm/h)	CRP (mg/dl)	Disease duration (months)	PDN dose (mg)	Age (years)	BMI	WC (cm)	ESR (mm/h)	CRP (mg/dl)	Disease duration (months)	PDN dose (mg)
FPG (mmol/l)	0.082 p=0.651	**0.726 p<0.001**	**0.568 p=0.001**	0.136 p=0.459	0.212 p=0.243	0.052 p=0.772	0.273 p=0.124	0.323 p=0.191	0.017 p=0.946	0.190 p=0.450	0.116 p=0.658	0.421 p=0.092	0.238 p=0.342	-0.048 p=0.851
2hPG (mmol/l)	0.306 p=0.083	0.243 p=0.174	0.189 p=0.308	0.328 p=0.067	0.225 p=0.217	0.107 p=0.554	0.183 p=0.309	-0.002 p=0.994	-0.058 p=0.818	-0.030 p=0.907	0.208 p=0.422	**0.754 p<0.001**	0.335 p=0.174	-0.177 p=0.483
FPI (pmol/l)	-0.199 p=0.266	**0.643 p<0.001**	**0.439 p=0.013**	0.018 p=0.920	-0.001 p=0.995	-0.147 p=0.413	0.157 p=0.383	**0.625 p=0.006**	0.125 p=0.621	0.187 p=0.458	**0.594 p=0.012**	0.174 p=0.504	-0.104 p=0.681	0.272 p=0.275
2hPI (pmol/l)	0.0264 p=0.138	0.235 p=0.189	0.212 p=0.253	0.338 p=0.059	0.066 p=0.721	0.162 p=0.368	0.044 p=0.810	**0.474 p=0.047**	0.199 p=0.429	0.304 p=0.220	0.186 p=0.473	**0.781 p<0.001**	0.371 p=0.130	0.093 p=0.714
HOMA-IR	-0.199 p=0.268	**0.655 p<0.001**	**0.419 p=0.019**	0.016 p=0.931	0.013 p=0.942	-0.134 p=0.457	0.160 p=0.372	**0.687 p=0.002**	0.103 p=0.684	0.224 p=0.371	**0.584 p=0.014**	0.282 p=0.273	-0.048 p=0.851	0.227 p=0.366
HbA1c (mmol/mol)	0.035 p=0.856	**0.583 p=0.001**	0.313 p=0.112	0.070 p=0.722	0.268 p=0.168	-0.189 p=0.325	0.129 p=0.506	**0.590 p=0.010**	-0.129 p=0.609	0.054 p=0.832	0.429 p=0.086	0.376 p=0.137	-0.042 p=0.868	-0.035 p=0.891
ISI (Belfiore)	-0.319 p=0.070	**-0.427 p=0.013**	-0.344 p=0.058	-0.129 p=0.481	-0.169 p=0.356	-0.200 p=0.264	-0.105 p=0.560	-0.456 p=0.057	-0.189 p=0.453	-0.299 p=0.229	-0.203 p=0.434	**-0.736 p=0.001**	-0.373 p=0.128	-0.036 p=0.888
EISI (Stumvoll)	-0.055 p=0.763	**-0.519 p=0.002**	**-0.383 p=0.033**	-0.217 p=0.233	-0.065 p=0.724	-0.006 p=0.972	-0.140 p=0.438	**-0.507 p=0.032**	-0.135 p=0.592	-0.230 p=0.358	-0.428 p=0.087	**-0.820 p<0.001**	-0.304 p=0.219	-0.085 p=0.737

BMI, Body mass index; WC, Waist circumference; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PDN, prednisone; CDAI, clinical disease activity index; SDAI, simplified disease activity index; DAS28, disease activity score 28; FPG, Fasting plasma glucose; 2hPG, 2-h post-OGTT plasma glucose; FPI, Fasting plasma insulin; 2hPI, 2-h post-OGTT plasma insulin; HOMA-IR, homeostatic model of insulin resistance; HbA1c, glycated hemoglobin; ISI, insulin sensitivity index; EISI, early insulin sensitivity index.

insulin resistance indices (HOMA-IR, ISI (Belfiore) and EISI (Stumvoll) impairment (data not shown). Significant predictors were then assessed in multivariate analysis adjusted for sex and prednisone use; BMI was the single variable associated with FPG, FPI and HOMA-IR elevation ($\beta>0.442$, $p<0.042$ for all). Prednisone use was the single predictor of 2hPG elevation ($\beta=0.371$, $p<0.016$), while we failed to identify predictors of impaired 2hPI, Hb1Ac, ISI (Belfiore) and EISI (Stumvoll). We have also checked for the effect of citrullinated peptide antibody status on glucose metabolism. No differences could be detected between seropositive (N 37) and seronegative (N 16) patients (data not shown).

We performed the same analysis for PsA patients; predictors (age, BMI, WC, ESR, CRP, prednisone daily dose, disease duration, disease activity) of FPG, 2hPG, FPI, 2hPI, Hb1Ac elevation and insulin resistance indices (HOMA-IR, ISI and EISI) impairment were assessed in univariate analysis (data not shown). Significant predictors were then included in a multivariate analysis model adjusted for sex and prednisone use. Disease duration was the only predictor of 2hPI elevation and ISI/EISI impairment ($p<0.03$).

Univariate and multivariate analysis were performed stratifying both RA and PsA patients according to disease activity. Results of univariate analysis are reported in Tables II, III and IV.

Variables with statistically significant associations were included in multivariate models adjusted for sex and prednisone use. Considering RA patients with residual disease activity, FPI elevation was predicted by ESR alone ($\beta=0.459$, $p=0.047$); accordingly, HOMA-IR was predicted by ESR and age ($\beta=0.445$, $p=0.020$; $\beta=0.432$, $p=0.028$, respectively). 2hPG and 2hPI were predicted by CRP alone ($\beta=0.915$, $p=0.0003$ and $\beta=0.772$, $p=0.0006$); accordingly, ISI and EISI were predicted by CRP and age (ISI: CRP, $\beta=-0.787$, $p=0.0006$; Age $\beta=-0.382$, $p=0.042$. EISI: CRP $\beta=-0.797$, $p=0.0001$; Age $\beta=-0.419$, $p=0.007$). Finally, Hb1Ac was only related to age

Table III - Predictors of glucose metabolism in RA: univariate analysis, associations with disease activity scores.

	Rheumatoid Arthritis in remission (DAS28 < 2.6)			Rheumatoid Arthritis with residual activity (DAS28 ≥ 2.6)		
	CDAI	SDAI	DAS28	CDAI	SDAI	DAS28
FPG (mmol/l)	0.202 p=0.259	-0.148 p=0.411	-0.117 p=0.532	-0.427 p=0.077	-0.339 p=0.169	-0.354 p=0.163
2hPG (mmol/l)	0.218 p=0.222	-0.095 p=0.598	-0.037 p=0.843	-0.236 p=0.346	-0.151 p=0.550	-0.088 p=0.736
FPI (pmol/l)	-0.010 p=0.954	-0.119 p=0.509	-0.078 p=0.678	0.308 p=0.214	-0.111 p=0.662	-0.177 p=0.496
2hPI (pmol/l)	0.165 p=0.358	-0.125 p=0.488	-0.042 p=0.822	-0.071 p=0.780	-0.005 p=0.984	-0.008 p=0.975
HOMA-IR	-0.022 p=0.903	-0.155 p=0.390	-0.108 p=0.564	0.187 p=0.458	-0.185 p=0.461	-0.249 p=0.336
HbA1c (mmol/mol)	0.143 p=0.458	0.188 p=0.328	0.294 p=0.137	-0.164 p=0.514	-0.245 p=0.327	-0.211 p=0.416
ISI (Belfiore)	-0.108 p=0.550	0.006 p=0.974	-0.057 p=0.760	-0.031 p=0.903	-0.083 p=0.743	-0.060 p=0.820
EISI (Stumvoll)	-0.104 p=0.563	0.142 p=0.431	0.070 p=0.707	-0.017 p=0.948	0.108 p=0.669	-0.110 p=0.674

BMI, Body mass index; WC, Waist circumference; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PDN, prednisone; CDAI, clinical disease activity index; SDAI, simplified disease activity index; DAS28, disease activity score 28; FPG, Fasting plasma glucose; 2hPG, 2-h post-OGTT plasma glucose; FPI, Fasting plasma insulin; 2hPI, 2-h post-OGTT plasma insulin; HOMA-IR, homeostatic model of insulin resistance; HbA1c, glycated hemoglobin; ISI, insulin sensitivity index; EISI, early insulin sensitivity index.

Table IV - Predictors of glucose metabolism in PsA: univariate analysis.

	Psoriatic Arthritis in remission							Psoriatic Arthritis with residual activity						
	Age (years)	BMI	WC (cm)	ESR (mm/h)	CRP (mg/dl)	Disease duration (months)	PDN dose (mg)	Age (years)	BMI	WC (cm)	ESR (mm/h)	CRP (mg/dl)	Disease duration (months)	PDN dose (mg)
FPG (mmol/l)	0.354 p=0.051	0.332 p=0.068	**0.363 p=0.049**	0.227 p=0.255	-0.095 p=0.639	0.287 p=0.124	-0.116 p=0.534	-0.154 p=0.615	**0.572 p=0.041**	0.209 p=0.493	**0.559 p=0.047**	-0.119 p=0.714	0.498 p=0.083	0.195 p=0.522
2hPG (mmol/l)	0.335 p=0.065	0.192 p=0.300	0.248 p=0.187	0.336 p=0.087	0.120 p=0.551	0.038 p=0.840	0.036 p=0.848	0.438 p=0.134	0.268 p=0.375	0.185 p=0.546	0.342 p=0.252	-0.027 p=0.934	**0.636 p=0.019**	0.383 p=0.196
FPI (pmol/l)	0.046 p=0.808	0.318 p=0.086	**0.449 p=0.015**	-0.091 p=0.650	0.027 p=0.894	0.088 p=0.651	-0.139 p=0.463	-0.033 p=0.913	**0.618 p=0.024**	0.465 p=0.109	0.210 p=0.492	-0.261 p=0.412	0.297 p=0.325	0.040 p=0.896
2hPI (pmol/l)	0.026 p=0.890	**0.401 p=0.028**	**0.390 p=0.036**	**0.409 p=0.034**	0.265 p=0.182	0.179 p=0.354	-0.114 p=0.548	0.281 p=0.352	0.148 p=0.629	-0.042 p=0.892	0.009 p=0.978	-0.210 p=0.512	**0.821 p=0.001**	0.348 p=0.243
HOMA-IR	0.076 p=0.689	0.299 p=0.109	**0.433 p=0.019**	-0.020 p=0.920	-0.012 p=0.952	0.079 p=0.685	-0.114 p=0.547	-0.045 p=0.884	**0.630 p=0.021**	0.431 p=0.141	0.315 p=0.295	-0.255 p=0.425	0.338 p=0.259	0.051 p=0.868
HbA1c (mmol/mol)	**0.428 p=0.020**	0.279 p=0.142	**0.431 p=0.022**	**0.424 p=0.035**	0.157 p=0.452	0.139 p=0.480	-0.020 p=0.919	0.220 p=0.470	0.296 p=0.326	0.149 p=0.627	-0.053 p=0.864	0.122 p=0.706	0.349 p=0.242	-0.184 p=0.547
ISI (Belfiore)	-0.037 p=0.844	-0.332 p=0.073	**-0.383 p=0.040**	-0.298 p=0.130	-0.213 p=0.287	-0.206 p=0.284	0.193 p=0.307	-0.184 p=0.548	-0.201 p=0.510	-0.107 p=0.728	-0.075 p=0.808	0.421 p=0.173	**-0.554 p=0.049**	-0.305 p=0.311
EISI (Stumvoll)	-0.112 p=0.554	**-0.382 p=0.037**	**-0.455 p=0.013**	-0.312 p=0.113	-0.211 p=0.291	-0.135 p=0.484	0.112 p=0.557	-0.261 p=0.389	-0.331 p=0.270	-0.157 p=0.609	-0.151 p=0.622	0.206 p=0.520	**-0.716 p=0.006**	-0.307 p=0.307

BMI, Body mass index; WC, Waist circumference; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PDN, prednisone; FPG, Fasting plasma glucose; 2hPG, 2-h post-OGTT plasma glucose; FPI, Fasting plasma insulin; 2hPI, 2-h post-OGTT plasma insulin; HOMA-IR, homeostatic model of insulin resistance; HbA1c, glycated hemoglobin; ISI, insulin sensitivity index; EISI, early insulin sensitivity index.

(β=0.542, p=0.007). In RA patients with no residual disease activity, as expected, the most relevant predictor for impairment of glucose and insulin metabolism was BMI, which was a significant predictor of FPG, FPI, HOMA-IR, Hb1Ac and ISI (β=0.589, p=0.004; β=0.659, p=0.007; β=0.726, p=0.002; β=0.553, p=0.004; -0.392, p=0.044 respectively); furthermore, prednisone use predicted FPG and 2hPG elevation (β=0.295, p=0.027; β=0.480, p=0.005 respectively).

Considering PsA patients with residual disease activity, no significant predictor was identified at multivariate analysis; in patients with no residual disease activity, WC was the only significant predictor of ISI impairment (β=-0.452, p=0.042), while age predicted Hb1Ac elevation (β=0.439, p=0.044).

DISCUSSION

Growing evidence has related insulin resistance to inflammatory arthritis (2, 3); in this OGTT-based study we have investigated this association both in RA and PsA. Interestingly, we found that the correlation between inflammation and insulin sensitivity is limited to patients with active RA, whereas it is not demonstrable in PsA.

Looking at the indices of glucose metabolism in RA patients, BMI was the strongest predictor of insulin resistance, in agreement with the literature suggesting that obesity is the main determinant of glucose tolerance (16). On the other hand, prednisone use was the only predictor of 2hPG, as expected considering the detrimental impact of prednisone on insulin sensitivity. In PsA, disease duration predicted higher insulin plasma concentration after OGTT; prednisone use was less relevant, its effect being more limited in PsA than in RA. Interestingly, we were not able to confirm previous studies which proved an altered insulin sensitivity in RA and PsA with respect to a control population (2, 17); recently, results consistent with ours have been reported in a population of patients affected by early RA, the insulin sensitivity of whom was not different from a control group (18). It could be argued that in our study the high percentage of patients in clinical remission may have created a bias; to avoid it, we evaluated whether inflammation and disease activity were able to predict the result of OGTT in those patients with residual disease activity. Interestingly, in RA, ESR was in direct relationship with baseline blood glucose levels and, accordingly, the HOMA-IR was higher in the presence of high ESR values. On the contrary, CRP was a predictor of the response to a glucose load, being directly related to ISI and EISI. The reason why different inflammatory markers predict different alterations of glucose metabolism is unclear. One possible explanation is that ESR marks inflammation on a longer time scale than CRP which, conversely, is a marker of inflammation spanning a shorter period.

In PsA the above mentioned associations were not confirmed, a finding that needs to be discussed at the light of the current literature. Recently, in fact, different authors have convincingly demonstrated an increased risk of type 2 diabetes mellitus (T2DM) in patients affected by PsA with respect to either a matched control group or patients affected by RA (19, 20). Two reasons may exist to explain this apparent discrepancy. Firstly, the patients enrolled in these studies had a significantly longer follow-up than our cohort PsA patients; secondly, for the present study we excluded PsA patients with a defined diagnosis of T2DM. As a matter of fact, we did not investigate incidence and prevalence of T2DM in PsA at all, since our aim was to give a cross-sectional picture of the association between inflammation and insulin sensitivity. On the other hand, the reason(s) why inflammatory markers are less predictive of glucose metabolism impairment in PsA than in RA could be: i) the heterogeneity of PsA; and/or ii) the fact that in PsA inflammatory markers reflect disease activity less well, especially among patients whose disease is mainly characterized by enthesopathy manifestations. Due to these limitations, we cannot entirely dismiss the hypothesis that a larger sample and a more disease-specific stratification of activ-

ity (cutaneous, articular or enthesopathy) could disclose an association between inflammation and insulin sensitivity in PsA as well as in RA.

Our study has other limitations. As just mentioned, its nature is explorative, with a relatively small sample size and short follow-up; a larger population is required to confirm our results and to allow a more comprehensive analysis. Specifically, it would be interesting to evaluate the response to OGTT, grouping patients according to the type of anti-rheumatic treatment in use, since it has been shown that some of the classical and biological DMARDs commonly employed in clinical practice have a positive impact on insulin sensitivity (5, 6, 21). On the other hand, we would like to point out that a novel aspect of the study is the comparison of glucose metabolism between RA and PsA. These two conditions are characterized by a very different biological behavior, which arguably is reflected on relevant differences in comorbidities.

CONCLUSIONS

In conclusion, appropriate management of comorbidities demands that an altered glucose metabolism should be ruled out for all patients affected by inflammatory arthritis. However, to interpret correctly the results of metabolic studies, clinicians need to be aware that the impact of disease activity is not necessarily similar for all rheumatic diseases. Our data indicate that they should be particularly alerted to its influence on patients with RA, among whom not only fasting insulin sensitivity, but also the response to an oral glucose load bears a relationship with inflammatory markers.

Conflicts of interest: the authors declare they have no conflicts of interest.

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