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Non-alcoholic fatty liver disease and psoriasis – is there a shared proinflammatory network?

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Summary

Psoriasis is an immune-mediated systemic inflammatory disease that is not limited to the skin but may be associated with arthritis, cardiovascular diseases, metabolic syndrome including diabetes and obesity and, as identified more recently, non-alcoholic fatty liver disease (NAFLD) that occurs in approximately 50 % of all patients with psoriasis. NAFLD is characterized by accumulation of fat in hepatocytes in the absence of excessive alcohol consumption. Over the last two decades, NAFLD has developed to the most common chronic liver disease with an estimated prevalence of 25 % in the Western population. NAFLD ranges from non-inflammatory or bland hepatic steatosis to inflammation of hepatic tissue (non-alcoholic steatohepatitis, NASH) and consecutive liver fibrosis. It is controversial whether the underlying systemic inflammation of psoriasis is contributing to development of NAFLD or if comorbid diseases such as obesity enhance NAFLD development. Recent findings indicate that cytokine-mediated inflammation through TNFα, interleukin (IL)-6 and IL-17 might be the common link between psoriasis and NAFLD. Considering the shared inflammatory pathways, IL-17 pharmacological blockade, which is already well-established for psoriasis, may be a promising strategy to treat both psoriasis and NAFLD. Therefore, early detection of NAFLD and a better understanding of its pathophysiology in the context of the systemic inflammation in psoriasis is important with regard to individualized treatment approaches.

Introduction

Psoriasis is a multifactorial skin disease influenced by underlying genetic predisposition, immune-mediated inflammation as well as environmental factors, and affects approximately 2–3 % of the population in Western industrialized countries. Psoriasis vulgaris is the most common clinical variant presenting with sharply demarcated, erythematous and scaly plaques [1]. Besides somatic impairments, patients suffer from stigmatization, report reduced levels of employment as well as income and experience a significant reduction in quality of life [2]. In recent years, it has been noted that psoriasis not only affects the skin but also represents a systemic inflammatory disease. Associations with arthritis, cardiovascular diseases, metabolic syndrome including diabetes mellitus and obesity, and, more recently, with non-alcoholic fatty liver disease (NAFLD) have been proved [3]. NAFLD comprises a wide spectrum of clinical features ranging from non-inflammatory or bland hepatic steatosis with intracytoplasmatic accumulation of triglycerides in hepatocytes (non-alcoholic fatty liver) to inflammation of hepatic tissue (non-alcoholic steatohepatitis, NASH) with consecutive ballooning, apoptosis of hepatocytes and liver cirrhosis [4]. NAFLD is characterized by the absence of excessive alcohol consumption (alcohol intake in women < 20 g/d and in men < 30 g/d) and needs to be differentiated from other causes of liver damage such as viral hepatitis, alcoholic steatohepatitis (ASH) and drug-associated steatohepatitis (DASH) [5]. Over the last two decades, NAFLD has developed to the most common chronic liver disease with a prevalence of around 25 % in the Western population [6]. The prevalence of NAFLD in Germany was about 22.9 % in 2016 and is expected to increase to 26.4 % in 2030 [7]. NAFLD is associated with an increased mortality because

of cardiovascular diseases, malignancies and the liver disease itself [8].

To foster a better understanding of the systemic relevance of chronic inflammation in psoriasis, this review intends to raise awareness of comorbidities of psoriasis, focusing on its relationship with NAFLD and suggesting a screening algorithm for NAFLD in daily dermatological care.

Electronic searches were carried out using PubMed/Medline databases for manuscripts published between January 1990 and April 2020. Search queries were restricted to publications in English and German language and included medical terms in various combinations such as "psoriasis", "psoriatic arthritis", "NAFLD", "non-alcoholic fatty liver disease", "steatohepatitis", "non-alcoholic steatohepatitis" and "NASH".

Pathogenesis

Psoriatic skin eruptions evolve as a consequence of hyperproliferation of the epidermis due to dysfunctional keratinocyte differentiation resulting in parakeratosis and acanthosis. Keratinocytes (KC) are stimulated by an inflammatory infiltrate consisting of T lymphocytes, dendritic cells, macrophages and neutrophils [9, 10]. T helper cells secreting pro-inflammatory IL-17 (Th17 lineage) are one of the central players in the pathogenesis of psoriasis: They are activated by pro-inflammatory cytokines such as IL-23 and can secrete, besides IL-17, a variety of factors including interferon-γ and IL-22. The latter is a strong mediator of KC proliferation and an enhancer of dermal inflammation via an activation of STAT3 (signal transducer and activator of transcription 3) [11]. The IL-17 family is composed of six members including IL-17A, B, C, D, E (also known as IL-25) and F. Of these, IL-17A is the best characterized and is referred to by most studies that mention IL-17. In psoriasis, IL-17A and F, produced by T helper cells, as well as IL-17C and E, mostly produced by KC, mediate inflammation by neutrophil recruitment and formation of microabscesses and therefore link the adaptive and innate immune system in the pathogenesis of psoriasis [12–14]. Such pro-inflammatory cascades have garnered considerable interest in recent years as they can be specifically targeted in the treatment of psoriasis. Apart from T cells and the innate immune system, recent findings suggest that anti-inflammatory IL-10-producing B cells (B_{regs}) are involved in psoriasis pathogenicity as B_{regs} have the capacity to ameliorate psoriasis development [15, 16]. Further studies are required to clarify the pathogenetic role of B cells in psoriasis.

Pathophysiologically, NASH is based on lipid-induced hepatocellular damage, immune cell-mediated inflammation and consecutive liver fibrosis [17]. The development of NAFLD is described by a "two-hit" hypothesis. Insulin resistance and obesity favor an excessive fat accumulation in hepatocytes (first hit), which increases the sensitivity of hepatocytes to oxidative stress, endotoxins and action of cytokines (second hit) with consecutive tissue inflammation. These events facilitate the transition from simple steatosis to steatohepatitis, in this case to NASH, which is characterized by *(1)* steatosis, *(2)* inflammatory cell infiltration and *(3)* hepatocyte ballooning and spotty necrosis [5]. Chronic inflammation and liver damage can result in cirrhosis, liver failure and/or hepatocellular carcinoma. Tissue inflammation is mediated by production of proinflammatory cytokines such as tumor necrosis factor α (TNFα), IL-6 and IL-17 by resident liver cells (hepatocytes, hepatic stellate cells) and immune cells (Kupffer cells, natural killer (NK) cells, neutrophils, NKT cells, T cells) [18, 19]. In mouse models of NAFLD, an increase in Th17 cells and a diminished population of regulatory T cells (T_{reg}) with consecutively higher levels of proinflammatory IL-6, IL-17 and IL-23 in comparison to controls were observed [20]. Similar findings of increased Th17 cells and a shift in the Th17/resting T_{reg} ratio has been observed in human NAFLD patients [21].

The contribution of IL-17 to the pathogenesis of both psoriasis and NAFLD is intriguing. Th17 cells can be detected in fat tissue and IL-17 itself regulates glucose metabolism and adipogenesis. Likewise, IL-17(A)-secreting Th17 cells may promote the progression from simple steatosis to steatohepatitis [22]. In line with this, studies on IL-17A and IL-17F knock-out mice revealed that not only IL-17A but also IL-17F contributes to inflammation in NAFLD [23]. Therefore, both psoriasis and NAFLD pathogenesis seem to be linked to the joint proinflammatory Th17 axis (and other cytokines such as TNFα and IL-6).

Interestingly, psoriasis disease duration and NAFLD are significantly associated with an enlarged spleen volume, possibly due to a low-grade systemic inflammation as the spleen is a major immune organ [24]. Importantly, not only NAFLD seems to be linked to psoriasis via a chronic inflammatory process: In recent years, evidence has been provided for an association between metabolic syndrome, including diabetes and obesity, or cardiovascular diseases such as atherosclerosis, and an IL-17–mediated inflammation [13, 25, 26]. Further studies are needed to clarify the underlying pathomechanisms of psoriasis and cardiometabolic disorders.

Diagnosing NAFLD in patients with psoriasis

Patients suffering from early stages of NAFLD are common. Usually, the first diagnostic step in patients with suspected liver disease is the evaluation of liver enzymes in blood samples. An elevation of alanine aminotransferase (ALT/GPT) with normal aspartate aminotransferase (AST/GOT) can be

a sign of NAFLD [27]. However, up to two-thirds of NAFLD patients present with normal liver enzymes [28]. Ultrasound examination of the liver may reveal steatosis hepatis (SH) but cannot distinguish between NAFLD and NASH. Moreover, sensitivity for detection of SH by ultrasound is reduced in low-grade steatosis [29]. Controlled attenuation parameter (CAP), transient elastography (FibroScan®) or magnetic resonance imaging (MRI) of the liver are more sensitive but often not as available as B-mode ultrasound [30]. CAP is a non-invasive method to quantify SH based on transient elastography which in turn is a one-dimensional technique using ultrasound as well as low-frequency elastic waves, whose propagation speed is closely related to tissue stiffness [31].

To identify patients at risk, surrogate scores like fibrosis-4 (FIB-4) and the NAFLD-specific fibrosis score (NFS) have been introduced (Table 1). For example, the NFS considers parameters such as age, body mass index (BMI), diabetes mellitus/impaired fasting glucose (IFG), blood platelet count, albumin and the De-Ritis-ratio (AST/ALT) [32]. Of note, both tests have a sensitivity of about 90 %, which also holds true for the negative predictive value. Although the FIB-4 score can be calculated easier using the parameters age, AST, ALT and platelet count, the positive predictive value is only 65 % compared to about 90 % in the case of NFS. Nonetheless, these non-invasive tools can help to determine liver steatosis and fibrosis. A clinical path for dermatologists to determine the risk of NAFLD-dependent liver fibrosis is depicted in Figure 1. Patients with non-invasive scores and measurements suggesting low risk have a high likelihood for absence of advanced liver fibrosis (high negative predictive value), whereas the positive predictive value in those with high risk is modest. Therefore, it is recommended that patients with moderate and high risk should be offered a liver histology to confirm the exact fibrosis stage [29]. Histology of NAFLD shows centrolobular steatosis in at least 5 % of liver tissue whereas NASH is defined by more than 5 % of steatosis, an inflammatory infiltrate and ballooning of hepatocytes [33]. In advanced stages, NASH fibrosis with less than 5 % steatosis can be observed. Fibrosis shows a "chicken-wire" like pattern and can progress to liver cirrhosis [34].

NAFLD and psoriasis

In 2001, Leonardo et al. first described the coexistence of psoriasis and biopsy-proven NASH in three cases [35]. Over the last few years, multiple studies have demonstrated that psoriasis is associated with NAFLD. The majority reported a prevalence of around 50 % (range 14.4 % to 65.5 %) for NAFLD in psoriasis patients [36, 37]. In an American case-control study, 150 patients suffering from psoriasis showed a significantly higher prevalence of NAFLD (21.2 %) than control patients (7.8 %, $P < 0.04$). However, psoriasis was not associated with NAFLD when matching for age, sex and BMI. Patients with both psoriasis and NAFLD were more likely to present with obesity than patients with solely psoriasis [38].

Table 1 Clinical scores to predict advanced stage liver fibrosis.

Score	Fibrosis-4 Score (FIB-4)	NAFLD-specific fibrosis-score (NFS)
Parameters	Age, AST, ALT, PLT count	Age, BMI, IFG or diabetes (yes = 1, no = 0), AST/ALT ratio, PLT count, albumin (g/dl)
Formula	$(age \times AST)/(PLT \times \sqrt{ALT})$	–1.675 + 0.037 x age + 0.094 x BMI + 1.13 x IFG/diabetes (yes = 1, no = 0) + 0.99 x AST/ALT ratio – 0.013 x PLT – 0.66 x albumin
Cut-off values	<1.45 excludes advanced fibrosis >3.25 presence of advanced fibrosis	<–1.455 excludes advanced fibrosis >0.676 presence of advanced fibrosis
Negative predictive value	90 %	88–93 %
Positive predictive value	65 %	82–90 %
Sensitivity	87 %	90 %
Online calculators	https://www.hepatitisc.uw.edu/page/clinical-calculators/fib-4	https://www.labor-limbach.de/laborrechner/labor-rechner/nafld-nonalcoholic-fatty-liver-disease-fibrose-score/

Age (years); AST, aspartate aminotransferase (U/L); ALT, alanine aminotransferase (U/L); PLT, platelet count (x 10^9/L); BMI, body mass index (kg/m^2); IFG, impaired fasting glucose [32].

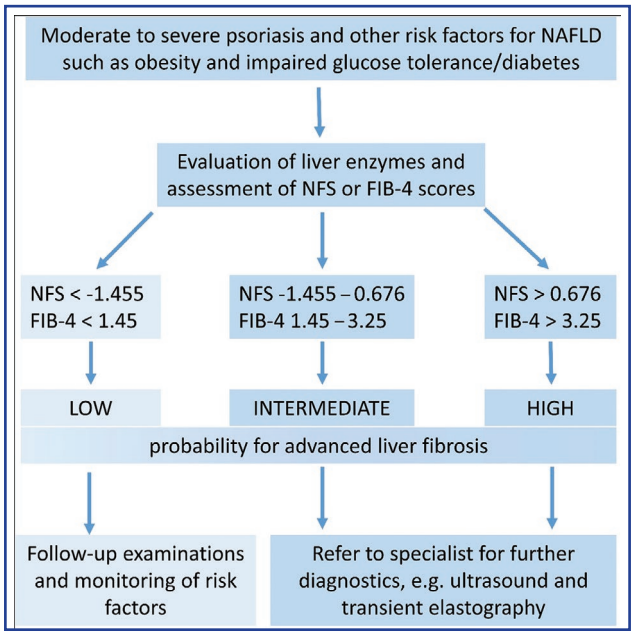

Figure 1 Screening algorithm for NAFLD in psoriasis patients in dermatological practice.

Therefore, the question arises whether psoriasis and NAFLD are two different diseases just co-existing in patients with metabolic syndrome or whether they share a common underlying molecular and/or immunological basis.

Studies addressing the prevalence of psoriasis and NAFLD have to be interpreted carefully in terms of diagnosis of NAFLD and the recruited patient cohorts. In most studies, NAFLD was diagnosed by ultrasound [36–42], three studies performed both ultrasound and elastography tests [43–45], one study did not include a specification of diagnostics [46] and only one study performed a liver biopsy [47] (Table 2). Another limitation in the comparison of study results are the different patient cohorts. For example, the European or North American differ from the Asian population in terms of comorbid diseases such as diet-related obesity. Other countries such as Iran, that prohibit consumption of alcohol, have a much lower prevalence of alcoholic liver disease as compared to Western countries, which therefore can be excluded as a major contributory factor to liver damage [36].

All studies detected a higher occurrence of NAFLD in psoriasis patients. Co-occurrence of psoriasis with NAFLD was significantly associated with metabolic syndrome and higher psoriasis area and severity index (PASI) scores with a prolonged persistence of skin manifestations as compared to psoriasis patients without NAFLD [37, 39]. Advanced liver fibrosis appears to be more frequent in patients with psoriasis (8.1 %) than in NAFLD patients without psoriasis (3.6 %, $P = 0.05$) even after adjustment of demographic, laboratory and lifestyle data (odds ratio [OR] 2.57, 95 % confidence interval [CI]: 1.00–6.63) [43]. Liver biopsies revealed a 22 % prevalence of NASH in psoriatic NAFLD patients [47]. Remarkably, NAFLD in patients with psoriasis was significantly associated with psoriatic arthritis (PsA) ($P = 0.036$, OR 3.94, 95 % CI: 1.07–14.46) when compared to non-NAFLD psoriasis control groups [41]. A meta-analysis of three studies with 505 patients showed a significantly greater risk for NAFLD in patients with PsA as compared to those with mild psoriasis (OR 2.25, 95 % CI: 1.37–3.71) [48]. However, another study investigating the contribution of PsA to the development of NAFLD did not identify arthritis as a significant predictor for NAFLD but an association of insulin resistance to NAFLD in psoriasis patients [44].

Overall, the level of inflammation seems to be higher in psoriasis patients with NAFLD than in those without NAFLD. Psoriasis patients with NAFLD have higher serum levels of C-reactive protein (CRP) and IL-6 while adiponectin levels are lower [39]. Adiponectin plays a role in metabolic disorders; it reduces hepatic and systemic insulin resistance and attenuates liver inflammation and fibrosis [49]. However, it is still controversial whether comorbidities like obesity enhance NAFLD development or whether the underlying systemic psoriatic inflammation is contributing to NAFLD development. The former is favored since adipose tissue acts as an endocrine organ producing cytokines associated with both psoriasis and NAFLD [50, 51]. The latter is supported by data showing that psoriasis patients had significantly increased serum levels of proinflammatory cytokines such as TNFα and IL-6 ($P < 0.05$) and lower levels of anti-inflammatory adiponectin ($P < 0.0001$) than matched controls [52]. Patients with diabetes, who were overweight or had a previous diagnosis of metabolic syndrome were excluded from this study. Still, the mean BMI was 23.4 ± 1.4 kg/m^2, thus demonstrating that systemic inflammation in psoriasis patients may occur independently from risk factors such as obesity [52]. A large prospective population-based cohort study (part of the Rotterdam Study) displayed similar results: Psoriasis remained a significant predictor for development of NAFLD after adjustment for alcohol intake, smoking, elevation of ALT and presence of metabolic syndrome as compared to controls ($P = 0.005$, OR 1.7, 95 % CI: 1.1–2.6) [42]. Ogdie and colleagues [46] compared the incidence of liver disease in patients with psoriasis, PsA and rheumatoid arthritis (RA). Rheumatoid arthritis, like psoriasis a Th1 and Th17 cell-mediated chronic inflammatory disease, is augmented by TNFα and other cytokines including IL-15, IL-1β, IL-6, IL-17 and IL-23 [53, 54]. Remarkably, results highlighted an increased risk for NAFLD in patients with psoriasis and PsA with systemic therapy but not in patients with RA with

Table 2 Evidence of associations between psoriasis and NAFLD.

Year	Lead author	Study design	Study population	Number of participants	Diagnosis of NAFLD	Associations Psoriasis and NAFLD
2009	Gisondi P [39]	Single center case–control study	Italian cohort	130 psoriasis patients 260 controls matched by age, sex and BMI	Ultrasonography after excluding other liver diseases	– Frequency of NAFLD was remarkably greater in psoriasis patients than in controls (47 % vs. 28 %, $P < 0.0001$) – Patients with psoriasis and NAFLD were more likely to have metabolic syndrome and had higher serum levels of CRP and IL–6, lower serum adiponectin levels and greater severity of psoriasis according to the PASI score (14.2 ± 12.6 vs. 9.6 ± 7.4, $P < 0.01$) – NAFLD was associated with higher PASI score independently of age, gender, BMI, psoriasis duration or alcohol consumption
2009	Miele L [41]	Single center prospective epidemiological study and retrospective cohort study	Italian cohort	142 psoriasis patients 125 controls with NAFLD matched by age and BMI	Ultrasonography and laboratory tests after excluding other liver diseases	– NAFLD in psoriasis patients was significantly correlated with metabolic syndrome ($P < 0.05$), obesity ($P = 0.043$), hypercholesterolemia ($P = 0.029$), hypertriglyceridemia ($P < 0.001$), De Ritis ratio > 1 ($P = 0.019$) and psoriatic arthritis ($P = 0.036$) – Psoriasis patients with NAFLD were likely to have severe NAFLD reflected by non–invasive NAFLD Fibrosis Scores and De Ritis ratio > 1 compared with non–psoriatic NAFLD patients
2012	Madanagobalane S [37]	Single center case–control study	South Indian cohort	333 psoriasis patients 330 controls matched by age, sex and BMI	Ultrasonography and liver enzymes after excluding other liver diseases	– Prevalence of NAFLD was higher in psoriasis patients than in controls (17.4 vs. 7.9 %, $P = 0.002$) – NAFLD patients with psoriasis were more likely to have metabolic syndrome ($P = 0.03$) and diabetes mellitus ($P = 0.02$) as compared to patients with psoriasis alone – Psoriasis patients with NAFLD had higher PASI scores ($P = 0.02$) – Psoriasis patients had more severe NAFLD than controls as reflected by the steatosis, NASH and fibrosis scores ($P = 0.001$, 0.003, 0.03, respectively)

Table 2 Continued.

Year	Lead author	Study design	Study population	Number of participants	Diagnosis of NAFLD	Associations Psoriasis and NAFLD
2014	v. d. Voort EA [42]	Prospective population–based cohort study (part of the Rotterdam Study)	Dutch cohort with elderly participants (> 55 years)	2292 participants	Ultrasonography after excluding other liver diseases	– 5,1 % had psoriasis – Prevalence of NAFLD was 46.2 % in patients with psoriasis compared to 33.3 % for the reference group without psoriasis ($P = 0.005$) – After adjustment for alcohol consumption, smoking status, metabolic syndrome and ALT psoriasis remained a significant predictor of NAFLD (adjusted OR 1.7, 95 % CI 1.1–2.6)
2015	Abedini R [36]	Single center case–control study	Iranian cohort	123 psoriasis patients 123 controls matched by age, sex and BMI	Ultrasonography after excluding other liver diseases	– Prevalence of NAFLD was significantly higher in the psoriatic group as compared with the control group (65.6 % vs. 35 %, $P < 0.01$, OR = 3.53) – NAFLD grade was significantly higher in patients with psoriasis compared to controls (grade 2 vs. grade 1, $P < 0.01$) – Waist circumference, PASI, liver function test abnormalities, hypertension and cigarette smoking were independent predictors of NAFLD grade
2015	Roberts KK [47]	Single center cross–sectional study	US American cohort	103 patients with psoriasis or psoriasis arthritis	Ultrasonography and laboratory tests, if conspicuous, liver biopsy was recommended	– Prevalence of NAFLD was 47 % – Prevalence of NASH was 22 % in those who underwent biopsy
2016	v. d. Voort EA [43]	Cross–sectional analysis from the population–based Rotterdam Study	Dutch cohort	1535 participants	Transient elastography, liver stiffness > 9.5 kPa suggested advanced liver fibrosis	– 4,7 % had psoriasis – Prevalence of advanced liver fibrosis was 8.1 % in psoriasis patients compared with 3.6 % in the reference group ($P = 0.05$) – After adjustment for demographics, lifestyle characteristics and laboratory findings, the risk of advanced liver fibrosis in psoriasis patients remained elevated (OR 2.57, 95 % CI 1.00–6.63).

Table 2 Continued.

Year	Lead author	Study design	Study population	Number of participants	Diagnosis of NAFLD	Associations Psoriasis and NAFLD
2016	Narayanasamy K [40]	Single center case study	Indian cohort	250 psoriasis patients	Ultrasonography	– Overall prevalence of NAFLD among psoriasis patients was 45.2 %
2018	Ogdie A [46]	Cohort study	US American cohort	197,130 psoriasis patients 12,308 psoriasis arthritis patients 54,251 rheumatoid arthritis patients 1,279,754 controls	Not mentioned	– Adjusted hazard ratios for any liver disease were elevated among patients with psoriasis (without systemic therapy [ST] 1.37, with ST 1.97), psoriasis arthritis (without ST 1.38, with ST 1.67), and rheumatoid arthritis without a ST (1.49) but not elevated in patients with rheumatoid arthritis prescribed an ST (0.96) – NAFLD was highest in patients with psoriasis prescribed an ST (2.23) and psoriasis arthritis with an ST (2.11) – Prevalence of liver disease and cirrhosis increased with increasing body surface area affected by psoriasis (moderate psoriasis: OR 1.82, 95% CI 1.01-3.28; severe psoriasis OR 4.21, 95% CI 2.14-8.27)
2018	Awosika O [38]	Single center case–control study	US American cohort	101 psoriasis patients 51 controls matched by age, sex and BMI	Ultrasonography after excluding other liver diseases	– NAFLD was more prevalent in psoriasis patients compared with controls (21.2 % vs. 7.8 %, $P < 0.04$) – Psoriasis was not associated with NAFLD when patients were matched by age, sex, and BMI (OR 2.63, 95 % CI 0.51–13.6, $P = 0.25$) – Psoriasis patients with NAFLD were more likely to be obese (BMI 34.9 vs. 27.2, 95 % CI 32.4–37.5 vs. 25.9–28.5, $P < 0.01$)
2019	Ortolan A [44]	Single center cross–sectional study	Italian cohort	33 psoriasis patients 43 psoriasis arthritis patients	Ultrasonography and transient elastography, liver stiffness ≥7 kPa = fibrosis	– Metabolic syndrome and liver fibrosis prevalence were similar between psoriasis arthritis and psoriasis (35 % vs. 33 %, $P = 0.88$, 31 % vs 28 %, $P = 0.77$, respectively) – NAFLD was more frequent in psoriasis (65 % vs. 35 %, $P = 0.044$) – Arthritis was not a significant predictor, while insulin–resistance index was independently associated with NAFLD and liver fibrosis (OR 1.34, 95 % CI 1.06-1.69, beta 0.88, 95 % CI 0.54-1.21, respectively)

Table 2 Continued.

Year	Lead author	Study design	Study population	Number of participants	Diagnosis of NAFLD	Associations Psoriasis and NAFLD
2019	Magdaleno–Taipal J [45]	Single center cross–sectional study	Spanish cohort	71 psoriasis patients	Ultrasonography and transient elastography, liver stiffness ≥7.6 kPa = moderate fibrosis	– 36 % of patients met the criteria for metabolic syndrome – 52 % of patients had steatosis hepatis – 14 % of patients had moderate liver fibrosis – In 30 % of patients with liver fibrosis, liver steatosis could not be observed by ultrasound

systemic therapy even after adjustment for age, sex, BMI, smoking, alcohol consumption, oral glucocorticoids and NSAID use (Hazard ratio [HR] 2.23 Psoriasis HR 2.11 PsA; HR 0.92 RA) [46]. Therefore, the systemic inflammation in psoriasis seems to enhance the risk for NAFLD in contrast to other systemic inflammatory diseases like RA. To sum up the findings of the above mentioned studies, chronic ongoing low-grade inflammation might be the missing link between psoriasis and NAFLD [55].

Treatment options

In recent years, many scientific advances and new drugs have revolutionized the treatment of psoriasis. For many years, methotrexate (MTX) and acitretin have been widely used as systemic drugs in psoriasis. However, there have been concerns regarding the liver toxicity of these drugs. Therefore, the German guidelines recommend screening for hepatitis infection prior to treatment initiation and surveillance of liver enzymes during drug treatment [56]. A meta-analysis of eight observational studies showed a polled risk difference for developing significant liver fibrosis of 9 % and for developing any fibrosis of 22 % in psoriasis patients treated with MTX [57] while other risk factors for liver fibrosis such as obesity, diabetes mellitus and alcohol abuse were under-reported. Acitretin, in turn, can cause hyperlipidemia, which is a risk factor for SH [58]. Conversely, a cross-sectional study evaluating the grade of SH showed no increased risk for patients treated with MTX or acitretin [45]. These results are in accordance with a study by Pongpit and colleagues who found that the cumulative dose of MTX did not correlate with the risk of liver fibrosis. In addition, another study found no elevated risk of NAFLD in patients treated with acitretin [41, 59]. Still, MTX or acitretin treatment of psoriasis patients who concomitantly suffer from obesity and hyperlipidemia should be evaluated carefully. Especially since modern psoriasis therapies, including biologics or small molecules such as apremilast, are available that in contrast to MTX and acitretin, appear to have a liver-protective effect. For example, the use of apremilast, an oral phosphodiesterase 4 inhibitor, may be favorable in obese patients because a weight loss of more than 5 % has been observed in about 20 % of treated psoriasis patients [60], thus reducing the pro-inflammatory capacity of excessive adipose tissue. In mouse models with high fat diet-induced SH, application of the TNFα inhibitor infliximab reduced inflammation, fibrosis and serum levels of AST and ALT [61]. In psoriasis patients with NAFLD and metabolic syndrome, the TNFα inhibitor etanercept significantly reduced the De Ritis ratio, CRP and fasting insulin levels after 24 weeks of treatment ($P < 0.05$) [62] but data on the prevalence of NAFLD upon etanercept treatment is lacking. The results were supported by another study that compared liver fibrosis in patients with PsA treated with or without TNFα

blockade for over six months. Thirty percent of the liver elastography (FibroScan®) results were abnormal in anti-TNFα-naïve patients compared to 4.3 % in the TNFα-antagonist-treated group [63] suggesting a positive effect of TNFα blockade on liver fibrosis in PsA patients. However, there are no controlled studies evaluating the efficacy of TNFα blockade on NAFLD. Of note, it has been observed that TNFα therapy can increase body weight and therefore may in fact be a potential risk factor for the development of SH [52, 58].

To date, no specific treatment for NAFLD is available. Two lifestyle intervention studies showed an improvement of NAFLD by weight reduction over a period of twelve months [64, 65]. Wong and colleagues described a remission of NAFLD independent from baseline BMI (non-obese: 67 % vs. 18 %, $P < 0.001$; obese: 61 % vs. 21 %, $P < 0.001$) [64]. In a real-life cohort of severely obese patients (BMI > 30 kg/m^2) weight reduction significantly decreased the percentage of patients with NAFLD from 98.1 % to 54.3 % ($P < 0.001$) [65]. Lifestyle modifications including hypocaloric diet and exercise are therefore strongly recommended but rarely achieve sustainable effects due to a lack of long-term patient adherence. Treatment of concomitant diseases in NAFLD patients such as diabetes or hyperlipidemia is recommended to reduce the overall systemic inflammation. Other systemic treatments for NAFLD are currently being investigated, for example obeticholid acid (a nuclear bile acid receptor FXR agonist), elafibranor (a dual PPARα/δ agonist), cenicriviroc (a CCR2/CCR5 chemokine antagonist) and selonsertib (an inhibitor of ASK-1) [30].

Considering the common TNFα, IL-17 and IL-23 mediated inflammation in both diseases, treatment with biologics may be a promising therapeutic strategy in patients suffering from both psoriasis and NAFLD. However, therapy with TNFα antagonists may lead to weight gain, which is why blockade of the IL-23/IL-17 pathway may be more promising. In mouse models, IL-17A blockade prevented NAFLD and restored insulin resistance [66]. In line with these findings, other studies reported reduced liver damage, attenuated hepatic lipid accumulation and decreased pro-inflammatory cytokine levels after IL-17 neutralization in NAFLD mouse models [67, 68].

An ongoing phase-III study is evaluating the effect of an anti-IL-17 therapy on NAFLD in psoriasis patients (EudraCT number: 2019-003168-37). Data on the effect of IL-23 antagonists on NAFLD in psoriasis patients are currently not available.

Conclusion

Over the last decade, it has become clear that psoriasis and NAFLD are diseases with presumably overlapping pathophysiologic concepts. It remains uncertain whether psoriasis and NAFLD are two different diseases co-incidentally occurring in patients with metabolic syndrome or whether they share the same molecular and immunological basis. Recent findings indicate that low-grade inflammation mediated by cytokines such as TNFα, IL-6 and IL-17 plays an important role in the pathogenesis of both diseases. Mantovani et al. postulated a hepato-dermal axis where KCs and T cells of lesional psoriatic skin produce pro-inflammatory cytokines that circulate systemically and contribute to the pathogenesis of metabolic disorders such as insulin resistance and NAFLD [69]. However, the opposite may also be true, implicating NAFLD itself is responsible for elevated pro-inflammatory cytokines that can promote the development and course of psoriasis by increasing skin inflammation and KC proliferation. In addition to the pro-inflammatory cytokines produced by liver and skin, the adipose tissue also seems to play a role in the pathogenesis of both diseases. Over the last few years multiple findings have indicated that adipose tissue, in addition to acting as energy storage, is in fact a large endocrine and secretory organ that produces multiple pro- and anti-inflammatory adipokines and cytokines, including TNFα and IL-6. In adipose tissue of psoriasis and NAFLD patients, the production of adiponectin is decreased and the production of pro-inflammatory adipocytokines including TNFα and IL-6 is increased [49–51]. Therefore, Mantovani et al. [69] postulated a triangle inflammatory relationship between adipositas (inflamed visceral adipose tissue), psoriasis and NAFLD (Figure 2).

In 2019, the American Academy of Dermatology (AAD) and the National Psoriasis Foundation (NPF) published novel guidelines on the management and treatment of psoriasis patients. They emphasize the importance of comorbidities like NAFLD and recommend awareness and early identification to prevent progression of liver damage in psoriasis patients [70]. In 2012, the European Academy of Dermatology and Venereology (EADV) released a "clinical practice guideline for an integrated approach to comorbidity in patients with psoriasis" including a flow chart for the management of different comorbidities and an overview of screening tools including, for instance, blood tests and the Goldberg anxiety and depression scale [71]. To date, the German S3 psoriasis guideline does not specially refer to comorbidity or extracutaneous screening recommendations [56, 72]. We therefore suggest a screening algorithm for NAFLD and other risk factors such as obesity and/or impaired glucose tolerance/diabetes in patients with psoriasis (Figure 1). Diagnostic work-up for NAFLD is important, not only for early identification of the comorbidity itself but also for the choice of treatment for psoriasis that should ideally also target NAFLD. Clinical trials are needed to clarify whether treatment with cytokine antagonists such

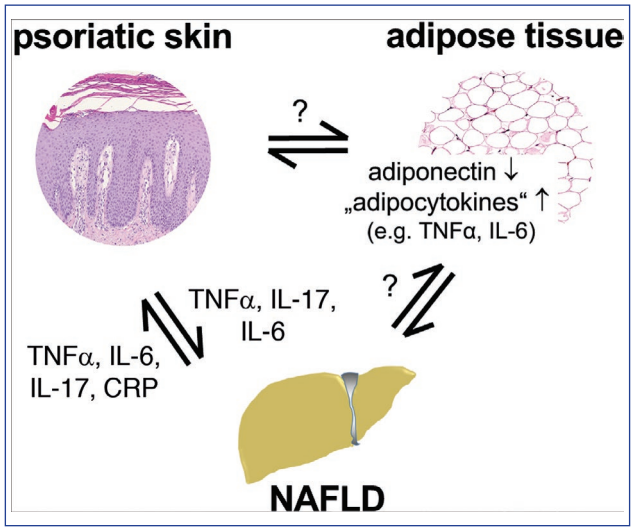

Figure 2 Putative skin/liver/adipose tissue inflammatory network in psoriasis, adapted from Mantovani et al. [69].

as anti-IL-17 antibodies may be a promising treatment approach that provides benefit for patients suffering not only from moderate to severe psoriasis but also from concomitant NAFLD.

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Conflict of interest

J. Heitmann and V. Frings declare no conflict of interest. A. Kerstan advises for Janssen-Cilag and LeoPharma. M. Goebeler one word served in advisory boards for Abbvie, Janssen-Cilag, Novartis and UCB. A. Geier serves in steering committees for Gilead, Intercept and Novartis, advises for AbbVie, Alexion, BMS, Gilead, Intercept, Ipsen, Novartis, Pfizer, Bayer, Merck, Merz, Sanofi and Sequana and has been speaker for AbbVie, Alexion, BMS, CSL Behring, Falk, Gilead, Intercept, Merz, Novartis and Sequana. He received unrestricted grants for the NAFLD CSG study group from Intercept and Falk.

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