Nonalcoholic Fatty Liver Disease and Psoriasis

What a Dermatologist Needs to Know

[a,b]RONALD PRUSSICK, MD; [a,c]LISA PRUSSICK, BSc, MS; [a]DILLON NUSSBAUM

[a]Washington Dermatology Center, Rockville, Maryland; [b]Department of Dermatology, George Washington University, Washington, DC; [c]Tufts University School of Medicine, Boston, Massachusetts

ABSTRACT

Psoriasis is a systemic inflammatory disease associated with a variety of comorbidities. It has been shown that psoriasis patients have an increased incidence of nonalcoholic fatty liver disease over controls. Patients with nonalcoholic fatty liver disease and psoriasis have more severe skin disease and are at higher risk of severe liver fibrosis than patients without psoriasis. The authors will review the diagnosis of nonalcoholic fatty liver disease and also discuss lifestyle changes and treatments for psoriasis that may benefit or worsen nonalcoholic fatty liver disease.
(*J Clin Aesthet Dermatol.* 2015;8(3):43–45.)

Fatty liver disease refers to a condition in which fat accumulates within hepatocytes. Nonalcoholic fatty liver disease (NAFLD) is diagnosed after other causes are eliminated, such as alcoholic fatty liver, autoimmune hepatitis, hepatitis C, primary biliary cirrhosis, and Wilson's disease.

NAFLD is a metabolic disorder that represents a disease spectrum. It ranges from steatosis (isolated fatty liver) without specific liver injury to nonalcoholic steatohepatitis (NASH) in which there is inflammation leading to scarring, fibrosis, and possibly cirrhosis.[1]

NAFLD is a manifestation of abnormal metabolism within the liver resulting in the accumulation of triglycerides within the hepatocytes. Risk factors include male gender, age, obesity, insulin resistance, and metabolic syndrome.[2] Proinflammatory adipokines or skin-derived cytokines may lead to insulin resistance and hepatic lipid accumulation.

It is not known why some patients develop more serious disease than others. Lifestyle risks that can influence severity include sedentary lifestyle, smoking, and diet. It is also thought that genetic predisposition plays a role. A mutation in the PNPLA3 (phospholipase domain containing protein 3) gene has been shown to confer risk.[3] Other factors resulting in more severe disease include excess proinflammatory cytokines/adipokines, mitochondrial dysfunction, and oxidative stress.[1] Certainly patients with autoimmune diseases, such as psoriasis, may be prone to more severe inflammation and therefore scarring of the liver. Thus, in NASH, some patients may develop cirrhosis and even more infrequently hepatocellular carcinoma. It has been estimated that NAFLD will be the leading cause of liver transplantation worldwide by 2020.[4]

EPIDEMIOLOGY OF NAFLD

It is important for healthcare providers to know that about 30 percent of the US population has fatty liver, making it the most prevalent liver disease, and approximately 3 to 10 percent of these have NASH. More than two-thirds of people with diabetes develop NAFLD. The risk of developing NASH is more than 33 percent in obese people but less that five percent in lean people. Fatty liver increases both in prevalence and severity as the degree of obesity increases. NAFLD is a risk factor for cardiovascular disease independent of metabolic syndrome. In these patients, death from major adverse cardiovascular events (MACE) is more common than liver-related deaths.[5] In the United States, the current obesity epidemic also includes children, and it is estimated that approximately 10 percent of children between 2 and 19 years of age have NAFLD. As with adults, the prevalence also increases with obesity, rising to 40 to 70 percent, and cases of cirrhosis in children have been reported.[2]

DIAGNOSIS OF NAFLD

Patients are usually asymptomatic unless the disease is

DISCLOSURE: Dr. Prussick is on the medical board of the National Psoriasis Foundation. He is a speaker for AbbVie, Celgene, Janssen, Leo, and Medicis/Galderma. He is also a consultant for Medimetriks. Ms. Prussick and Mr. Nussbaum report no relevant conflicts of interest.
ADDRESS CORRESPONDENCE TO: Ronald Prussick, MD; E-mail: drprussick@aol.com

advanced. Rarely, the liver is enlarged enough to cause tenderness upon palpation. When advanced, the symptoms of cirrhosis of the liver may appear. NAFLD is often diagnosed after finding mildly elevated liver function tests (LFTs), although up to two-thirds of patients can have normal LFTs. Alanine aminotransferase (ALT) is usually greater than aspartate aminotransferase (AST), but rarely greater than three times upper limit normal. Alkaline phosphatase may be slightly elevated and gamma-glutamyltransferase (GGT) is frequently elevated. Low albumin and hyperbilirubinemia indicate advanced disease. The Fatty Liver Index (FLI) was developed as a simple algorithm to predict fatty liver using the following four variables: waist circumference, body mass index (BMI), GGT, and serum triglyceride levels.[1] The most common way to diagnose NAFLD is via ultrasound, computerized tomography (CT), or magnetic resonance imaging (MRI).

The only way to distinguish whether a patient has fatty liver disease or the more severe NASH is by liver biopsy. High-risk patients for NASH that may be candidates for liver biopsy are those with metabolic syndrome, obesity (BMI>30), and diabetes.[1]

NAFLD IN PSORIASIS

Multiple hospital-based observational studies suggest patients with psoriasis are 1.5-fold to threefold more likely to have NAFLD.[3] In an Italian prospective study, 59 percent of psoriatic patients were diagnosed with NAFLD. It was significantly correlated with metabolic syndrome, obesity, and psoriatic arthritis. The psoriatic patients were more likely to have more severe liver fibrosis over the non-psoriatic cohort as measured by noninvasive NAFLD fibrosis scores.[6]

Another Italian study included 130 psoriatic patients versus matched controls. NAFLD was significantly greater in psoriasis (47%) versus controls (28%). Psoriasis patients with NAFLD (PV-NAFLD) were more likely to have metabolic syndrome, higher C-reactive protein, and greater psoriasis area and severity index (PASI) scores than psoriasis patients without NAFLD. A subgroup of this PV-NAFLD group had elevated interleukin-6 (IL-6) and lower adiponectin levels.[7]

An Indian case-control study included 333 patients with psoriasis versus matched non-psoriasis patients. NAFLD was found in 17.4 percent of psoriasis versus 7.9 percent of controls. Psoriatic patients with NAFLD had more severe and longer duration of skin disease than psoriasis patients without NAFLD. Also, they were more likely to have multiple sclerosis and diabetes. Psoriatic patients had more severe liver disease than the non-psoriatic population.[8]

Both psoriasis and NAFLD are associated with metabolic conditions, such as metabolic syndrome and obesity. Thus it has been unclear whether psoriasis itself is independently associated with NAFLD. This issue was examined in the Rotterdam study, a prospective population-based cohort study, which included patients 55 years and older in the Netherlands. Psoriasis was independently associated with a 70 percent increased likelihood of NAFLD. Two strong predictors of disease were psoriasis, with odds ratio of 1.7 and metabolic syndrome with an odds ratio of 3.5. Psoriasis patients were 60 percent more likely to have the more severe forms of the liver disease. This was after adjusting for variables, such as alcohol intake, age, and gender.[3]

TREATMENT OPTIONS FOR NAFLD

Weight loss of 10 percent can decrease liver fat. Vigorous exercise can also achieve not only a decrease in liver fat, but a reduction of inflammation in NASH. The long-term prevention of cirrhosis in these patients with diet or exercise is unknown.

Studies have shown diets high in saturated fats or high fructose corn syrup can both lead to NAFLD. Thus, a diet minimizing these would likely be beneficial.[9] It has been shown that progression to liver fibrosis is correlated with the degree of insulin resistance.[10]

Those who drink more than two cups of coffee per day have less scarring or fibrosis of their liver. Adding coffee to the diet is therefore recommended.[11] Vitamin D deficiency can result in increased inflammation via a decrease in the function of T suppressor cells and should be corrected.[12] Finally, minimizing alcohol is mandatory in psoriasis patients with NAFLD.

Vitamin E supplementation, at dosages usually 800IU/day, can be used to reduce inflammation and fibrosis in NASH patients, but the long-term safety and effectiveness is unknown.[5]

Small studies have shown omega-3 fatty acids have reduced liver fat in NAFLD, and larger studies are underway.[13] This supplement has also been shown to reduce cardiovascular mortality in high-risk patients for MACE events.

BIOLOGICS AND TREATMENT OF NAFLD

In a study comparing etanercept with psoralen and ultraviolet A (PUVA), 89 patients with psoriasis, metabolic syndrome, and NAFLD were treated in either group for up to 24 weeks. Only the etanercept group showed reductions in enzymes aspartate transaminase and alanine transaminase (AST/ALT) ratio, C-reactive protein, fasting insulin levels, homeostasis model assessment index (HOMA), and a significant decrease in insulin sensitivity check index (QUICK). It was concluded that since the risk of progression to fibrosis is directly related to insulin resistance, etanercept could be more efficacious to reduce the risk of developing hepatic fibrosis than PUVA.[10]

A retrospective study evaluated 32 psoriasis patients with moderate-to-severe liver disease treated with biologics. Of the 32 patients, three had fatty liver disease. During a five-year follow up on adalimumab, there was no progression of liver disease or liver-related adverse events.[14]

BIOLOGICS IMPROVE NAFLD IN OTHER AUTOIMMUNE DISEASES

A case report described the use of adalimumab in a 21-year-old woman with rheumatoid arthritis with NASH, but

no significant fibrosis. After four months, there was a decline and then normalization in gamma-glutamyl transferase (GGT) levels. After 10 months, ALT, AST, and GGT levels remained normal.[15]

PSORIASIS TREATMENTS TO AVOID IN NAFLD

Methotrexate should be avoided in patients with renal, hepatic, or hematologic abnormalities.[16] Patients with psoriasis are more likely to experience methotrexate-induced liver damage compared with controls and patients with rheumatoid arthritis.[17]

The kidney is the main organ of concern with cyclosporine although it can increase lipid levels and thus potentially worsen NAFLD.[16] Acitretin has been associated with elevated LFTs, although progression to liver disease is very rare. It frequently causes hyperlipidemia, which should be avoided in NAFLD patients.[16]

CONCLUSION

Understanding whether a patient with psoriasis has an underlying fatty liver disease is important for two reasons. The first is that fatty liver is a clue to the predisposition toward underlying diseases, such as cardiovascular disease, metabolic syndrome, diabetes, and obesity. Other associations are fatty pancreas, hypothyroidism, polyps of the colon, elevated uric acid, vitamin D deficiency, and polycystic ovaries. About 50 percent of those with NAFLD have obstructive sleep apnea.[18] The second reason is that NASH patients are at increased risk for developing cirrhosis and hepatocellular carcinoma. This information is vital in deciding which psoriasis treatment options would be best to limit hepatic toxicity.

Giving advice on lifestyle changes, such as weight loss, exercise, avoiding alcohol, smoking, and minimizing saturated fats and high fructose corn syrup can benefit patients. Supplementation with oral vitamin D3, vitamin E, and omega-3 has also shown to be helpful in some patients. A few case reports reveal that TNF-alpha antagonists may benefit psoriatic patients with NAFLD, although large controlled studies are needed.

REFERENCES

1. Dowman JK, Tomlinson JW, Newsome PN. Systematic review: the diagnosis and staging of non-alcoholic fatty liver disease and non-alcoholic steatohepatitis. *Ailment Pharmacol Ther.* 2011;33(5):525–540.
2. Bellentani S, Scaglioni F, Marino M, Bedogni G. Epidemiology of non-alcoholic fatty liver disease. *Dig Dis.* 2010;28:155–161.
3. Van der Voort EAM, 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 Amer Acad Dermatol.* 2014;70: 517–524.
4. Musso G, Gambino R, Cassader M, et al. Meta-analysis: natural history of non-alcoholic fatty liver disease (NAFLD) and diagnostic accuracy of non-invasive tests for liver disease severity. *Ann Med.* 2011;43:617–649.
5. Smith BW, Adams LA. Non-alcoholic fatty liver disease. *Crit Rev Clin Lab Sci.* 2011;48(3):97–113.
6. 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;51:778–786.
7. Gisondi P, Targher G, Zoppini G, Girolomoni G. Non-alcoholic fatty liver disease in patients with chronic plaque psoriasis. *J Hepatol.* 2009;51:758–764.
8. 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(3):190–197.
9. Harrison SA, Day CP. Benefits of lifestyle modification in NAFLD. *Gut.* 2007;56:1760–1769.
10. Campanati A, Ganzetti G, DiSario 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(7):839–846.
11. Gutierrez-Grobe Y, Chavez-Tapia N, Sanchez-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;11:350–355.
12. Eliades M, Spyrou E, Agrawal N, et al. Meta-analysis: vitamin D and non-alcoholic fatty liver disease. *Aliment Pharmacol Ther.* 2013;38:246–254.
13. Scorletti E, Byrne CD. Omega-3 fatty acids, hepatic lipid metabolism, and nonalcoholic fatty liver disease. *Annu Rev Nutr.* 2013;33:231–248.
14. Vilarrasa E, Puig L, Alomar A. Biologic treatments for psoriasis in patients with hepatitis C virus infection and other liver diseases: experience in 29 patients. *JEADV.* 2010;24:P013.
15. Schramm C, Schneider A, Marx A, et al. Adalimumab could suppress the activity of non alcoholic steatohepatitis (NASH). *Z Gastroenterol.* 2008;46:1369–1371.
16. Bhutani T, Hong J, Koo J. *Contemporary Diagnosis and Management of Psoriasis*, 5th ed. Newtown, PA: Handbooks in Healthcare; 2011:50–59.
17. Taylor WJ, Korendowych E, Nash P, et al. Drug use and toxicity in psoriatic disease: focus on methotrexate. *J Rheumatol.* 2008;35:1454–1457.
18. Mirrakhimov AE, Polotsky VY. Obstructive sleep apnea and nonalcoholic fatty liver disease. *Front Neurol.* 2012;3:149–190.