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ORIGINAL ARTICLE

Metabolic syndrome, non-alcoholic fatty liver disease and liver stiffness in psoriatic arthritis and psoriasis patients

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Abstract

Objectives Non-alcoholic fatty liver disease (NAFLD), potentially evolving into liver fibrosis (LF), is frequent in psoriasis (PsO), but data in psoriatic arthritis (PsA) are lacking. Our study aimed to investigate the prevalence of NALFD and LF in PsA/PsO and the contribution of arthritis in their onset.

Method PsA and PsO patients were consecutively enrolled. Exclusion criteria were liver diseases causing fibrosis (except NAFLD), alcohol ≥ 20 g/day, daily use of non-steroidal anti-inflammatory drugs and current/previous methotrexate use. Clinical history, biochemical and clinimetrical data and insulin-resistance index HOMA (homeostatic model assessment) were assessed. Patients underwent a liver ultrasound to identify steatosis (therefore NAFLD) and transient elastography, to evaluate LF (stiffness≥ 7 kPa = fibrosis). Statistical analysis included basic statistics, logistic and linear regression analyses (to assess the contribution of arthritis to NAFLD and LF grading, respectively) and Spearman's correlations; $p \leq 0.05$ was considered significant.

Results Seventy-six patients were enrolled (PsA/PsO 43/33). MetS and LF prevalence were similar between PsA and PsO (35% vs 33%, $p = 0.88$; 31% vs 28%, $p = 0.77$, respectively). NAFLD was more frequent in PsO (65% vs 35%, $p = 0.044$). In multivariable models with NAFLD and LF grading as outcomes, arthritis was not a significant predictor, while HOMA was independently associated with both (OR 1.34; 95%CI 1.06, 1.69; beta 0.88; 95%CI 0.54, 1.21, respectively). Female sex was independently associated with LF grading (beta 1.81; 95%CI 0.05, 3.57).

Conclusions NAFLD was more frequent in PsO, but MetS and LF prevalence were similar in PsA and PsO. Insulin resistance is the main determinant of NAFLD and LF, while additional contribution of arthritis seems small.

Key Points
- *The prevalence of metabolic comorbidities, including liver fibrosis, is overall quite similar between psoriatic arthritis and psoriasis.*
- *NAFLD is more frequently found in psoriasis than psoriatic arthritis.*
- *The contribution of arthritis in the onset of metabolic comorbidities seems small.*

Keywords Fibroscan · Liver fibrosis · Metabolic syndrome · Non-alcoholic fatty liver disease · Psoriasis · Psoriatic arthritis

Introduction

Psoriasis (PsO) is a chronic inflammatory skin disease, with a worldwide prevalence of 0.9–8.5% [1]. Psoriatic arthritis (PsA) is a seronegative, chronic, inflammatory arthropathy often associated with Pso with an estimated prevalence from 0.16 to 0.25% [2]; it can affect between 20 and 30% of patients with Pso [3].

In both patients with PsO and PsA, metabolic syndrome (MetS) is known to be more prevalent in comparison with the general population [4, 5]. This association is thought to be sustained by the inflammatory burden, characteristic of these two conditions, where the presence of pro-inflammatory cytokines such as, e.g., IL-6, IL-17 and TNF-α can be

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responsible of an increased insulin resistance, a key mechanism in the induction of MetS [6, 7].

One of the consequences of MetS can be the development of a non-alcoholic fatty liver disease (NAFLD), which range from steatosis to steatohepatitis, and even cirrhosis in the later stages [8]. Furthermore, NAFLD has shown to be independently correlated with PsO severity [9], and a patient with PsO seems to be more prone to develop LF [10, 11] even if a causal link between PsO and liver fibrosis has not been demonstrated yet. Nowadays, non-invasive evaluation of LF can be easily performed thanks to transient elastography, an ultrasound-based technique which was first applied to patients with chronic viral hepatitis, and more recently also to NAFLD [12, 13].

While various studies have been performed about the association of PsO with different comorbidities, including MetS, NAFLD and LF [4, 14–16], data in PsA are lacking. Only a few studies compared the prevalence of MetS between PsO and PsA, with contrasting results [17, 18]. Besides, no studies specifically focused on metabolic liver disease in PsO compared with PsA, even though data from the Biobadaderm registry suggested there are no significant differences between the two conditions in the prevalence of metabolic comorbidities (only hypertension and chronic liver disease were considered), after correction for age and sex [19]. It could be argued that PsO and PsA share various common pathogenic pathways; therefore, it could be expected that the prevalence of metabolic comorbidities is similar [20]. However, the presence of PsA over PsO might increase the inflammatory burden and the risk of systemic involvement compared with isolated PsO, especially due to disease severity, which has been shown to be an independent predictor of MetS in PsA [21]. Therefore, the aims of our study were (1) to investigate if the presence of arthritis, over PsO, could determine any difference in the prevalence of MetS, NAFLD and LF and (2) to assess the prevalence of NALFD and LF and their determinants in PsA and PsO. The information would be helpful for the clinicians in implementing diagnostic and treatment algorithms for metabolic comorbidities in PsA and PsO.

Materials and methods

Patients selection

Patients with PsO with or without arthritis ("PsO patients" for those with PsO only, and "PsA patients" for those with additional arthritis), attending the Rheumatology Unit and the Dermatology Clinic of the University of Padova (Italy) over a 9-month period were consecutively enrolled. The diagnosis of PsO was confirmed by the dermatologist, while PsA was diagnosed by the rheumatologist. In addition, all PsA patients fulfilled the classification criteria for psoriatic arthritis (CASPAR criteria) [22]. Inclusion criteria were age ≥ 18 years and current or previous history of PsO ascertained by a rheumatologist or dermatologist. Exclusion criteria were (1) liver diseases (other than NAFLD) potentially causing LF, (2) alcohol consumption ≥ 20 g/day [8], (3) daily use of non-steroidal anti-inflammatory drugs for a period ≥ 1 month in the past year, (4) current use of methotrexate [23], or use of methotrexate in the previous year and (5) other overlapping rheumatic diseases (mycrocristalline arthritis, rheumatoid arthritis, etc).

The present study was conducted in accordance with the Declaration of Helsinki. The local Ethics committee has approved the research protocol and informed consent has been obtained from all subjects.

Clinical and biochemical data

Demographic and clinical variables, including metrological data (blood pressure, height, weight, waist circumference), were collected from each patient. In the serum samples, collected the day after the evaluation to ensure patients' fast, we tested the following biomarkers: total cholesterol, high-density lipoprotein and low-density lipoprotein cholesterol (HDL and LDL, respectively), triglycerides, fasting glucose, insulin, glycosylated haemoglobin (HbA1c), alanine aminotransferase (ALT), aspartate aminotransferase (AST), blood urea nitrogen (BUN), creatinine, uric acid, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR).

The normal ranges of our laboratory were as follows: total cholesterol ≤ 200 mg/dL; HDL cholesterol ≥ 40 mg/dL; LDL cholesterol ≤ 128 mg/dL; triglycerides ≤ 150 mg/dL; fasting glucose ≤ 100 mg/dL; insulin 0–29, 100 mU/L; HbA1c ≤ 48 mmol/mol; ALT 7–35 U/L females,10–50 U/L males; AST 10–35 U/L females, 10–45 U/L males; BUN 2.5–7.5 mmol/L; creatinine 45–84 umol/L; 59–104 umol/L; uric acid ≤ 6 mg/dL; CRP 0–6 mg/L; ESR 0–28 mm/h female, 2–38 mm/h male.

Insulin resistance was evaluated through HOMA (homeostatic model assessment) index, using the following formula: fasting plasma glucose (mg/dL) × fasting plasma insulin (IU/mL)/405 [24]. HOMA yields an estimate of insulin sensitivity and β-cell function and represents a good indicator for insulin resistance to be used in epidemiological studies. The higher the value, the higher the severity of insulin resistance, with cut-offs variably defined between 1.8 and 3.8 indicating a pathologically altered insulin sensitivity [25]. However, its use is also appropriate in the normal population if data have to be compared with patients with abnormal glucose tolerance [24]. The presence of MetS was assessed according to National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) [26].

Disease activity was assessed through Psoriasis Area Severity Index—PASI for the skin involvement and Disease

Activity index for Psoriatic Arthritis—DAPSA for the articular involvement.

Ultrasound examination and transient elastography

All patients underwent both standard liver ultrasound, to assess the presence of steatosis, and transient elastography to evaluate the presence and grading of LF (stiffness ≥ 7 kPa = fibrosis).

The examinations were carried out on the same day by a single specifically trained technician.

Ultrasound examinations were performed using a MyLab 70 Esaote machine with a 3.5–5 MHz transducer. If typical ultrasound features, such as diffuse hyper-echogenicity, ultrasound attenuation, poor visualisation of intra-hepatic structures, were present, liver steatosis was diagnosed. Liver stiffness (LS) was measured by TE using a FibroScan ® (EchoSens, Paris, France). Measurements were performed on the right lobe of the liver, through intercostal spaces with the patient lying in dorsal decubitus with the right arm in maximal abduction. The tip of the transducer probe was covered with coupling gel and placed on the skin, between the rib bones at the level of the right lobe of the liver. The operator, assisted by a time-motion ultrasound image, located a liver portion at least 6-cm thick and free of large vascular structures. When the target area had been located, the operator pressed the probe button to commence the measurements. The measurement depth was between 20 and 60 mm. Ten validated measurements were performed on each patient. The success rate was calculated as the number of validated measurements divided by the total number of measurements. The results were expressed in kilopascals (kPa). The median value was considered representative of the elastic modulus of the liver. The whole examination lasted less than 5 min. Only procedures with 10 validated measurements and a success rate of at least 60% were considered reliable.

Statistical analysis

The Mann-Whitney *U* test or *T* test for continuous measurement, and chi-square test or Fisher's exact test for categorical measurement, as appropriate, were used to evaluate differences between PsA and PsO patients. Multivariable regression models aimed at assessing the contribution of arthritis, properly adjusted for confounders, in determining NAFLD and the grading of liver stiffness, were performed in the whole patient cohort (PsA and PsO together). Logistic regression analysis was used to identify determinants of NAFLD, while linear regression analysis was used to identify determinants of liver stiffness grading. Confounders of the association between arthritis and NALFD as well as arthritis and grading of liver stiffness were selected based primarily on previous scientific literature [27] and secondarily on the results of an exploratory univariable analysis. With regard to the latter, independent variables associated with the outcome with a p value < 0.2 were considered for the multivariable model, but finally included only if they did not present significant collinearity with others. Results of logistic regression analyses were expressed in terms of odds ratio (OR), and 95% confidence interval (95%CI), while those of linear regression were expressed as regression coefficient (beta) and 95% confidence interval (95%CI). Spearman's correlations were used to examine correlations between parameters of interest and to inspect the presence of collinearity.

Data analysis was performed using STATA SE version 15 (StataCorp, College Station, TX, USA) and a level of significance of ≤ 0.05 was considered.

Results

Seventy-six patients attending the Rheumatology Unit and the Dermatology Clinic of the University of Padova (Italy) were enrolled. These patients were attending the clinic either for regular follow-up visits or for infusion of biologic drug. Among the 43 PsA patients, 23 (53%) were treated with TNF-inhibitors, 9 (21%) with salazopyrine, 5 (12%) with leflunomide and 6 (14%) with hydroxychloroquine. Among the 33 PsO patients, 16 (48.5%) were treated with TNF-inhibitors, 7 (21.2%) with topic medications, 1 (3.0%) with cyclosporine A and 9 (27.3%) were not undergoing any specific treatment at the time of evaluation.

Patients with PsA and PsO (Table 1) had similar characteristics regarding age (60.2 ± 8.4 vs 54.5 ± 19.6 years), sex distribution (males 32(74%) vs 21(63%)) and disease duration (duration in years of PsA and PsO 12.6 ± 8.5 and 18.2 ± 14.2). PsO patients displayed higher body mass index (BMI) (29.1 ± 6.3 vs 25.7 ± 3.4, $p = 0.009$), PASI (5.0 ± 4.0 vs 1.5 ± 2.5, $p = 0.035$) and basal level of insulin (14.8 ± 6.5 vs 11.9 ± 7, $p = 0.020$) in comparison with PsA patients. Serum uric acid (4.9 ± 1.5 vs 5.7 ± 1.4 mg/dL, $p = 0.0001$) was instead lower in PsO than PsA. Regarding extra-articular manifestations (data not shown in Table 1), 16 patients (37%) had a past history of/ had current inflammatory back pain, 19 (43%) had a past history of/ had current enthesitis, 2 had an ascertained history of dactylitis (5%) but none of them presented it as a current manifestation.

MetS and LS prevalence were similar between PsA and PsO 15 (35%) vs 11 (33%) and 12 (28%) vs 8 (24%) (p = ns). NAFLD was instead significantly higher in PsO (6 (13.9%) vs 11 (33.3%), $p = 0.044$) (Fig. 1).

The mean value of liver stiffness (in kPa) was rather low in both patients groups, but there were some individuals presenting with liver fibrosis (Fig. 2).

The univariable logistic regression analysis having NAFLD as outcome showed that several factor were

Table 1 Demoghaphics, clinical characteristics, biochemical data and comorbidities in patients with psoriasis (PsO) and psoriatic arthritis (PsA)

	PsA	PsO	*p* value
Number of patients, *n*	43	33	–
Age (years), mean ± SD	60.2 ± 8.4	54.5.2 ± 19.6	0.10
Male, *n* (%)	32 (74)	21 (64)	0.31
Arthritis duration (years), mean ± SD	12.6 ± 8.5	–	–
Psoriasis duration (years), mean ± SD	20 ± 12.2	18.2 ± 14.2	–
PASI, mean ± SD	*1.5 ± 2.5*	*5 ± 4.6*	*0.035*
CRP (mg/dl), mean ± SD	0.5 ± 0.7	0.7 ± 0.9	0.93
DAPSA, mean ± SD	11.7 ± 7.3	–	–
HAQ, mean ± SD	0.69 ± 0.5	–	–
VAS pain (cm) 0–10, mean ± SD	3.9 ± 2.1	–	–
VAS global assessment (cm) 0–10, mean ± SD	3.7 ± 2.1	–	–
BMI (kg/m^2), mean ± SD	*25.7 ± 3.4*	*29.1 ± 6.3*	*0.009*
Waist circumference (cm), mean ± SD	99.7 ± 12.1	103.1 ± 13.1	0.18
Fasting glucose (mg/dl), mean ± SD	103.5 ± 22.3	112.5 ± 52	0.49
Insulin (mU/L), mean ± SD	*11.9 ± 7*	*14.8 ± 6.5*	*0.020*
HbA1c, mean ± SD	5.6 ± 0.6	5.9 ± 1.2	0.80
HOMA index, mean ± SD	3.3 ± 2.5	4 ± 2.5	0.08
Total cholesterol (mg/dl), mean ± SD	213.7 ± 36.4	202 ± 39.5	0.13
HDL cholesterol (mg/dl), mean ± SD	54.3 ± 15.4	49.4 ± 13.9	0.10
LDL cholesterol (mg/dl), mean ± SD	132.9 ± 32.8	137.6 ± 35.4	0.36
Triglycerides (mg/dl), mean ± SD	109.7 ± 52.5	130.3 ± 32.9	0.32
Uric acid (mg/dl), mean ± SD	*4.9 ± 1.5*	*5.7 ± 1.4*	*< 0.0001*

The values in italics are significant to a 0.05 significance level

PsA, psoriatic arthritis; *PASI*, Psoriasis Area Severity Index; *CRP*, C-reactive protein; *DAPSA*, Disease Activity index for Psoriatic Arthritis; *HAQ*, health assessment questionnaire; *VAS pain*, visual analogue scale of pain; *VAS global assessment*, visual analogue scale of patient global assessment; *BMI*, body mass index; *HbA1c*, glycosilated haemoglobin; *HOMA*, homeostatic model assessment; *HDL*, high-density lipoprotein; *LDL*, low-density lipoprotein

associated with NAFLD with a p value < 0.2: PASI (OR 1.14; 95% CI 0.01, 0.26; $p = 0.034$), BMI (OR 1.21; 95%CI 1.07, 1.36; $p = 0.002$), waist circumference (OR 1.06; 95%CI 1.01, 1.12; $p < 0.001$), triglycerides (OR 1.00; 95%CI 0.99, 1.01; $p = 0.123$), HOMA (OR 1.32; 95%CI 1.07, 1.63; $p = 0.009$), glycosylated haemoglobin (OR 4.61; 95%CI 1.55, 13.63; $p = 0.006$), diabetes mellitus (OR 7.85; 95%CI 2.19, 28.03; $p = 0.002$), uric acid (OR 1.68; 95%CI 1.14, 2.49; $p = 0.009$) and hypertension (OR 3.57; 95%CI 1.15, 11.08; $p = 0.027$). Interestingly, the presence of arthritis seemed to be negatively correlated to NAFLD at univariable analysis (OR 0.32; 95% CI 0.10, 1; $p = 0.050$).

In order to limit the number of predictor in the final multivariable model (Table 2), the presence of hypertriglyceridemia or hypercholesterolemia was a combined binary variable "dyslipidemia". Moreover, several variables displayed, as expected, a correlation with HOMA and thus were excluded from the model: BMI ($r = 0.44$, $p = 0.0001$), waist circumference ($r = 0.48$, $p < 0.0001$), diabetes mellitus ($r = 0.57$, $p < 0.0001$), glycosylated haemoglobin ($r = 0.59$, $p < 0.0001$), hypertension ($r = 0.35$, $p = 0.001$), hyperuricemia ($r = 0.55$, $p < 0.0001$). In the final multivariable model, the only variable showing an independent association with the presence of NAFLD was HOMA, while arthritis was not significantly associated with the outcome.

The results of linear regression analysis having liver stiffness grading, expressed in kPa, as outcome, showed that at univariable analysis, several factors were associated with LS with a p value < 0.2: HOMA (beta 0.51; 95%CI 0.45, 1.08; $p < 0.0001$), glycosylated haemoglobin (beta 0.42; 95%CI 0.83, 2.6; $p < 0.0001$), diabetes mellitus (beta 0.59; 95%CI 4.17, 8.33; $p < 0.0001$), uric acid (beta 0.22; 95%CI − 0.03, 1.36; $p = 0.062$) and hypertension (beta 0.25; 95%CI 1.14, 3.88; $p = 0.035$) were positively associated with the outcome. Total cholesterol (beta − 0.26; 95%CI − 0.04, − 0.01; $p = 0.027$) and LDL cholesterol (beta − 0.28; 95%CI − 0.05, − 0.01; $p = 0.018$) were inversely associated with LS. For the final selection of predictors in the multivariable model (Table 2), the same consideration as in the logistic regression model for NAFLD where applied. In the final multivariable model, the only variables displaying an independent and positive correlation with the outcome were HOMA and female sex, while arthritis was not a significant predictor.

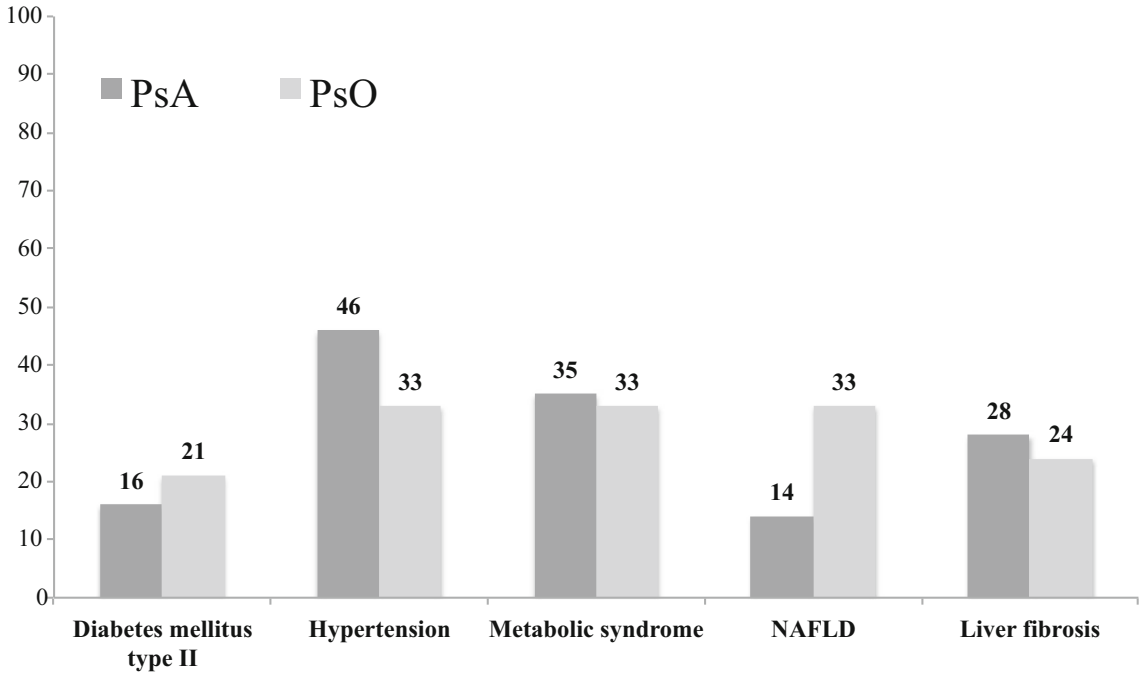

Fig. 1 Percentage of comorbidities in patients with psoriatic arthritis (PsA) and psoriasis (PsO)

When studying correlations between metabolic parameters and LS grading, particularly strong correlation emerged between uric acid and HOMA ($r = 0.80$, $p < 0.0001$) and uric acid and LS ($r = 0.73$, $p < 0.0001$) in patients with PsO only. In the whole population of PsA and PsO, the strength of the correlations was weaker although still significant: $r = 0.47$, $p < 0.0001$ and $r = 0.29$, $p = 0.01$, respectively.

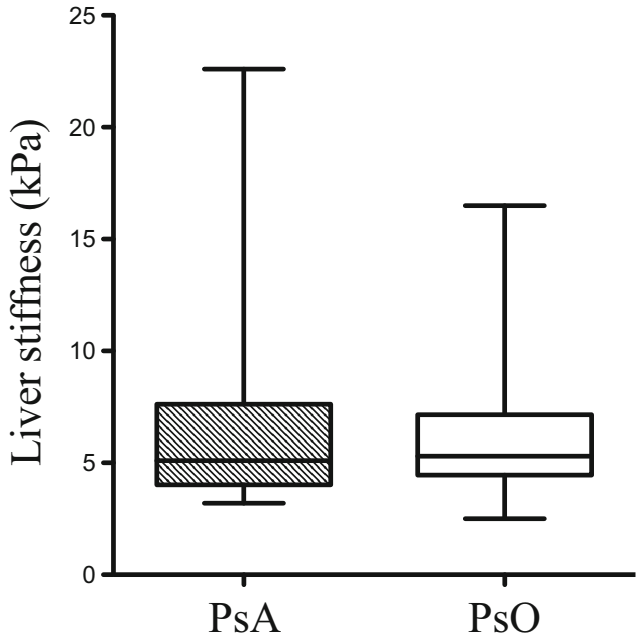

Fig. 2 Liver stiffness grading (in kPa) in patients with psoriatic arthritis (PsA) and psoriasis (PsO)

Discussion

Previous studies demonstrated that MetS and related NAFLD are frequent comorbidities in PsO patients and significantly contribute to their morbidity and mortality [28]. Mechanisms linking PsO with NAFLD are complex and the two conditions share common pathways. The existence of a "hepato-dermal axis" has even been postulated, to indicate that psoriatic skin-derived lymphocytes and keratinocytes produce inflammatory cytokines (IL-6, IL-17 and TNF-α), circulating systemically to the liver and inducing an array of metabolic derangements that promote insulin resistance, a hallmark feature of NAFLD [29, 30]. However, it also seems possible that NAFLD may conversely act on psoriasis by releasing pro-inflammatory, pro-oxidant and pro-atherogenic mediators from the steatotic and inflamed liver (e.g., C-reactive protein, fibrinogen, IL-6, plasminogen activator inhibitor-1, transforming growth factor-β). These mediators could increase psoriasis severity provoking increased keratinocyte proliferation, inflammation and upregulation of vascular adhesion molecules [29]. Naturally, PsO is only one of the factors that may worsen NAFLD, a disease with a multifactorial aetiology, where peripheral insulin resistance seems to be the initial hit of a multistep development [28]. Insulin resistance is often caused by expanded visceral fat. Adipose tissue, in fact, increases release of non-esterified fatty acids, produces hormones and pro-inflammatory adipocytokines (including TNF-α, IL-6, leptin, visfatin and resistin) and decreases production of adiponectin [29]. In the presence of obesity and insulin resistance, there is an increased influx of non-esterified fatty acids to the liver

Table 2 Multivariable logistic regression model with non-alcoholic fatty liver disease (NAFLD) as an outcome and multivariable linear regression model with liver stiffness (in kPa) as outcome in the whole population

	NAFLD		Liver stiffness (kPa)	
	OR (95% CI)	*p* value	Beta (95% CI)	*p* value
Arthritis	0.39 (0.10, 1.53)	0.18	0.63 (− 1.36, 2.62)	0.52
Female sex	1.38 (0.36, 5.29)	0.63	*1.81 (0.05, 3.57)*	*0.044*
Age	1.01 (0.92, 1.22)	0.39	0.01 (− 0.05, 0.08)	0.79
PASI	1.06 (0.87, 1.22)	0.67	− 0.14 (− .038, 0.08)	0.21
HOMA	*1.34 (1.06, 1.69)*	*0.014*	*0.87 (0.54, 1.21)*	*< 0.0001*
Dyslipidemia	0.35 (0.05, 2.30)	0.28	− 0.42 (− 2.58, 1.73)	0.69

Italics indicates significant results

CI, confidence interval; *NAFLD*, non-alcoholic fatty liver disease; *PASI*, Psoriasis Area Severity Index; *HOMA*, homeostatic model assessment; *OR*, odds ratio

which is responsible for the steatosis. Steatosis, in turn, renders the liver more susceptible to oxidative stress and inflammatory injuries, with a possible transition to steatohepatitis and finally fibrosis [28].

Considering the intriguing pathogenetic links between NAFLD and PsO, it could be questioned whether patients presenting with a long-course inflammation, or arthritis in addition to PsO, may have an increased risk of developing liver disease, and/or progress to more advanced stages of the disease such as fibrosis.

Our study did not show substantial differences in metabolic comorbidities (diabetes, hypertension. MetS, liver fibrosis, Fig. 1) in patients with PsA compared with patients with PsO. Only the prevalence of NAFLD seemed to be higher in PsO patients.

When examining general characteristics of the population, PsO patients displayed on average a more severe cutaneous disease as described by the PASI and had a higher BMI compared with those with PsA. Moreover, while in the PsO group, the proportion of overweight or obese patients was 61%, in the PsA group, this proportion was lower (50%), differently from what has been reported in a Canadian case-control study [31]. This highlighted the fact that PsA patients seemed to be overall less obese, thus presumably less metabolic compromised. This confounding factor has been taken into account in the multivariable models by introducing the insulin-resistance parameter (HOMA) as a covariate. In fact, as expected and as previously demonstrated in the literature, our data showed a high correlation between BMI and HOMA [32]: thus, in order to avoid collinearity, just one out of the 2 variables could be included in the models. Our decision was to adjust for insulin resistance (HOMA), since this is known to be better representative of the metabolic status than BMI, which can fail to pick patients with increased visceral adiposity and does not necessarily represent a status increased insulin resistance [32, 33].

As far as bioumoral data are concerned, the two groups of patients did not differ significantly, in keeping with previous data [17], except for the higher uric acid level found in PsO patients. This could have been correlated to PsO extension [34], but it is also known to be a frequent finding associated with insulin resistance and NAFLD [17].

In this context, the increased NAFLD prevalence in PsO patients of our study could be attributed to the higher BMI/metabolic impairment in the PsO subgroup, but it appears, in view of the above pathogenetic consideration, that PsO may represent an explanation per se. Besides, in a recent large cross-sectional study, patients with PsO were found to have a higher risk for NAFLD, whose magnitude correlated with PsO severity [30] independently from BMI. Furthermore, in some cases, PsO patients have been described to present more frequently with NAFLD independently of MetS [35].

However, in the multivariable model, both NAFLD and liver stiffness were mostly associated with the occurrence of insulin resistance, without any apparent contribution from arthritis.

Logistic regression, having NAFLD as an outcome, underlined how several factors can be associated with the development of a metabolic disease in the liver: at univariable analysis, most "classic" cardiovascular risk factor, but also PASI, displayed an association with NAFLD. However, in the multivariable model, only insulin resistance seemed to be an independent predictor of NAFLD.

In linear regression analysis exploring factors associated with liver stiffness, at univariate analysis, results were similar, with many cardiovascular risk factors, but not PASI or arthritis, associated with the outcome. Again, in the multivariable model, though, HOMA and female sex were the only independent positive predictors for liver stiffness grading. These results underline how insulin resistance is indeed a key player in the development of MetS, NAFLD and ultimately LF [21]. Besides, female sex was already described to be more frequently associated with LS [10]. Of course, it may be difficult to disentangle the contribution of inflammatory diseases (such as PsO or PsA) to NAFLD, from other cofactors such as obesity, MetS or systemic therapies. However, studies consistently showed a critical role of PsO in enhancing the risk of

NAFLD and eventually LF [10, 36] Therefore, even though in the present study, this association was only highlighted at univariate analysis, this could reveal a true relation. By contrast, little is known about the contribution of arthritis to metabolic comorbidities and, to the best of our knowledge, no studies showed that arthritis could represent an independent risk factor for NAFLD. Since the pathogenic link between PsO and metabolic liver disease could be a low-grade chronic inflammation [10], a high prevalence of NAFLD could also be expected in PsA. However, our results do not support an association between arthritis and NAFLD or liver fibrosis.

It may be argued that in our study PsA seems to be on average rather low to allow an evaluation of the independent effect of arthritis on the inflammatory load, thus on the comorbidities. However, this is a cross-sectional study; therefore, disease activity has been described on a single timepoint and cannot be considered adequately representative of previous disease activity statuses. Besides, though it is true that anti-TNF treatment could have played a role in controlling disease activity (both in PsO or PsA) and related comorbidities, it must be acknowledged that even in anti-TNF-treated patients, a subclinical, long-term inflammation could persist and be responsible for metabolic alterations [37]. Moreover, inclusion of treated patients was considered acceptable for two reasons: firstly, the majority of the other studies in the literature assessing the effect of PsO/PsA on metabolic comorbidities also enrolled treated patients [10, 11, 30, 35]. Secondly, a further treatment-based exclusion would have created serious feasibility issues, considering the already limited amount of eligible patients (Supplementary Figure). Surely, our small sample size limits the generalizability; nonetheless, our findings seem to suggest that the occurrence of arthritis does not increase the risk for metabolic complications. This negative observation may also depend from differences in therapeutic strategies between PsA and PsO: PsA more often receives a systemic treatment than PsO alone, possibly resulting in a more effective control of inflammation [38]. Yet, PsA patients under treatment present persistent active skin disease in a significant percentage of cases [39, 40], which could explain the stronger association of NAFLD with PsO severity rather than the joint disease.

The main limitation of the present study is the small sample size; however, the study did not include patients on methotrexate, a drug frequently used as first-line therapy in both PsA and PsO patients [41, 42] and that may be one of the major confounders when assessing liver disease in PsA patients. The exclusion of patients with previous recent methotrexate exposure is thus quite challenging, though necessary to ensure NALFD cases purely related to a metabolic condition. A further limitation is the cross-sectional design of the study, which allows to draw conclusions on association but not causality. However, the exclusion of patients with any other form of liver disease represented a strength from the standpoint of data reliability.

In conclusion, in our study population, the prevalence of MetS and liver fibrosis was similar between PsA and PsO patients, while NAFLD was found more frequently in PsO patients. Insulin resistance, which plays a key role in MetS, seems to represent the main determinant of liver disease, in terms of NAFLD and liver fibrosis. Data from the literature support an independent contribution for PsO, while the additional role of arthritis remains to be further elucidated.

Compliance with ethical standards

The present study was conducted in accordance with the Declaration of Helsinki. The local Ethics committee has approved the research protocol and informed consent has been obtained from all subjects.

Disclosures None.

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