Nonalcoholic fatty liver disease in patients with psoriasis: a consequence of systemic inflammatory burden?*

R.B. Prussick1,2 and L. Miele3,4

1Washington Dermatology Center, Rockville, MD, U.S.A.
2Department of Dermatology, George Washington University, Washington, DC, U.S.A.
3Institute of Internal Medicine, Catholic University of Sacred Heart of Rome, Rome, Italy
4Gastroenterological Area, Gastroenterology and Endocrine-Metabolic Sciences Department, Fondazione Policlinico Universitario A. Gemelli, Rome, Italy

Linked Comment: Nobili. Br J Dermatol 2018; 179:6.

Summary

Patients with psoriasis are at an increased risk for nonalcoholic fatty liver disease (NAFLD) compared with the general population. However, the pathophysiology underlying this comorbidity and elucidation of effective treatment strategies are unclear. This review provides insights into the possible role of chronic, low-grade inflammation in the pathogenesis of NAFLD in patients with psoriasis. Both conditions are associated with increased levels of proinflammatory adipokines (such as tumor necrosis factor-α and interleukin-6) and hepatokines, and decreased levels of adiponectin, an anti-inflammatory adipokine. This imbalance in inflammatory mediators could result in insulin resistance and, thereby, facilitate the occurrence and progression of NAFLD in a multistep manner. All patients with psoriasis should, therefore, be considered candidates for NAFLD screening and managed accordingly. Given the common aetiology of inflammation between these conditions, it is hypothesized that biological therapies for psoriasis may attenuate the systemic inflammatory process and progression of NAFLD in patients with psoriasis.

What’s already known about this topic?
- Patients with psoriasis have an increased risk of nonalcoholic fatty liver disease and increased levels of proinflammatory adipokines and hepatokines.

What does this study add?
- This article explores the possible role of chronic, low-grade inflammation in the pathogenesis of nonalcoholic fatty liver disease.
- All patients with psoriasis should be screened for nonalcoholic fatty liver disease.
fibrosis (Tables 1 and 2). Patients with NAFLD are at increased risk for diabetes and cardiovascular disease; hypertension, sleep apnoea and vitamin D deficiency have been associated with the progression of NAFLD. Patients with NASH are at risk for progression to advanced liver diseases, such as cirrhosis and hepatocellular carcinoma. In the U.S.A., the prevalence of NAFLD is estimated at 19–20%.17

Dermatologists need to recognize the link between psoriasis and NAFLD. Understanding this association enables proper assessment of psoriasis and informed decision making about which pharmacological treatments to prescribe (e.g. those without hepatotoxic or lipid-elevating potential). Furthermore, dermatologists can engage in appropriate patient education and consultation with a hepatologist if warranted.

The evidence: a link between psoriasis and nonalcoholic fatty liver disease

Insulin resistance and MetS are very common in both psoriasis and NAFLD. The release of inflammatory adipokines associated with these comorbidities drives further low-grade inflammation, leading to a vicious cycle that causes worsening of liver damage and progression of NAFLD. This inflammation may also drive the progression of psoriasis. See Table 3 for evidence supporting the association between psoriasis and NAFLD.

Initial case reports documented psoriasis in three patients with NASH, a patient with NASH and comorbid type 2 diabetes and psoriasis, and a patient with psoriasis, increased insulin resistance markers, elevated liver enzymes and NASH. Thereafter, investigations into a possible link between psoriasis and NAFLD ensued, and in each controlled retrospective or prospective study, the prevalence of NAFLD was significantly higher in patients with psoriasis than in healthy or matched controls (17–66% vs. 8–35%, respectively). Additionally, patients with psoriasis were at significantly increased risk for NAFLD than controls (odds ratio 2.15) in a systematic review and meta-analysis of seven case-controlled studies, six of which assessed risk of NAFLD among individuals with and without psoriasis.

In several studies, the presence and severity of psoriasis correlated with the prevalence, severity, and NAFLD risk (Fig. 2). Compared with patients with psoriasis alone, patients with psoriasis and NAFLD had more severe psoriasis, and NAFLD was a significant predictor of higher Psoriasis Area and Severity Index (PASI) scores. Conversely, PASI was a significant and independent predictor of NAFLD grade. Additionally, patients with mild-to-moderate psoriasis were less likely than those with moderate-to-severe psoriasis to have comorbid liver disease. Furthermore, patients with psoriasis and NAFLD were significantly more likely than patients with NAFLD alone to have severe NAFLD, including steatosis, fibrosis and NASH.

Although both psoriasis and NAFLD are associated with metabolic conditions, such as MetS, insulin resistance and obesity, it was unclear whether psoriasis could be independently associated with NAFLD. Recently, two studies demonstrated that psoriasis was a significant predictor of liver disease, and in elderly patients, psoriasis was independently associated with a 70% increased likelihood for developing NAFLD. When patients with and without psoriasis were compared, NAFLD Fibrosis Scores (−1.57 vs. −3.10; P ≤ 0.0001), presence of steatosis (44.3% vs. 34.0%; P = 0.02) and presence of advanced liver fibrosis (8.1% vs. 3.6%; P = 0.05) were significantly higher in patients with psoriasis; drug exposure was not evaluated. Furthermore, psoriasis is a significant predictor of NAFLD severity and the likelihood of having advanced NAFLD was increased by approximately 60% when psoriasis was present. Moreover, another study confirmed that patients with psoriasis were at increased risk for NASH; almost half (48/103; 47%) of patients with psoriasis or PsA had NAFLD, and nearly half these patients (23/48; 48%) had NASH. This finding is consistent with results of prior studies: one, in which three of
| Description/Characteristics | NAFLD | NASH |
|-----------------------------|-------|------|
| **Definition/characteristics** | Comprehensive term encompassing the entire spectrum of fatty liver disease not caused by significant alcohol consumption | Advanced form of NAFLD in which hepatic steatosis and inflammation with hepatocyte injury (ballooning) is present |
| | • NAFLD can be histologically categorized as NAFL or NASH | • NASH can progress to cirrhosis, liver failure and/or liver cancer |
| | • NAFL, which is generally benign, is defined as the presence of hepatic steatosis with no evidence of hepatocellular injury (ballooning) | • Noninvasive imagining techniques such as ultrasound-based transient elastography are used to determine severity of liver fibrosis/degree of steatosis |
| | • NAFLD is typically asymptomatic until the condition progresses to liver cirrhosis | • Tools such as the NAFLD fibrosis score (based on age, body mass index, hyperglycaemia, platelet count, albumin and AST: ALT ratio) are used to identify advanced fibrosis in patients with NAFLD |
| **Diagnosis** | Determined by three criteria: | NAFLD fibrosis score and presence of metabolic syndrome may be used to identify candidates for liver biopsy |
| | • Detection of steatosis by imaging or histology | • Liver biopsy is the only method used to conclusively diagnose NASH |
| | ○ Abdominal ultrasound is used to detect 2 of 4 characteristics, including increased hepatorenal contrast, liver brightness, deep attenuation and/or vascular blurring | ○ Necessary histopathological abnormalities include: |
| | ○ If imaging tools are not available, serum biomarkers may be used to diagnosis steatosis | |  ■ Steatosis accentuated in zone 3 (macrovesicular steatosis > microvesicular steatosis) |
| | • Steatosis must be nonalcohol induced | • Mixed/mild lobular inflammation |
| | • Other liver diseases (i.e. alcoholic liver diseases, viral hepatitis, autoimmune liver diseases, and metabolic or hereditary liver disease) must be excluded | • Hepatocellular ballooning |
| **Treatment** | Lifestyle modification | Lifestyle modifications and treatment of metabolic comorbidities are continued |
| | ○ Weight loss | Additional treatments to prevent progression in NASH |
| | ▪ Weight loss of ≥ 3–5% of body weight necessary to improve steatosis | ○ Foregut bariatric surgery (not an established treatment option in NASH) may be considered in patients with NASH (without cirrhosis) that are unresponsive to lifestyle changes and pharmacotherapy |
| | ▪ Weight loss of 10% may improve necroinflammation | ○ Pioglitazone (studied mostly in nondiabetic patients; long-term safety and efficacy of pioglitazone in patients with NASH is not known) |
| | ○ Exercise | ○ Vitamin E (daily dose of 800 IU daily) in nondiabetic adults with biopsy-proven NASH |
| | ▪ 150–200 min a week of moderate intensity aerobic physical activities (over 3–5 sessions) | |
| | ▪ Resistance training encouraged | |
| | ○ Alcohol intake | |
| | ▪ Limit daily intake (30 g in men; 20 g in women; in cases of NASH-cirrhosis, total abstinence is required) | |
| | ○ Nutrition | |
| | ▪ Avoid fructose-containing products | |
| | ▪ Ketogenic diet | |
| | • Treat associated metabolic comorbidities | |
| | ○ Obesity, hyperlipidaemia, insulin resistance, type 2 diabetes | |
| | ▪ Progression to liver fibrosis is correlated with degree of insulin resistance | |
| | ▪ In simple steatosis without fibrosis, specific liver treatments are not needed |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; NAFL, nonalcoholic fatty liver.
five patients with psoriasis and NAFLD who underwent biopsy had NASH, and others, in which surrogate serum markers of fibrosis [C-reactive protein (CRP) and transaminases] were increased. Drugs that increase liver toxicity, such as methotrexate, can be another ‘hit’ towards progression of NAFLD in a susceptible liver. Moreover, MetS and NASH are associated with several risk factors for methotrexate-mediated liver damage, such as obesity, diabetes and hyperlipidaemia.

**The common thread: low-grade chronic inflammation**

Chronic, low-grade inflammation appears to be the common aetiological factor between psoriasis and NAFLD, and comorbidities such as MetS. Adipose tissue acts as an endocrine organ, producing adipocytokines or adipokines, which play important roles in psoriasis and NAFLD pathogenesis (Fig. 3). These include leptin, adiponectin and resistin, which are important for energy balance, lipid and glucose metabolism, insulin sensitivity, blood pressure and angiogenesis, in addition to tumour necrosis factor-α (TNF-α) and interleukin-6 (IL-6), which are vital to the inflammatory process. These mediators allow crosstalk between adipose tissue and organs such as the liver, which responds by producing hepatokines such as fibroblast growth factor 21, fetuin-A, CRP, TNF-α, and IL-6 (Fig. 3). These molecules are released by hepatocytes and directly affect lipid and glucose metabolism in a similar way to adipocytokines, exerting affects in metabolic disease, including NAFLD. Furthermore, some of these immune mediators play dominant roles in development of MetS, such as elevated levels of leptin and decreased levels of adiponectin, both of which are observed in obesity and MetS.

Levels of pro- and anti-inflammatory adipocytokines are imbalanced in patients with psoriasis (significantly higher levels of TNF-α, IL-6, leptin, resistin and visfatin, and significantly lower levels of adiponectin) compared with healthy controls. In a study evaluating the prevalence of NAFLD in psoriasis, individuals with both conditions had significantly higher levels of IL-6 and lower serum levels of adiponectin than those with psoriasis alone. In another study, patients with psoriasis and NAFLD had significantly higher leptin, cytokeratin 18 and IL-6 levels and lower adiponectin levels than those without NAFLD.

Although the pathophysiology of NAFLD has not been completely elucidated, the ‘multiple hit model’ describes it as complex, multistep liver injury (Fig. 4). Insulin resistance – which may, in part, arise from overproduction of proinflammatory cytokines in patients with psoriasis – leads to hepatic accumulation of triglycerides. Subsequent steatosis renders the liver susceptible to further inflammatory insults, which may result in mitochondrial dysfunction, oxidative damage, dysregulated hepatocyte apoptosis, activation of the profibrogenic transforming growth factor-β (TGF-β) pathway, hepatic stellate cell activation and injury caused by adipocytokines and other inflammatory cytokines. Steatosis may also accelerate proinflammatory adipocytokines and systemic inflammation, resulting in greater insulin resistance. An imbalance between creation and disposal of triglycerides subsequently occurs, steatosis transitions to NASH and another imbalance develops between hepatocyte death and regeneration. These steps are further intensified by the presence of psoriasis and accompanying inflammatory processes and altered TNF-α: adiponectin ratio, which promotes liver disease progression. Thus, a vicious cycle of iterative liver damage
| Year | Lead author, study design and location | Patients | Prevalence of liver disease | Laboratory/clinical associations | PsO/NAFLD severity associations |
|------|--------------------------------------|----------|-----------------------------|---------------------------------|---------------------------------|
| 2009 | Gisondi et al.,27 retrospective, cross-sectional Italian study (Italy) | PsO patients (n = 130) vs. healthy controls (n = 260) | NAFLD: 47% vs. 28%; P < 0.0001 | • PsO + NAFLD (n = 61) vs. PsO (n = 69) | PsO + NAFLD vs. PsO |
|      |                                      |          |                             | • Significantly more likely to have MetS, higher CRP concentrations, higher ALT (P < 0.01) | • More severe PsO (per PASI score; P < 0.01) |
|      |                                      |          |                             | • Frequency of NAFLD greater with PASI score ≥10 vs. <10 | • NAFLD: only significant predictor of higher PASI score (P = 0.038) |
|      |                                      |          |                             | • PsO + NAFLD vs. PsO | |
|      |                                      |          |                             | • More severe PsO (per PASI score; P < 0.01) | |
|      |                                      |          |                             | • Frequency of NAFLD greater with PASI score ≥10 vs. <10 | |
|      |                                      |          |                             | • NAFLD: only significant predictor of higher PASI score (P = 0.038) | |
|      |                                      |          |                             | • PsO + NAFLD vs. PsO | |
|      |                                      |          |                             | • More severe PsO (per PASI score; P < 0.01) | |
|      |                                      |          |                             | • Frequency of NAFLD greater with PASI score ≥10 vs. <10 | |
|      |                                      |          |                             | • NAFLD: only significant predictor of higher PASI score (P = 0.038) | |
| 2010 | Miele et al.,15 prospective, cross-sectional cohort and noninterventional case-control study (Italy) | PsO patients (n = 142) vs. matched non-PsO, NAFLD patients (n = 125) | NAFLD: 59% | • PsO vs. no PsO: significantly higher odds of comorbid liver diseases | Odds of comorbid liver diseases: |
|      |                                      |          |                             | • NAFLD: significant correlations with MetS, obesity, hypercholesterolemia, hypertriglyceridemia, AST : ALT > 1 and PsA (P ≤ 0.05) | • Mild–moderate PsO: 1.02%; OR, 1.714 (95% CI 0.80–3.67); P = 0.1601 |
|      |                                      |          |                             |                                           | • Severe PsO: 10.85%; OR, 20.18 (95% CI 8.96–45.46); P ≤ 0.00001 |
| 2011 | Al-Mutairi et al.,13 retrospective, case–control cohort study (Kuwait) | PsO patients (n = 1835) vs. controls (n = 1835) (66.2% severe PsO) | Fatty liver: 35.7% NAFLD: 17.4% vs. 7.9%; P = 0.002 | • PsO vs. no PsO: higher odds of comorbid liver diseases (adjusted OR 1.34) | Odds of comorbid liver diseases: |
|      |                                      |          |                             | • PsO vs. no PsO: higher odds of comorbid liver diseases (adjusted OR 1.34) | • Mild PsO (n = 1384); OR 1.30 (1.09–1.57) |
|      |                                      |          |                             | • PsO vs. no PsO: higher odds of comorbid liver diseases (adjusted OR 1.34) | • Severe PsO (n = 301); OR 1.53 (1.10–2.14) |
|      |                                      |          |                             | • PsO vs. no PsO: higher odds of comorbid liver diseases (adjusted OR 1.34) | |
|      |                                      |          |                             | • PsO vs. no PsO: higher odds of comorbid liver diseases (adjusted OR 1.34) | |
| 2012 | Madanagobalane and Anandan,28 prospective, hospital-base, cross-sectional, case–control cohort study (India) | PsO patients (n = 333) vs. controls (n = 330) (14.4% severe PsO; mean ± SD PASI score: 5.15 ± 6.06) | Fatty liver: 35.7% NAFLD: 17.4% vs. 7.9%; P = 0.002 | • PsO + NAFLD (n = 58) vs. PsO (n = 254) | • PsO + NAFLD vs. PsO |
|      |                                      |          |                             | • Significantly more likely to have MetS and diabetes (P < 0.05) | • Significantly more severe PsO per PASI scores (P = 0.02) |
|      |                                      |          |                             | • PsO vs. no PsO: higher odds of comorbid liver diseases (adjusted OR 1.34) | • PsO + NAFLD (n = 58) vs. NAFLD (n = 26) |
|      |                                      |          |                             | • PsO vs. no PsO: higher odds of comorbid liver diseases (adjusted OR 1.34) | • Significantly more severe NAFLD (fibrosis, steatosis, NASH, P < 0.05) |

(continued)
| Year | Lead author, study design and location | Patients | Prevalence of liver disease | Laboratory/clinical associations | PsO/NAFLD severity associations |
|------|--------------------------------------|----------|----------------------------|---------------------------------|-------------------------------|
| 2014 | van der Voort et al., 29 prospective, cross-sectional, population-based cohort study (the Netherlands) | Elderly participants from the Rotterdam study \( n = 118 \) with PsO + NAFLD, \( n = 2174 \) with NAFLD) (most had mild PsO) | NAFLD: 46.2% vs. 33.3%; \( P = 0.005 \) | ● PsO + NAFLD vs. NAFLD  
- Significant increased prevalence of NAFLD of 70% (adjusted OR 1.7, 95% CI 1.1–2.6), independent of common NAFLD risk factors  
- Significantly higher prevalence of MetS and significantly higher ALT, AST and HOMA-IR \( (P < 0.01) \)  
- Increased the likelihood of having more severe NAFLD by approximately 60% (adjusted OR 1.58, 95% CI 1.06–2.38) | PsO + NAFLD vs. NAFLD |
| 2015 | Abedini et al., 31 prospective, cross-sectional cohort study (Iran) | 123 PsO patients vs. 123 healthy controls \( ^a \) | NAFLD: 65.6% vs. 35%; \( P < 0.01 \); OR = 3.53 | ● PsO + NAFLD vs. PsO  
- NAFLD grade significantly greater (grade 2 vs. 1; \( P < 0.01 \))  
- Significantly higher frequency of hypertension, high LFT levels, and MetS \( (P < 0.01) \)  
- Significantly higher BMI; WC; PASI scores; and serum triglyceride, cholesterol and fasting blood sugar levels \( (P < 0.01) \)  
- PASI score, WC, hypertension, cigarette smoking and elevated LFT levels were independent predictors of NAFLD grade | |
|      | Roberts et al., 37 prospective, cross-sectional cohort study (U.S.A.) | 103 PsO or PsA patients | NAFLD: 47%  
NASH: 22% | ● PsO + NAFLD vs. PsO: significantly higher WC, BMI, markers of glucose homeostasis, ferritin levels and PASI scores \( (P < 0.01) \)  
- Variables independently associated with NAFLD: hypertriglyceridaemia, hyperglycaemia, fibroscan, PASI score, duration and sex \( (P < 0.05) \) | |
| 2016 | Narayanasamy et al., 108 prospective, hospital-based, observational study (India) | 250 PsO patients | NAFLD: 45.2% | ● Variables independently associated with NAFLD: hypertriglyceridaemia, hyperglycaemia, fibroscan, PASI score, duration and sex \( (P < 0.05) \) | |

\( ^a \) PsO patients vs. healthy controls
| Year | Lead author, study design and location | Patients | Prevalence of liver disease | Laboratory/clinical associations | PsO/NAFLD severity associations |
|------|--------------------------------------|----------|-----------------------------|--------------------------------|--------------------------------|
| 2016 | Gisondi et al.,30 cross-sectional cohort study (Italy) | 124 PsO patients vs. 79 healthy controls [mean ± SD PASI score: 13 ± 10 (range: 1–58)] | NAFLD: 44% vs. 26%, P < 0·001 | • NAFLD-FS: −1·57 ± 1·4 vs. −3·10 ± 1·5 (P ≤ 0·0001) | • PsO: significant predictor of advanced liver fibrosis (by NAFLD-FS), independently of age, sex, BMI, hypertension and diabetes |
|      | van der Voort et al.,36 Cross-sectional, population-based cohort study (The Netherlands) | 1535 elderly patients 74 with PsO vs. 1461 controls without PsO 39 with PsO + NAFLD vs. 375 controls with NAFLD | Steatosis: 44·3% vs. 34·0%; P = 0·02 Advanced fibrosis: 8·1% vs. 3·6% (P = 0·05; OR 2·39, 95% CI 0·99–5·76) | • PsO vs. no PsO | • PsO: associated with advanced fibrosis (adjusted OR 2·36, 95% CI 0·95–5·85) |
|      |                                      |          |                             | PsO: predictor of fibrosis severity (P = 0·03), independent of age, sex, alcohol consumption, ALT, MetS and steatosis (P = 0·04) | PsO + NAFLD vs. NAFLD: significantly increased risk for advanced fibrosis (OR 4·2, 95% CI 1·1–16·0) independent of age, sex, alcohol consumption, ALT level and MetS (OR 4·1, 95% CI 1·01–17·0) |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CI, confidence interval; CRP, C-reactive protein; HOMA-IR, homeostatic model assessment of insulin resistance; LFT, liver function test; MetS, metabolic syndrome; NASH, nonalcoholic steatosis; NAFLD-FS, NAFLD Fibrosis Score; OR, odds ratio; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsO, psoriasis; SD, standard deviation; WC, waist circumference. aNo PsO and matched for age, sex and BMI. bNo PsO and matched for age and BMI. "No PsO and matched for age and sex.
continues, wherein risk of progression is increased when psoriasis, particularly severe psoriasis, is present. In turn, psoriasis severity may be worsened by reactive oxygen species, CRP, IL-6 and other proinflammatory cytokines released from the damaged liver. 

Interestingly, some, but not all, patients with psoriasis have NAFLD in the absence of MetS. Furthermore, psoriasis is significantly associated with NAFLD, independently of MetS components or other confounders. In our experience, patients with psoriasis may develop progressive NAFLD even in the

### Common risk factors

- Proinflammatory cytokines
- Dyslipidaemia/hyperlipidaemia
- Inflammation
- Stressors
- Obesity
- Diet
- Insulin resistance
- Genes

---

Fig 2. Significant associations and common risk factors between psoriasis and nonalcoholic fatty liver disease (NAFLD). PsO, psoriasis.

**Psoriasis**

| Pro-inflammatory cytokines | Pro-inflammatory adipokines | Anti-inflammatory adipokines |
|----------------------------|-----------------------------|----------------------------|
| Keratinocyte proliferation, pro-inflammatory cytokines, angiogenesis | TNF-α | Adiponectin |
| Keratinocyte proliferation, adhesion molecule expression, pro-inflammatory cytokines | IL-1 | |
| Keratinocyte proliferation | IL-6 | |
| Keratinocyte proliferation, Th1 response, angiogenesis | Leptin | |
| Proinflammatory cytokines | Resistin | |
| Proinflammatory hepatokines | Visfatin | |
| | Ghrelin | |

---

Fig 3. Levels and roles of adipokines and hepatokines in psoriasis and nonalcoholic fatty liver disease (NAFLD). CRP, C-reactive protein; ERG, ergosterol; FGF, fibroblast growth factor; IL, interleukin; MAP, mitogen-activated protein; TNF, tumour-necrosis factor.
Fig 4. Multihit hypothesis for development and progression of nonalcoholic fatty liver disease.\textsuperscript{51} IL, interleukin; LPL, lipoprotein lipase; NASH, nonalcoholic steatohepatitis; ObR, leptin receptor; PNPLA, patatin-like phospholipase 3; TLR, Toll-like receptor; TNF, tumour-necrosis factor; VLDL, very-low-density lipoprotein. Figure reprinted from: Takaki A, Kawai D, Yamamoto K. Multiple hits, including oxidative stress, as pathogenesis and treatment target in nonalcoholic steatohepatitis (NASH). \textit{Int J Mol Sci} 2013; \textbf{14}:20704–28.

Table 4 Recommended evaluations by a hepatologist for the diagnosis of nonalcoholic fatty liver disease (NAFLD) in psoriasis

| Category                              | Evaluation                                                                 |
|---------------------------------------|----------------------------------------------------------------------------|
| Medical history                       | Alcohol intake > 20 g daily (female) or > 30 g daily (male)\textsuperscript{76}                                |
|                                       | Family history of diabetes mellitus, hypertension, cardiovascular disease or cryptogenic cirrhosis |
|                                       | Diet, lifestyle and physical activity/exercise                                |
|                                       | Previously and currently prescribed medications                             |
| Anthropometric records                | Body mass index                                                              |
|                                       | Waist circumference                                                           |
|                                       | Blood pressure                                                               |
| Diagnostic tests                      | Complete blood count                                                         |
|                                       | ALT, AST, GGT, total bilirubin, alkaline phosphatase                          |
|                                       | Triglycerides, total cholesterol, HDL cholesterol, LDL cholesterol, uric acid |
|                                       | Fasting blood glucose, haemoglobin A1c, OGTT, fasting insulin (HOMA-IR)       |
|                                       | Prothrombin time, INR, albumin                                                |
|                                       | TSH, 25-hydroxy vitamin D                                                     |
|                                       | Ultrasound of the liver                                                       |
|                                       | Noninvasive evaluation of fibrosis                                            |
|                                       | Liver biopsy (only if indicated after consultation with a hepatologist)       |
| Exclude other causes of liver disease | Hepatitis B and C test                                                        |
|                                       | Ferritin and transferrin saturation                                           |
|                                       | Celiac disease screen                                                         |
|                                       | Other liver disease tests: Wilson disease, autoimmune disease, α1-antitrypsin deficiency |

ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transferase; HDL, high-density lipoprotein; HOMA-IR, homeostatic model assessment of insulin resistance; INR, international normalized ratio; LDL, low-density lipoprotein; OGTT, oral glucose tolerance test; TSH, thyroid-stimulating hormone.
absence of MetS or other possible cofactors, such as congenital errors of metabolism, viral hepatitis and hepatotoxic drugs. NAFLD is a genetically complex disease and polymorphisms in key genes can determine susceptibility to NAFLD and disease progression.\textsuperscript{16,41,50,56–60}

Several candidate genes have been evaluated with a hypothesis-driven approach. For example, some genes linked to NAFLD are related to lipid metabolism (hepatic lipase and lipin-1 (LPIN1), regulation of triglyceride levels; peroxisome proliferator-activated receptor, glucose and lipid metabolism regulation; microsomal triglyceride transfer protein, phospholipid and triglyceride development; and phosphatidylcholine, hepatic formation and secretion of very-low-density lipoproteins) and fibrogenesis (TGF-β1, angiotensinogen, angiotensin receptors) or encode cytokines/adipocytokines (TNF-α, leptin, adiponectin)).\textsuperscript{18,57,61,62}

Vitamin D deficiency has also been implicated in the pathogenesis of psoriasis and NAFLD.\textsuperscript{63,64} In patients with NAFLD, low levels of vitamin D cause activation of Toll-like receptors, which exacerbates hepatic inflammation and vitamin D levels have been correlated with disease severity.\textsuperscript{63} Additionally, vitamin D is involved in the regulation of the cutaneous immune system, downregulating the expression of proinflammatory cytokines including TNF-α, IL-6 and IL-8.\textsuperscript{65}

More recently, genome-wide association studies have identified new polymorphisms in candidate genes such as the I148M polymorphism in PNPLA3,\textsuperscript{66} a gene involved in lipid metabolism, which plays an important role in susceptibility to progressive NAFLD,\textsuperscript{60,67} and the TM6SF2 polymorphism that increases risk for NAFLD and fibrosis.\textsuperscript{68,69}

**Diagnosis of nonalcoholic fatty liver disease**

All patients with psoriasis should be screened for NAFLD as NAFLD is present in 7% of lean individuals and severity of NAFLD is independent of liver enzymes levels.\textsuperscript{76,71} We recommend that liver ultrasound and evaluation of liver enzymes should be performed at the time of psoriasis diagnosis. Generally, patients with NAFLD are asymptomatic; however, when symptoms are present, they are typically nonspecific (fatigue, malaise and right upper quadrant discomfort). Therefore, taking a thorough history (including alcohol consumption, previously or currently prescribed medications, physical activity, weight change, history of MetS or components, dietary habits, viral hepatitis risk and family history of liver disease) and conducting a physical examination [vital signs, weight, waist circumference and body mass index (BMI)] with appropriate laboratory testing [liver function tests (LFTs), hepatitis C antibody, hepatitis B surface antigen, hepatitis B core antibody, fasting glucose, haemoglobin A\textsubscript{1C} and cholesterol and lipid panel] are essential in patients with suspected NAFLD based on initial ultrasound and liver enzyme findings and should be conducted by a hepatologist (Table 4).

Serum enzyme [alanine aminotransferase (ALT) and aspartate aminotransferase (AST)] levels can be mildly elevated, more often in NASH (AST : ALT > 1)\textsuperscript{72} than NAFLD (AST : ALT < 1). Alkaline phosphatase levels may be slightly elevated; gamma-glutamyl transferase (GGT) levels are frequently elevated; and bilirubin and albumin levels are normal.\textsuperscript{72,73} Notably, enzyme abnormalities may occur with certain psoriasis medications (methotrexate, acitretin, ciclosporin, nonsteroidal anti-inflammatory drugs, infliximab and, rarely, etanercept, adalimumab or ustekinumab).\textsuperscript{72–75} With advanced disease, hepatomegaly and tenderness and other signs and symptoms of cirrhosis such as dark urine, jaundice, markedly elevated LFTs, elevated serum bilirubin levels, low serum albumin levels and altered prothrombin time may occur. NASH can progress from cirrhosis to liver failure and, more rarely, to hepatic cancer.\textsuperscript{11}

When NAFLD is suspected, consultation or referral to a hepatologist is recommended. Presumptive diagnosis of NAFLD can be made if serum enzyme elevations are confirmed and other potential causes (hepatotoxic medications, excessive alcohol consumption, hereditary disorders) are ruled out. It should be noted that a diagnosis of NAFLD is possible in the absence of elevated serum enzymes.\textsuperscript{72} A definitive diagnosis is made when fat is observed in the liver during diagnostic testing (ultrasound, enhanced computed tomography, magnetic resonance imaging). The only way to confirm diagnosis of NASH definitively is with liver biopsy.\textsuperscript{76} High-risk patients who may be candidates for this procedure are those with obesity (BMI ≥ 28 kg/m\textsuperscript{2}) and diabetes and/or AST : ALT ≥ 0.8.\textsuperscript{72}

**Treatment of nonalcoholic fatty liver disease**

No specific guidelines exist for the treatment of psoriasis and comorbid NAFLD. However, goals of NAFLD treatment are to prevent or reverse hepatic injury and fibrosis, and treatment guidelines are available from the American Association for the Study of Liver Diseases and European Association for the Study of the Liver.\textsuperscript{11,76} According to the guidelines, pharmacological treatment should be limited to NASH because patients with simple steatosis without presence of fibrosis are at low progression risk.

The first-line approach applied to all patients displaying early signs of NAFLD should include lifestyle modification, minimization of alcohol consumption and treatment of underlying conditions and comorbidities (e.g. diabetes/insulin resistance, hyperlipidaemia, hypertension, sleep apnoea, vitamin D deficiency). Progression to liver fibrosis is correlated with the degree of insulin resistance, making this an important aspect of treatment.\textsuperscript{77}

Weight loss and increased physical activity/exercise can normalize AST and/or ALT levels, reduce necroinflammation and improve insulin resistance, steatosis and liver histology. Loss of ≥ 5% total body weight resulted in higher rates of steatohepatitis resolution and weight loss of > 7% may provide substantial improvement in steatosis, lobular inflammation, ballooning and disease activity.\textsuperscript{78}

Several supplements, including vitamin D, vitamin E and omega-3 fatty acids, have shown promise, but evidence is limited. Vitamin D deficiency can contribute to increased...
inflammation by decreased function of T suppressor cells.\textsuperscript{13,79}
A recent randomized clinical trial of vitamin D treatment in NAFLD reported no significant changes in serum levels of liver enzymes.\textsuperscript{80} However, a significant decrease in levels of malondialdehyde, a marker of lipid peroxidation, was observed, suggesting that vitamin D could be considered as an adjunctive therapy to attenuate systemic inflammation. Levels of α-tocopherol are decreased in NASH, and studies have demonstrated that vitamin E therapy can improve NASH in patients without diabetes.\textsuperscript{81,82} Although not currently recommended for the specific treatment of NAFLD or NASH, omega-3 fatty acids have reduced liver fat and may be considered as first-line treatment of hypertriglyceridemia in patients with NAFLD in the U.S.A.\textsuperscript{11,83} A meta-analysis of omega-3 fatty acids in treatment of hypertriglyceridemia in patients with NAFLD concluded that they have a beneficial effect on liver fat and levels of GGT and blood lipids; treatment with omega-3 fatty acids may therefore slow progression of NAFLD.\textsuperscript{84} Diets high in saturated fats or high fructose corn syrup may cause NAFLD, and minimizing these substances may be beneficial.\textsuperscript{85} High intake of coffee or oral supplementation of cysteine-rich whey protein has been demonstrated to reduce hepatic steatosis in NAFLD.\textsuperscript{86,87}

A recent meta-analysis did not find any significant association between total caffeine consumption and prevalence of NAFLD, but did report that regular caffeine intake (from coffee only) was significantly associated with reduced hepatic fibrosis in NAFLD.\textsuperscript{88} The authors suggested that patients with NAFLD should be encouraged to consume coffee daily. Low levels of folic acid have been observed in patients with NASH and NAFLD;\textsuperscript{89} however, a 6-month open-label pilot study that investigated the effects of treatment with folic acid in 10 patients with NASH reported no significant changes in levels of serum aspartate or ALT.\textsuperscript{90}

Although a healthy diet and increased physical activity/exercise provide the best chance for long-term success and overall benefit, evidence indicates physical activity, particularly prolonged activity sessions (increased by ≥ 60 min or maintained at 150 min per week), provides a significant advantage.\textsuperscript{91} Nonbiological and biological treatments have been evaluated in NAFLD; however, no drugs are approved. There are no ongoing trials investigating the treatment of NASH in patients with psoriasis.

**The confounders: effect of psoriasis drugs on the liver**

Because psoriasis is associated with many comorbidities, choosing appropriate treatment is challenging. A number of psoriasis medications can elevate lipid levels, exacerbate liver disease or be hepatotoxic, necessitating careful consideration for their use in people with psoriasis with hepatic abnormalities.

Patients with psoriasis are more likely to experience methotrexate hepatotoxicity than patients with rheumatoid arthritis (RA), probably because of higher rates of NAFLD, dyslipidaemia, obesity and diabetes.\textsuperscript{92} Maybury et al. performed a review of eight small observational studies in patients with psoriasis receiving treatment with methotrexate.\textsuperscript{93} Overall, their review found no statistically significant risk for developing significant liver fibrosis, but there was an increased risk for any fibrosis and cirrhosis. A larger group of prospectively recruited patients with psoriasis and sequential biopsies are needed to draw causal conclusions. Monitoring of liver chemistry in patients with psoriasis taking methotrexate may help detect liver fibrosis; however, comorbidities such as diabetes may confound results.

Elevated levels of amino-terminal propeptide of type III collagen (PIIINP) have been observed in patients with psoriasis who developed liver fibrosis; PIIINP is therefore monitored by some dermatologists but its reliability in identifying liver damage is questionable.\textsuperscript{94} Although renal toxicity is of greatest concern with ciclosporin, it can increase lipid levels\textsuperscript{94} and possibly worsen NAFLD. Acitretin is associated with abnormal LFTs, hyperlipidaemia and liver disease risk factors, but is rarely associated with liver damage.\textsuperscript{95} Because some patients tolerate these systemic treatments, they may be occasionally used in comorbid NAFLD if patients are selected carefully and routinely monitored for liver disease progression.\textsuperscript{73,76,97}

For patients with moderate-to-severe psoriasis and no contraindications, biologics, such as TNF-α inhibitors (etanercept, adalimumab, and infliximab), anti-IL-12/23 agents (ustekinumab) and anti-17A antibodies (secukinumab and ixekizumab) are appropriate. Patients with psoriasis, MetS and NAFLD were treated with etanercept or psoralen–ultraviolet A (PUVA) over 24 weeks.\textsuperscript{77} In patients treated with etanercept, there were significant reductions from baseline in AST : ALT measurements, CRP and fasting insulin levels, and homeostasis model assessment index, and a significant increase in quantitative insulin sensitivity check index values. It was concluded that etanercept could be more effective than PUVA in reducing the risk for hepatic fibrosis by decreasing insulin resistance.

A subsequent study confirmed a partial rebalancing of pro- and anti-inflammatory cytokines, primarily because of reduced proinflammatory cytokine levels, after etanercept treatment.\textsuperscript{97} Because the risk for liver disease progression is directly correlated with insulin resistance and TNF-α plays a role in NAFLD pathogenesis, TNF-α inhibitors may serve a dual function in treating psoriasis and limiting the progression of liver disease. However, some patients receiving etanercept gained significant weight and experienced increased waist-to-hip ratios and BMI, which are independent risk factors for fibrosis. Furthermore, drug-related liver toxicity has been observed in clinical studies of patients with psoriasis treated with infliximab; up to 8% of patients developed markedly elevated levels of AST and ALT.\textsuperscript{78} These effects were observed independently of other signs of impaired liver function (e.g. abnormal bilirubin levels). Similar effects have not been reported for adalimumab, although the monitoring of liver enzymes during treatment is recommended.\textsuperscript{98}

Ustekinumab is another potential treatment option, given that drug-related liver toxicity is mild and uncommon, even in pre-existing liver disease and those who experienced liver-
related events with other psoriasis drugs, including TNF-α inhibitors. Finally, the efficacy and safety of IL-17A inhibition by secukinumab or ixekizumab in psoriasis was demonstrated in phase III clinical trials. Importantly, there were no clinically relevant changes in liver biochemical tests reported for secukinumab or ixekizumab.

In clinical trials of the phosphodiesterase four inhibitor apremilast, adverse events such as renal and liver toxicity were not observed. Thus, it may be suitable for patients with psoriasis and NAFLD.

Conclusions

Psoriasis and its comorbidities have a negative impact on health, quality of life and overall well-being. Each patient with psoriasis should be screened for NAFLD and other comorbidities. Fatty liver disease often provides an indication of potential underlying diseases, including cardiovascular disease, MetS, diabetes, obstructive sleep apnoea and obesity. Other less-common associations are fatty pancreas, hypothyroidism, colon polyps, elevated uric acid levels, vitamin D deficiency and polycystic ovaries.

Furthermore, appropriate steps should be taken to choose suitable treatments and reduce risk for liver disease progression. Counselling patients on diet and lifestyle changes and tailoring treatment to meet each patient’s needs is integral to successful outcomes. Large, prospective controlled studies are needed to determine if newer biological treatments can prevent progression of NAFLD in psoriasis.

Acknowledgments

Technical assistance with editing and styling of the manuscript for submission was provided by Oxford PharmaGenesis Inc. and was funded by Novartis Pharmaceuticals Corporation.

References

1 Rachakonda TD, Schupp CW, Armstrong AW. Psoriasis prevalence among adults in the United States. J Am Acad Dermatol 2014; 70: 512–6.

2 World Health Organization. Global Report on Psoriasis. World Health Organization, 2016. Available at: http://apps.who.int/iris/bitstream/10665/204417/1/9789241565189_eng.pdf (last accessed 16 October 2016).

3 Griffiths CE, Barker JN. Pathogenesis and clinical features of psoriasis. Lancet 2007; 370: 263–71.

4 Machado-Pinto J, Diniz Mdos S, Bavoso NC. Psoriasis: new comorbidities. An Bras Dermatol 2016; 91: 8–14.

5 de Oliveira M, de Oliveira Rocha B, Vieira Duarte G. Psoriasis: classical and emerging comorbidities. An Bras Dermatol 2015; 90: 9–20.

6 Ganzetti G, Campanati A, Offidani A. Non-alcoholic fatty liver disease and psoriasis: So far, so near. World J Hepatol 2015; 7: 315–26.

7 Puig-Sanz L. Psoriasis, a systemic disease? Actas Dermosifiliogr 2007; 98: 396–402. (in Spanish).

8 Sommer DM, Jenisch S, Suchan M et al. Increased prevalence of the metabolic syndrome in patients with moderate to severe psoriasis. Arch Dermatol Rs 2006; 298: 321–8.

9 Yeung H, Takeshita J, Mehta N et al. Psoriasis severity and the prevalence of major medical comorbidity: a population-based study. JAMA Dermatol 2013; 149: 1173–9.

10 Svedbom A, Dalén J, Mamolo C et al. Increased cause-specific mortality in patients with mild and severe psoriasis: a population-based Swedish register study. Acta Derm Venereol 2015; 95: 809–15.

11 Chalasani N, Younossi Z, Lavine JE et al. The diagnosis and management of non-alcoholic fatty liver disease: practice guideline by the American Gastroenterological Association, American Association for the Study of Liver Diseases, and American College of Gastroenterology. Gastroenterology 2012; 142: 1592–609.

12 Puri P, Sanyal AJ. Nonalcoholic fatty liver disease: definitions, risk factors, and workup. Clin Liver Dis 2012; 1: 99–103.

13 Eliades M, Spyrou E, Agrawal N et al. Meta-analysis: vitamin D and non-alcoholic fatty liver disease. Aliment Pharmacol Ther 2013; 38: 246–54.

14 Mirrakhimov AE, Polosky VY. Obstructive sleep apnea and non-alcoholic fatty liver disease: is the liver another target? Front Neurol 2012; 3: 149.

15 Kwok RM, Torres DM, Harrison SA. Vitamin D and nonalcoholic fatty liver disease (NAFLD): is it more than just an association? Hepatology 2013; 58: 1166–74.

16 Ansee QM, Targarh G, Day CP. Progression of NAFLD to diabetes mellitus, cardiovascular disease or cirrhosis. Nat Rev Gastroenterol Hepatol 2013; 10: 330–44.

17 Vernon G, Baranova A, Younossi ZM. Systematic review: the epidemiology and natural history of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis in adults. Aliment Pharmacol Ther 2011; 34: 274–85.

18 Lazo M, Hernaæez R, Eberhardt MS et al. Prevalence of nonalcoholic fatty liver disease in the United States: the Third National Health and Nutrition Examination Survey, 1988–1994. Am J Epidemiol 2013; 178: 38–45.

19 Gisondi P, Tessari G, Conti A et al. Prevalence of metabolic syndrome in patients with psoriasis: a hospital-based case-control study. Br J Dermatol 2007; 157: 68–73.

20 Paschos P, Paletas K. Non alcoholic fatty liver disease and metabolic syndrome. Hippokratia 2009; 13: 9–19.

21 Gaggini M, Morelli M, Buzzigoli E et al. Non-alcoholic fatty liver disease (NAFLD) and its connection with insulin resistance, dyslipidemia, atherosclerosis and coronary heart disease. Nutrients 2013; 5: 1544–60.

22 Gyldenlove M, Storgaard H, Holst JJ et al. Increased cause-specific mortality among adults in the United States. J Am Acad Dermatol 2015; 72: 599–605.

23 Meli R, Mattace Raso G, Calignano A. Role of innate immune response in non-alcoholic fatty liver disease: metabolic complications and therapeutic tools. Front Immunol 2014; 5: 177.

24 Lonardo A, Loria P, Carulli N. Nonalcoholic steatohepatitis and psoriasis. Report of three cases from the POLI.S-T.E.N.A. study. Dig Liver Dis 2001; 33: 86–7.

25 Itoh S, Kanazuka A, Akimoto T. Combined treatment with ursodeoxycholic acid and pioglitazone in a patient with NASH associated with type 2 diabetes and psoriasis. Dig Dis Sci 2003; 48: 2182–6.

26 Matsumoto T, Suzuki N, Watanabe H et al. Nonalcoholic steatohepatitis associated with psoriasis vulgaris. J Gastroenterol 2004; 39: 1102–5.

27 Gisondi P, Targarh G, Zoppini G et al. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009; 51: 758–64.

28 Madanagobalane S, Anandan S. The increased prevalence of non-alcoholic fatty liver disease in psoriatic patients: a study from South India. Australas J Dermatol 2012; 53: 190–7.

29 van der Voort EA, Koehler EM, Dowlatshahi EA et al. Psoriasis is independently associated with nonalcoholic fatty liver disease in
patients 55 years old or older: results from a population-based study. J Am Acad Dermatol 2014; 70:517–24.
30 Gisondi P, Barba E, Girolomoni G. Non-alcoholic fatty liver disease fibrosis score in patients with psoriasis. J Eur Acad Dermatol Venereol 2016; 30:282–7.
31 Abedini R, Salehi M, Lajevardi V et al. Patients with psoriasis are at a higher risk of developing nonalcoholic fatty liver disease. Clin Exp Dermatol 2015; 40:722–7.
32 Candia R, Ruiz A, Torres-Robles R et al. 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.
33 Al-Mutairi N, Al-Farag S, Al-Mutairi A et al. Comorbidities associated with psoriasis: an experience from the Middle East. J Dermatol 2010; 37:146–55.
34 Yang YW, Keller JJ, Lin HC. Medical comorbidities associated with psoriasis in adults: a population-based study. Br J Dermatol 2011; 165:1037–43.
35 Miele L, Vallone S, Cefalo C et al. Prevalence, characteristics and severity of non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. J Hepatol 2009; 51:778–86.
36 van der Voort EA, Koehler EM, Nijsten T et al. Increased prevalence of advanced liver fibrosis in patients with psoriasis: a cross-sectional analysis from the Rotterdam Study. Acta Derm Venereol 2016; 96:213–7.
37 Roberts KK, Cochet AE, Lamb PB et al. The prevalence of NAFLD and NASH among patients with psoriasis in a tertiary care dermatology and rheumatology clinic. Aliment Pharmacol Ther 2015; 41:293–300.
38 Terra X, Augustet T, Quesada I et al. Increased levels and adipose tissue expression of visfatin in morbidly obese women: the relationship with pro-inflammatory cytokines. Clin Endocrinol 2012; 77:691–9.
39 Kershaw EE, Flier JS. Adipose tissue as an endocrine organ. J Clin Endocrinol Metab 2004; 89:2548–56.
40 Ganzetti G, Campatani A, Molinelli E et al. Psoriasis, non-alcoholic fatty liver disease, and cardiovascular disease: Three different diseases on a unique background. World J Cadinol 2016; 8:120–31.
41 Stojaljević S, Gomercić Pačić M, Virović Jukić L et al. Adipokines and proinflammatory cytokines, the key mediators in the pathogenesis of nonalcoholic fatty liver disease. J World Gastroenterol 2014; 20:18070–91.
42 Panera N, Della Corte C, Crudele A et al. Recent advances in understanding the role of adipocytokines during non-alcoholic fatty liver disease pathogenesis and their link with hepatokines. Expert Rev Gastroenterol Hepatol 2016; 10:393–403.
43 Dushay J, Chiu PC, Gopalanrishnan GS et al. Increased fibroblast growth factor 21 in obesity and nonalcoholic fatty liver disease. Gastroenterology 2010; 139:456–63.
44 Uysal S, Yılmaz FM, Karatoprak K et al. The levels of serum pentraxin3, CRP, fetuin-A, and insulin in patients with psoriasis. Eur Rev Med Pharmacol Sci 2014; 18:3453–8.
45 Wisse BE. The inflammatory syndrome: the role of adipose tissue cytokines in metabolic disorders linked to obesity. J Am Soc Nephrol 2004; 15:2792–800.
46 Monteiro R, Azevedo I. Chronic inflammation in obesity and the metabolic syndrome. Mediators Inflamm 2010; 2010: pii:289645.
47 Campanati A, Ganzetti G, Giuliodori K et al. Serum levels of adipocytokines in psoriasis patients receiving tumor necrosis factor-α inhibitors: results of a retrospective analysis. Int J Dermatol 2015; 54:839–45.
48 Tilg H, Moschen AR. Evolution of inflammation in nonalcoholic fatty liver disease: the multiple parallel hits hypothesis. Hepatology 2010; 52:1836–46.
49 Yilmaz Y. Review article: is non-alcoholic fatty liver disease a spectrum, or are steatosis and non-alcoholic steatohepatitis distinct conditions? Aliment Pharmacol Ther 2012; 36:815–23.
50 Naik A, Kośir R, Rozman D. Genomic aspects of NAFLD pathogenesis. Genomics 2013; 102:84–95.
51 Takai A, Kawai D, Yamamoto K. Multiple hits, including oxidative stress, as pathogenesis and treatment target in non-alcoholic steatohepatitis (NASH). Int J Mol Sci 2013; 14:20704–28.
52 Onyekwere CA, Ogbera AO, Samaila AA et al. Nonalcoholic fatty liver disease: Synopsis of current developments. Niger J Clin Pract 2015; 18:703–12.
53 Berlanga A, Guiri-Jurado E, Porras JA et al. Molecular pathways in non-alcoholic fatty liver disease. Clin Exp Gastroenterol 2014; 7:221–39.
54 Neuschwander-Tetri BA. Hepatic lipotoxicity and the pathogenesis of nonalcoholic steatohepatitis: the central role of nontriacylglyceride fatty acid metabolites. Hepatology 2010; 52:774–88.
55 Carter-Kent C, Zein NN, Feldstein AE. Cytokines in the pathogenesis of fatty liver disease and disease progression to steatohepatitis: implications for treatment. Am J Gastroenterol 2008; 103:1036–42.
56 Miele L, Beale G, Patman G et al. The Kruppel-like factor 6 genotype is associated with fibrosis in nonalcoholic fatty liver disease. Gastroenterology 2008; 135:282–91.e1.
57 Dvunjak M, Barsić N, Tomasić V et al. Genetic polymorphisms in non-alcoholic fatty liver disease: clues to pathogenesis and disease progression. World J Gastroenterol 2009; 15:6023–7.
58 Dowman JK, Tomlinson JW, Newsome PN. Pathogenesis of non-alcoholic fatty liver disease. QJM 2010; 103:71–83.
59 Wang CW, Lin HY, Shin SJ et al. The PNPLA3 I148M polymorphism is associated with insulin resistance and nonalcoholic fatty liver disease in a normoglycaemic population. Liver Int 2011; 31:3126–31.
60 Dongiovanni P, Donati B, Fares R et al. PNPLA3 I148M polymorphism and progressive liver disease. World J Gastroenterol 2013; 19:6969–78.
61 Chen Y, Rui BB, Tang LY et al. Lipin family proteins—key regulators in lipid metabolism. Ann Nutr Metab 2015; 66:10–8.
62 Hussain MM, Rava P, Walsh M et al. Multiple functions of microsomal triglyceride transfer protein. Nutr Metab 2012; 9:14.
63 Eliaides M, Spyrou E. Vitamin D: a new player in non-alcoholic fatty liver disease? World J Gastroenterol 2015; 21:1718–27.
64 Barrea L, Savanelli MC, Di Somma C et al. Vitamin D and its role in psoriasis: An overview of the dermatologist and nutritionist. Rev Endocr Metab Disord 2017; 18:195–205.
65 Caltone EK, Keane KN, Newsholme P et al. The impact of vitamin D levels on inflammatory status: a systematic review of immune cell studies. PLoS ONE 2015; 10:e0141770.
66 Romeo S, Kozilita J, Xing C et al. Genetic variation in PNPLA3 confers susceptibility to nonalcoholic fatty liver disease. Nat Genet 2008; 40:1461–5.
67 Singal AG, Manjunath H, Yopp AC et al. The effect of PNPLA3 on fibrosis progression and development of hepatocellular carcinoma: a meta-analysis. Am J Gastroenterol 2014; 109:325–34.
68 Liu YL, Reeves HL, Burt AD et al. TM6SF2 rs58542926 influences hepatic fibrosis progression in patients with non-alcoholic fatty liver disease. Nutr Commun 2014; 5:4309.
69 Kozilita J, Smagris E, Stender S et al. Exome-wide association study identifies a TM6SF2 variant that confers susceptibility to nonalcoholic fatty liver disease. Nat Gentr 2014; 46:352–6.
70 Fracanzani AL, Valentí L, Bugianesi E et al. Risk of severe liver disease in nonalcoholic fatty liver disease with normal aminotransferase levels: a role for insulin resistance and diabetes. Hepatology 2008; 48:792–8.
71 Younossi ZM, Stepanova M, Negro F et al. Nonalcoholic fatty liver disease in lean individuals in the United States. Medicine (Baltimore) 2012; 91:319–27.
Nonalcoholic fatty liver disease in psoriasis, R.B. Prussick and L. Miele 29

72 Downman JK, Tomlinson JW, Newsome PN. Systematic review: the diagnosis and staging of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. Aliment Pharmacol Ther 2011; 33:525–40.

73 Wenk KS, Arrington KC, Ehrlich A. Psoriasis and non-alcoholic fatty liver disease. J Eur Acad Dermatol Venereol 2011; 25:383–91.

74 Llamas-Velasco M, Concha-Garzón MJ, García-Diez A et al. Liver injury in psoriasis patients receiving ustekinumab: a retrospective study of 44 patients treated in the clinical practice setting. Actas Dermosifiligr 2015; 106:470–6.

75 Bessone F. Non-steroidal anti-inflammatory drugs: What is the actual risk of liver damage? World J Gastroenterol 2010; 16:5651–61.

76 European Association for the Study of the Liver (EASL). European Association for the Study of Diabetes (EASD), European Association for the Study of Obesity (EASO). EASL-EASD-EASO Clinical Practice Guidelines for the management of non-alcoholic fatty liver disease. J Hepatol 2016; 64:1388–402.

77 Campanati A, Ganzetti G, Di Sario A et al. The effect of etanercept on hepatic fibrosis risk in patients with non-alcoholic fatty liver disease, metabolic syndrome, and psoriasis. J Gastroenterol 2013; 48:839–46.

78 Vilar-Gomez E, Martinez-Perez Y, Calzadilla-Bertot L et al. Weight loss through lifestyle modification significantly reduces features of nonalcoholic steatohepatitis. Gastroenterology 2015; 149:367–78; quiz e14–5.

79 Chambers ES, Hawrylowicz CM. The impact of vitamin D on regulatory T cells. Curr Allergy Asthma Rep 2011; 11:29–36.

80 Sharifi N, Amani R, Hajjani E et al. Does vitamin D improve liver enzymes, oxidative stress, and inflammatory biomarkers in adults with non-alcoholic fatty liver disease? A randomized clinical trial. Endocrine 2014; 47:70–80.

81 Pacana T, Sanyal AJ. Vitamin E and nonalcoholic fatty liver disease. Curr Opin Clin Nutr Metab Care 2012; 15:641–8.

82 Sanyal AJ, Chalasani N, Kowdley KV et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med 2010; 362:1675–85.

83 Scerletti E, Byrne CD. Omega-3 fatty acids, hepatic lipid metabolism, and nonalcoholic fatty liver disease. Annu Rev Nutr 2013; 33:231–48.

84 Lu W, Li S, Li J et al. Effects of omega-3 fatty acid in nonalcoholic fatty liver disease: a meta-analysis. Gastroenterol Res Pract 2016; 2016:1459790.

85 Harrison SA, Day CP. Benefits of lifestyle modification in NAFLD. Gut 2007; 56:1760–9.

86 Gutiérrez-Grobe Y, Chávez-Tapia N, Sánchez-Valle V et al. High coffee intake is associated with lower grade nonalcoholic fatty liver disease: the role of peripheral antioxidant activity. Ann Hepatol 2012; 11:350–5.

87 Chitapanarux T, Tienboon P, Pojchamarnwiputh S et al. Open-labeled pilot study of cysteine-rich whey protein isolate supplementation for nonalcoholic steatohepatitis patients. J Gastroenterol Hepatol 2009; 24:1045–50.

88 Shen H, Rodriguez AC, Shiani A et al. Association between caffeine consumption and nonalcoholic fatty liver disease: a systemic review and meta-analysis. Therap Adv Gastroenterol 2016; 9:113–20.

89 Setola E, Monti LD, Galluccio E et al. Insulin resistance and endothelial function are improved after folate and vitamin B12 therapy in patients with metabolic syndrome: relationship between homocysteine levels and hyperinsulinemia. Eur J Endocrinol 2004; 151:483–9.

90 Characharoensinwitaya P, Levy C, Angulo P et al. Open-label pilot study of folic acid in patients with nonalcoholic steatohepatitis. Liver Int 2007; 27:220–6.

91 St George A, Bauman A, Johnston A et al. Independent effects of physical activity in patients with non-alcoholic fatty liver disease. Hepatology 2009; 50:68–76.

92 Taylor WJ, Korendowycz E, Nash P et al. Drug use and toxicity in psoriatic disease: focus on methotrexate. J Rhumatol 2008; 35:1454–7.

93 Maybury CM, Jabbar-Lopez ZK, Wong T et al. Methotrexate and liver fibrosis in people with psoriasis: a systematic review of observational studies. Br J Dermatol 2014; 171:17–29.

94 Ballantyne CM, Podet EJ, Patsch WP et al. Effects of cyclosporine therapy on plasma lipoprotein levels. JAMA 1989; 262:53–6.

95 Soratane [prescribing information]. Research Triangle Park, NC: Stiefel Laboratories, Inc., 2015.

96 Mantovanini A, Gisondi P, Lonardo A et al. Relationship between non-alcoholic fatty liver disease and psoriasis: a novel hepato-dermal axis? Int J Mol Sci 2016; 17:217.

97 Ng LC, Lee YY, Lee CK et al. A retrospective review of methotrexate-induced hepatotoxicity among patients with psoriasis in a tertiary dermatology center in Malaysia. Int J Dermatol 2013; 52:102–5.

98 Nas A, Gisondi P, Ormerod AD et al. European S3–Guidelines on the systemic treatment of psoriasis vulgaris—Update 2015—Short version—EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol 2015; 29:2277–94.

99 Langley RG, Elewski BE, Lebwohl M et al. Secukinumab in plaque psoriasis—results of two phase 3 trials. N Engl J Med 2014; 371:326–38.

100 Griffiths CE, Reich K, Lebwohl M et al. Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. Lancet 2015; 386:541–51.

101 van de Kerkhof PC, Griffiths CE, Reich K et al. Secukinumab long-term safety experience: A pooled analysis of 10 phase II and III clinical studies in patients with moderate to severe plaque psoriasis. J Am Acad Dermatol 2016; 75:83–986e.

102 Prussick R, Prussick L, Nussbaum D. Nonalcoholic fatty liver disease and psoriasis: what a dermatologist needs to know. J Clin Aesthet Dermatol 2015; 8:43–5.

103 Moro F, De Simone C, Morciano A et al. Psoriatic patients have an increased risk of polycystic ovary syndrome: results of a cross-sectional analysis. Fertil Steril 2013; 99:936–42.

104 Hashimoto E, Tanai M, Tokushige K. Characteristics and diagnosis of NAFLD/NASH. J Gastroenterol Hepatol 2013; 28(Suppl. 4):64–70.

105 Neuschwandt-Tetri BA, Caldwell SH. Nonalcoholic steatohepatitis: summary of an AASLD Single Topic Conference. Hepatology 2003; 37:1202–19.

106 Takahashi Y, Fukusato T. Histopathology of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis. World J Gastroenterol 2014; 20:15539–48.

107 Kleiner DE, Brunst EM, Van Natta M et al. Design and validation of a histological scoring system for nonalcoholic fatty liver disease. Hepatology 2005; 41:1313–21.

108 Narayanasamy K, Sanmarkan AD, Rajendran K et al. Relationship between psoriasis and non-alcoholic fatty liver disease. Praz Gastroenterol 2016; 11:263–9.

Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher’s website:
Powerpoint S1. Journal Club Slide Set.