Risk of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis: an updated systematic review and meta-analysis of observational studies

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Introduction

In the past decade, several observational studies have documented that chronic plaque psoriasis is strongly associated with multiple cardiometabolic co-morbidities, including cardiovascular disease (CVD), obesity, type 2 diabetes (T2DM) or metabolic syndrome [1]. Non-alcoholic fatty liver disease (NAFLD) is considered a purely metabolic liver disease, which includes a spectrum of progressive pathologic liver conditions, ranging from simple steatosis to steatohepatitis (NASH) and cirrhosis. To date, NAFLD has reached epidemic proportions and is the most common cause of chronic liver disease in Western countries (affecting up to 30% of adults in the general population and up to ~70% of people with T2DM) [2].

Recently, some observational studies, although not all, have reported that individuals with chronic plaque psoriasis have an increased risk of having NAFLD compared with those without psoriasis. Presently, however, the magnitude of this risk and whether the risk changes with the underlying severity of psoriasis remains uncertain. To our knowledge, there are only two small meta-analyses (published in 2015 and 2019, respectively) that have investigated the association between psoriasis and risk of prevalent NAFLD [3,4]. These two small meta-analyses reported that psoriasis is associated with an increased risk of prevalent NAFLD, but the available data on the association of NAFLD with the severity of psoriasis or psoriatic arthritis remain inconclusive. We undertook an updated systematic review and meta-analysis of observational studies to quantify the magnitude of the association between psoriasis and risk of prevalent and incident NAFLD, as well as to examine whether the severity of chronic plaque psoriasis or presence of psoriatic arthritis were associated with a higher risk of prevalent NAFLD.

Methods

Data sources and searches

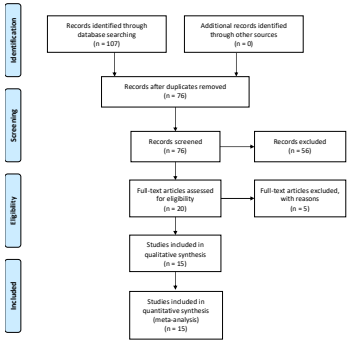
We performed the systematic review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and following the reporting items proposed by Meta-analysis Of Observational Studies in Epidemiology (MOOSE) for the meta-analysis of these studies. We conducted a systematic literature search from the inception date to May 3, 2021 through PubMed, Scopus and Web of Science to identify observational studies examining the risk of prevalent NAFLD amongst individuals with and without chronic plaque psoriasis. Search text terms were as follows: (("Arthritis, Psoriatic"[Mesh]) OR ("Psoriasis"[Mesh])) AND ("Non-alcoholic Fatty Liver Disease" OR "NAFLD" [Mesh]). There were no restrictions in terms of sex, race, language, or geographic area. Additionally, we reviewed references from relevant original papers and review articles to identify further eligible studies not covered by the original database searches.

Study Selection

Studies were included in the meta-analysis if they meet the following criteria: 1) observational studies examining the association between chronic plaque psoriasis and risk of NAFLD; 2) studies reporting odds ratios (ORs) with 95% confidence intervals (95% CIs) values for the outcome of interest; 3) studies in which the diagnosis of both psoriasis and psoriatic arthritis were based on clinical examinations and specific international criteria, namely CASPAR criteria; 4) studies in which the psoriasis severity was estimated using the psoriasis area and severity index (PASI); and 5) studies in which the diagnosis of NAFLD was based on liver biopsy, imaging techniques or International Classification of Diseases, 9th Revision (ICD-9) or ICD-10 codes, in the absence of significant alcohol consumption or other competing causes for hepatic steatosis. Criteria for exclusion of the studies from the meta-analysis were as follows: 1) congress abstracts, case reports, theses, reviews, commentaries, editorials, or practice guidelines; 2) studies not reporting ORs and 95% CIs for the outcome of interest; and 3) studies conducted in paediatric population.

Data extraction and quality assessment

Data from studies eligible for the aggregate data meta-analysis were extracted by two authors independently (FB and PG). Any disagreements were resolved by consensus and a third author if needed (GG). For all eligible studies, we extracted information on publication year, study design, study country, sample size, population characteristics, methods used for the diagnosis of psoriasis and NAFLD, psoriasis severity assessed by PASI score, psoriatic arthritis (PsA), matching and confounding factors included in multivariable regression analyses. In case of multiple publications, we included the most up-to-date or comprehensive information. Since the eligible studies were non-randomized, the Newcastle-Ottawa Scale (NOS) was used to judge the quality of the studies included in the meta-analysis, as recommended by the Cochrane Collaboration. We judged studies that received a NOS score of at least 8 stars to be at low risk of bias, thereby reflecting the highest quality.



Data synthesis and analysis

The primary outcome measure of the meta-analysis was the risk of having NAFLD in patients with chronic plaque psoriasis and non-psoriatic control subjects. The ORs with 95% CIs were considered as the effect size for all eligible studies. When studies had several adjustment models, we extracted those that reflected the maximum extent of adjustment for potentially confounding risk factors. The adjusted ORs of all eligible studies were then pooled, and an overall estimate of effect size was calculated using the DerSimonian-Laird random-effects model. The psoriasis severity, as assessed by PASI score, in patients with and without NAFLD was displayed as weighted mean difference (WMD) and 95% CIs for the changes of mean PASI score between psoriatic patients with and without coexisting NAFLD. Visual inspection of the forest plot was used to investigate the possibility of statistical heterogeneity. Statistical heterogeneity was also assessed by the I^2-statistics, which provides an estimate of the percentage of variability across studies that is due to heterogeneity rather than chance alone. According to Higgins and Thompson, I^2-values of approximately 25% represent low heterogeneity; approximately 50% represent medium heterogeneity; and approximately 75% represent high heterogeneity. Publication bias was evaluated using the funnel plot, Begg's rank correlation test and Egger's regression test.

To explore the possible sources of heterogeneity among the eligible studies and to test the robustness of the observed associations, we performed subgroup analyses stratifying the eligible studies by study country, methodology used for the diagnosis of NAFLD, NOS scale (i.e. the 'high-quality' studies), or whether they had adjustment at least for age, sex and body mass index (BMI). Additionally, we performed univariable meta-regression analyses to evaluate the impact of specific moderators (i.e., age, sex and BMI) on the effect size of the risk of having psoriasis-related NAFLD across the eligible studies. We also tested for possible excessive influence of individual studies using a meta-analysis influence test that eliminated each of the included studies one at a time. All statistical tests were two sided and used a significance level of $p<0.05$. We used Review Manager version 5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) and STATA® software v16.1 (StataCorp, College Station, Texas, USA) for all statistical analyses.

This systematic review and meta-analysis is registered in PROSPERO, number: CRD42021247549.

Results

Characteristics of the included articles

From a total of 76 retrieved articles (after excluding duplicates), a total of 20 eligible studies from PubMed, Scopus or Web of Science databases were identified based on the titles and abstracts. After full text examination of these 20 potentially eligible studies, we excluded five studies because unsatisfactory inclusion criteria or unacceptable outcome measures. After of this exclusion, a total of 15 observational studies were analysed in the meta-analysis. Of these 15 eligible studies, 11 studies were included in the pooled primary analysis that compared the risk of prevalent NAFLD between psoriatic patients and non-psoriatic controls; 8 studies were included in the analysis examining the association between NAFLD and psoriasis severity, as assessed by PASI score; 5 studies were included in the secondary analysis assessing the risk of prevalent NAFLD among psoriatic patients with and without PsA. Of note, the study by Ogdie et al. included both a cross-sectional and a cohort design.

The main characteristics of the 11 eligible studies assessing the risk of prevalent NAFLD are reported in **Table 1.** Overall, these cross-sectional or case-control studies had aggregate data on 249,933 psoriatic patients (mean age 55 years, mean BMI 27.7 kg/m2, 54% were men, 49% had NAFLD) and 1,491,402 non-psoriatic healthy controls (mean age 53 years, mean BMI 26.7 kg/m2, 49% were men, 36% had NAFLD). Four studies were carried out in the Europe (Italy and the Netherlands), 3 studies were carried out in Asia (Iran and Taiwan) and 4 studies were carried out in the United States. NAFLD was diagnosed by ultrasonography in 7 studies and by ICD-9/10 codes in 4 studies. No studies with liver biopsy data were available for the meta-analysis.

The main characteristics of the 8 eligible studies examining the association between NAFLD and psoriasis severity, as assessed by PASI score, are reported in **Table 2.** In particular, the main characteristics of the 11 eligible studies assessing the risk of prevalent NAFLD are reported in **Table 1**. Overall, these cross-sectional or case-control studies had aggregate data on 249,933 psoriatic patients (mean age 55 years, mean BMI 27.7 kg/m2, 54% were men, 49% had NAFLD) and 1,491,402 non-psoriatic healthy controls (mean age 53 years, mean BMI 26.7 kg/m2, 49% were men, 36% had NAFLD). Four studies were carried out in the Europe (Italy and the Netherlands), 3 studies were carried out in Asia (Iran and Taiwan) and 4 studies were carried out in the United States. NAFLD was diagnosed by ultrasonography in 7 studies and by ICD-9/10 codes in 4 studies. The main characteristics of the 8 eligible studies examining the association between NAFLD and psoriasis severity, as assessed by PASI score, are reported in **Table 2**. Of these 8 studies, 4 recruited European individuals, 2 studies involved Asian subjects and 2 studies involved United States individuals. NAFLD was diagnosed by imaging techniques (mostly ultrasonography) in all eligible studies, although 2 ones also used biopsy in a small subset of psoriatic patients (for a total of 57 cases).

Risk of prevalent NAFLD in patients with and without chronic plaque psoriasis

The distribution of the 11 eligible studies by estimate of the association between presence of psoriasis and risk of NAFLD, stratified by methods used for NAFLD diagnosis (ultrasonography vs. ICD codes), is plotted in Figure 2. Overall, patients with chronic plaque psoriasis had an approximately doubled OR of NAFLD compared to non-psoriatic control subjects (pooled random effects OR 1.96, 95% CI 1.70-2.26, I2=97%, p<0.001). Similar results were observed when the studies were stratified by the methods of NAFLD diagnosis, i.e. either by ultrasonography (n=7; pooled random effects OR 2.02, 95% CI 1.78-2.28, I2=13%, p=0.33) or by ICD codes (n=4; pooled random effects OR 1.83, 95% CI 1.45-2.32, I2=97%, p<0.001). Notably, as shown in the figure, there was no significant heterogeneity across the eligible studies that used ultrasonography to diagnose NAFLD (I^2=13%).

Psoriasis severity in patients with and without NAFLD

Figure 3 shows the pooled estimates of mean PASI score among psoriatic patients with and without coexisting NAFLD across 8 eligible studies. Psoriatic patients with NAFLD had significantly greater mean PASI score than their counterparts without NAFLD (pooled WMD: 3.93, 95% CI 2.01-5.84; I^2=88, p<0.0001).

Risk of incident NAFLD in patients with and without psoriasis

In a subgroup of patients, the study conducted by Ogdie et al. also assessed the risk of developing incident NAFLD in patients with psoriasis or in those with other autoimmune diseases. In particular, in this study involving 197,130 patients with psoriasis, 12,308 patients with PsA, 54,251 patients with rheumatoid arthritis and 1,279,754 healthy controls, Ogdie *et al.* showed that compared to control subjects, patients with psoriasis had a higher risk of developing NAFLD (as detected by ultrasonography) over a mean follow-up period of nearly 10 years, even after adjustment for age, sex, BMI and other metabolic risk factors. Notably, this risk increased across severity of psoriasis with an adjusted-hazard ratio of 1.18 [95% CI 1.07-1.30] for patients with mild psoriasis and adjusted hazard ratio of 2.23 [95% CI 1.73-2.87] for patients with moderate to severe psoriasis, respectively.

Risk of prevalent NAFLD in patients with and without psoriatic arthritis

Figure 4 shows the risk of prevalent NAFLD in psoriatic patients with and without coexisting PsA across 5 eligible studies (including a total of 725 psoriatic patients, 514 of whom had PsA). Patients with PsA tended to have a higher risk of NAFLD compared to those without PsA (pooled random effects OR 1.83, 95% CI 0.98-3.43; I^2=64%, p=0.06), but this difference did not reach statistical significance.

Subgroup analyses and meta-regressions

Subgroup analyses were performed to investigate potential causes of heterogeneity across the 11 eligible articles. The stratification of the articles by study country, NOS quality scale, or degree of covariate adjustment did not influence the association between psoriasis and risk of NAFLD. We also examined the potential excessive impact of individual studies through an analysis that excluded each of the included studies one at a time. The exclusion of each of the studies from the pooled primary analysis did not affect the overall risk of NAFLD. Finally, **Figures 4-6** show the results of univariable meta-regressions. These analyses did not show any significant effects of age, β=-0.01, 95% CI -0.03-0.1, R^2=33.65% (panel A), male sex β=0.01, 95% CI -0.02-0.04, R^2=-41.25% (panel B) or body mass index β=0.12, 95% CI -0.18-0.42, R^2=1.36% (panel C) on the association between chronic plaque psoriasis and risk of having NAFLD.

Risk of bias

As shown in **Figure 7,** the ranking on the NOS was higher than eight points (i.e. low risk of bias) in four studies, equal to seven points (i.e. medium risk of bias) in 2 studies, and six or fewer points in the remaining 5 studies (i.e. high risk of bias). Publication bias was estimated unlikely because no asymmetry of the funnel plots was found, Begg's rank correlation test (p=0.436), Egger's regression test (p=0.183) (**Figure 8**).

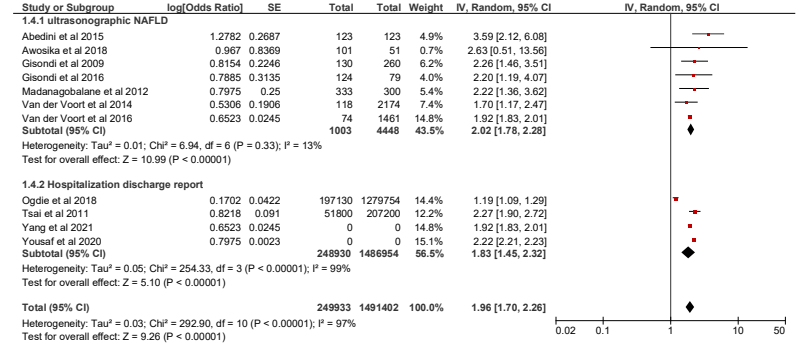


Figure 1

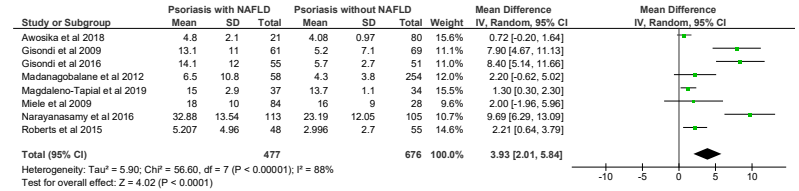


Figure 2

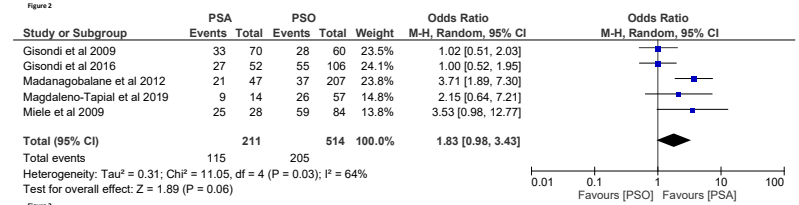
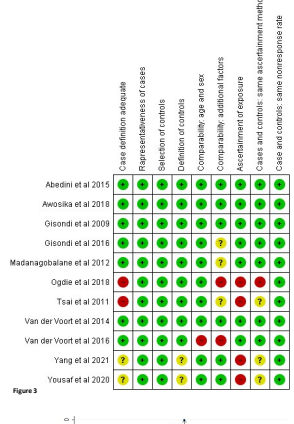


Figure 3



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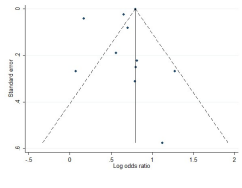

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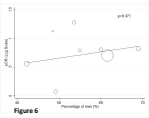

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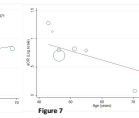

Figure 7

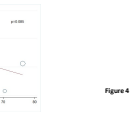

Table 1. Characteristics of the eligible observational studies assessing the risk of prevalent and incident NAFLD in patients with and without psoriasis

Author, year (PMID)	Country	Psoriasis patients, n	Healthy controls, n	Age, years§	PASI§	Diagnosis of NAFLD	Crude risk of NAFLD (OR 95%CI)	Covariate adjustment	Adjusted risk of NAFLD (OR 95%CI)	Risk of NAFLD in PsA vs. PsO (OR 95%CI)
Gisondi P et al 2009 (19560226)	Italy	130	260	51.2 ± 13.4	NR	US	-	Age, sex, BMI (matched)	2.26 (1.46-3.51)	1.02 (0.51-2.03)
Tsai TF et al. 2011 (21543188)	Taiwan	51,800	207,200	47.5 ± 16.4	NR	ICD	NR	Age, sex, urbanization level	2.27 (1.90-2.71)	NR
Madanagobalane S et al. 2012 (22672067)	India	333	330	46.26 ± 11.5	5.16 ± 6.06	US and TE	NR	Age, sex, BMI (matched)	2.22 (1.36-3.63)	3.71 (1.89-7.30)
Van der Voort EA et. al 2014 (24373781)	Netherlands	118	2174	76.2 ± 6.0	2.9 ± 2.8	US	1.70 (1.17-2.46)	^	1.70 (1.13-2.58)	NR
Abedini R et al. 2015 (25958919)	Iran	123	123	43 (30–56)*	9 (4–16)*	US	-	Age, sex, BMI	3.59 (2.12-6.07)	NR
Gisondi P et al. 2016 (26537911)	Italy	124	79	55 ± 12	13 ± 10	US	2.20 (1.19-4.06)	NA	NR	1.00 (0.52-1.95)
Van der Voort EA et. al 2016 (26062958)	Netherlands	74	1535	71.2 ± 6.5	2.0 (3.2)*	US and TE	1.07 (0.63-1.72)	NA	NR	NR
Awosika O et al. 2018 (29942422)	United States	101	51	44.2±13.6	NR	US	3.08 (1.00-9.53)	Age, sex, BMI	2.63 (0.51-13.6)	NR
Ogdie A et al. 2018 [29104161]	United States	Cross-sectional study 4539 (mild PsO)	87,596	45.67 ± 11	NR	ICD	NR	Age, sex	1.29 (0.92-1.81)	NR
		3133 (moderate PsO)		45.27 ± 11					1.32 (0.89-1.97)	
		Longitudinal study 1088 (severe PsO)		44.49 ± 11					1.28 (0.66-2.48)	
		592 (mild PsO)	3,654	NR			1.18 (1.08-1.28) †	^^	1.18 (1.07-1.30)†	
		75 (moderate to severe PsO)		NR			3.09 (2.46-3.88) †		2.23 (1.73-2.87)†	
Yousaf A et al. 2020 (32965553)	United States	NR	NR	NR	NR	ICD	NR	^^^	2.22 (2.21-2.23)	NR
Yang JJ et al. 2021 (33722548)	United States	14,593	1,935,906	NR	NR	ICD	NR	^^^^	1.92 (1.83-2.01)	NR

PASI: Psoriasis Area Severity Index; BMI: body mass index; CI: confidence interval; ICD: International Classification of Diseases codes; NA: not applicable; NR: not reported; OR: odds ratio; PASI: Psoriasis Area Severity Index; PsA: psoriatic arthritis; PsO: psoriasis; §mean ± standard deviation; *median (IQR); interquartile range; ^Age, sex, alcohol consumption, pack-years and smoking status, metabolic syndrome, alanine aminotransferase; ^^ Age at start date, sex, smoking, alcohol intake, body mass index category, and use of oral glucocorticoids and NSAID in the baseline period; ^^^ Age, sex, race, income, insurance status, obesity, smoking, and alcohol consumption; ^^^^Age, sex, income quartile, race, smoking, alcoholism, metabolic syndrome, HIV/AIDS, and type 2 diabetes; †hazard ratio.

Table 2. Characteristics of the eligible studies evaluating the psoriasis severity (assessed by PASI score) in psoriatic patients with and without NAFLD.

Author, year (PMID)	Country	Patients, n	Age, years§	PASI§	Diagnosis of NAFLD	Prevalence of NAFLD, n (%)	Risk of NAFLD in PsA vs. PsO (OR 95%CI)	Mean PASI difference in patients with NAFLD (IV, 95%CI)
Gisondi P et al 2009 (19560226)	Italy	130	51.2 ± 13.4	13.1 ± 11.0	US	61 (47)	1.02 (0.51-2.03)	7.90 (4.67-11.13)
Miele L et al. 2009 (19664838)	Italy	84	50.1 ± 15	16.4 ± 10.0	US, biopsy (5 cases)	84 (59.2)	3.53 (0.98-12.77)	2.00 (-1.96-5.96)
Madanagobalane S et al. 2012 (22672067)	India	333	46.3 ± 11.5	6.5 ± 10.8	US and TE	58 (17.4)	3.71 (1.89-7.30)	2.20 (-0.62-5.02)
Roberts KK et al. 2015 (25521607)	United States	103	52.7 ± 12	5.2 ± 4.9	TE, biopsy (52 cases)	48 (46.6)	NR	2.21 (0.64-3.79)
Gisondi P et al. 2016 (26537911)	Italy	124	55.0 ± 12.0	13.0 ± 10.0	US	55 (44)	1.00 (0.52-1.95)	8.40 (5.14-11.66)
Narayanasamy S et al. 2016 (28053681)	India	210	44.7 ±12.0	27.8 ±13.5	US and TE	113 (45.2)	NR	9.69 (6.29-13.09)
Awosika O et al. 2018 (29942422)	United States	101	44.2 ±13.6	4.8 ± 2.1	US	21 (21.2)	NR	0.72 (-0.20-1.64)
Magdaleno-Tapial J et al. 2020 (31731325)	Spain	71	46.7 ± 14	14.4 ± 6.5	US and TE	37 (52.1)	2.15 (0.64-7.21)	1.30 (0.30-2.30)

NR: not reported; OR: odds ratio; US: ultrasonography; IV: interval variable; TE: transitional elastography; PASI: Psoriasis Area Severity Index; PsA: psoriatic arthritis; *median (IQR); § mean ± standard deviation.

Discussion

We found that patients with chronic plaque psoriasis had a nearly 2-fold higher odds of prevalent NAFLD compared to non-psoriatic controls. The magnitude of this risk remained unchanged when the comparison was stratified by study country, modality of NAFLD diagnosis, NOS quality scale or degree of covariate adjustment. Notably, the risk of NAFLD appeared to increase further with the severity of psoriasis, given that psoriatic patients with NAFLD had significantly higher mean PASI score than their counterparts without NAFLD. Furthermore, the risk of NAFLD also tended to be higher among patients with PsA than among those with skin psoriasis alone.

To date, the precise underlying mechanisms linking chronic plaque psoriasis and NAFLD are poorly understood. Psoriasis and NAFLD may share multifactorial, and overlapping metabolic abnormalities [5]. In particular, insulin resistance plays a pathogenic role in the development of NAFLD, as it promotes an increased free fatty acid flux from visceral adipose tissue into the liver, thereby increasing hepatic de novo lipogenesis. On the other hand, hepatic fat accumulation may further aggravate insulin resistance and promote increased hepatic glucose production. Additionally, overlapping mechanisms of the so-called "metaflammation" may also contribute to the complex link between psoriasis and NAFLD. Indeed, we found that both psoriasis severity and PsA correlated with an increased risk of prevalent NAFLD. The secretion of pro-inflammatory, pro-thrombotic and oxidative stress mediators in both psoriatic skin and adipose tissue might act systemically and promote insulin resistance and other metabolic derangements that promote the development and progression of NAFLD [6-8]. Our findings also imply that psoriatic patients might be screened with an ultrasonographic exam in case of metabolic features associated with NAFLD. However, the optimal method of screening in these patients is currently unknown. In view of the intrinsic limitations of measurement of serum liver enzymes alone as initial screening test for NAFLD, we believe that liver US combined with the use of non-invasive markers of advanced fibrosis (such as NAFLD fibrosis score [NFS] or Fibrosis-4 score [FIB-4]) or, alternatively, transient elastography might be fruitful as first-line choice in identifying psoriatic patients with NAFLD and advanced fibrosis, in order to refer to a hepatologist. In addition, all psoriatic patients with NAFLD should be followed routinely to assess the development of liver-related, metabolic and CVD complications. In conclusion, this meta-analysis of more than 1.7 million individuals shows that psoriasis is significantly associated with a nearly 2-fold increased odds of prevalent NAFLD. This risk parallels the underlying severity of chronic plaque psoriasis. Given the observational design of the eligible studies and the fact that most eligible studies used ultrasonography for detecting NAFLD, the findings of this meta-analysis pave the way for novel large, prospective, histologically based studies.

References

1. Gisondi P, Bellinato F, Girolomoni G, Albanesi C. Pathogenesis of chronic plaque psoriasis and its intersection with cardio-metabolic comorbidities. Front Pharmacol 2020; 11: 117.
2. Mantovani A, Gisondi P, Lonardo A, Targher G. Relationship between non-alcoholic fatty liver disease and psoriasis: a novel hepato-dermal axis? Int J Mol Sci 2016; 17: 217.
3. Candia R, Ruiz A, Torres-Robles R, Chávez-Tapia N, Méndez-Sánchez N, Arrese M. Risk of non-alcoholic fatty liver disease in patients with psoriasis: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol 2015; 29: 656-62.
4. Phan K, Oreggo J, Charlton O, Smith SD. Relationship between psoriasis and non-alcoholic fatty liver disease - Updated systematic review and adjusted meta-analysis. Australas J Dermatol 2019; 60: e352-e355.
5. Week KS, Arrington KC, Ehrlich A. Psoriasis and non-alcoholic fatty liver disease. J Eur Acad Dermatol Venereol 2011; 25: 383-91.
6. Eslam M, Newsome PN, Sarin SK, Anstee QM, Targher G, Romero-Gomez M, et al. A new definition for metabolic dysfunction-associated fatty liver disease: An international expert consensus statement. J Hepatol 2020; 73: 202-9.
7. Lim S, Kim JW, Targher G. Links between metabolic syndrome and metabolic dysfunction-associated fatty liver disease. Trends Endocrinol Metab 2021; 32: 500-14.
8. Davidovici BB, Sattar N, Prinz J, Puig L, Emery P, Barker JN, et al. Psoriasis and systemic inflammatory diseases: potential mechanistic links between skin disease and co-morbid conditions. The Journal of investigative dermatology 2010; 130: 1785-96.