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OPINION ARTICLE

Nonalcoholic Fatty Liver Disease and Psoriasis

Hígado graso no alcohólico y psoriasis

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Psoriasis is an inflammatory immune-mediated disease that mainly affects the skin and is often associated with obesity, type 2 diabetes, dyslipidemia, and insulin resistance, all of which are components of the so-called metabolic syndrome.[1,2]

Nonalcoholic fatty liver disease is an anatomical-clinical spectrum that encompasses the mildest form of simple steatosis, nonalcoholic steatohepatitis, and fatty cirrhosis, the most severe form. It is considered as the manifestation of metabolic syndrome in the liver, is the most common cause of elevated transaminase levels, and the most prevalent form of liver disease in developed countries, affecting around a third of the population overall.[3,4] Although we have known of this entity for over 25 years, little importance has been placed on its relation to patient health. Only recently has the significance of nonalcoholic fatty liver been recognized and studied: while individuals with simple steatosis have a life expectancy similar to that of the general population and a low risk of developing terminal liver disease, those with steatohepatitis have a 37% risk of progressing to fibrosis in 3.2 years, in the presence of a high body mass index (BMI) and diabetes.[5] Moreover, mortality attributable to both liver and cardiovascular causes is also higher in patients with nonalcoholic steatohepatitis.[6] Although liver biopsy is the gold standard for diagnosis, other noninvasive methods include ultrasound of the liver and FibroScan (Echosens SA, Paris, France). For a diagnosis of nonalcoholic fatty liver disease significant use of ethanol (>20 g/d), hepatotoxic drugs in the last 5 years, autoimmune liver disease, and hepatitis B or C virus infection must first be ruled out. Nonalcoholic fatty liver disease is treated by reducing the BMI and recovering insulin sensitivity because there is no approved drug for treatment as yet. It is therefore very important that dermatologists become directly involved in ensuring that patients with psoriasis and obesity reach an appropriate BMI.

Given that psoriasis is often associated with metabolic syndrome and nonalcoholic fatty liver disease is yet another manifestation of that syndrome, it is unsurprising that fatty liver disease is more common in patients with psoriasis. References to nonalcoholic fatty liver disease in the context of psoriasis were few[7] before 2009 and no epidemiologic studies had ever been done until 2 Italian papers were published that year.[8,9]

In Verona, Girolomoni et al[8] compared 130 patients with plaque psoriasis with 260 controls matched for age, sex, BMI, and alcohol consumption. They found nonalcoholic fatty liver disease to be more common in patients with psoriasis than in controls (47% vs 28% $P<.0001$). Analysis of the subgroup of patients with both psoriasis and nonalcoholic fatty liver disease (n=61) revealed a higher frequency of metabolic syndrome, higher serum levels of C-reactive protein, and greater severity of psoriasis according to the Psoriasis Area and Severity Index (PASI) than in patients with psoriasis alone. A multivariate regression analysis showed that nonalcoholic fatty liver disease in patients with psoriasis was associated with a

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higher PASI score irrespective of age, sex, BMI, duration of psoriasis, and alcohol consumption.

Miele and coworkers[9] in Rome prospectively examined the prevalence and characteristics of nonalcoholic fatty liver disease in 142 patients with psoriasis vulgaris, two thirds of whom had PASI scores over 20. The second stage of the study retrospectively compared the subgroup of patients with psoriasis and nonalcoholic fatty liver disease (n=84) with a control group of patients diagnosed with nonalcoholic fatty liver disease but without psoriasis (n=125). These authors found nonalcoholic fatty liver disease in 59.2% of the patients with psoriasis and they linked nonalcoholic fatty liver disease in patients with psoriasis with metabolic syndrome, obesity, hypercholesterolemia, hypertriglyceridemia, and a ratio of aspartate aminotransferase to alanine aminotransferase level higher than 1, and psoriatic arthritis. Logistic regression analysis found psoriatic arthritis to be an independent predictor of nonalcoholic fatty liver disease in patients with psoriasis (odds ratio [OR], 3.94; confidence interval, 1.07-14.446; *P*=<.005). The authors found that patients with both nonalcoholic fatty liver disease and psoriasis had a higher risk of liver fibrosis than those without psoriasis alone.

Once again, these studies show that psoriasis is not merely a skin problem. Every day we discover new comorbidities and gather more information to help us manage patients' conditions more safely and effectively. New studies that reveal a greater prevalence of nonalcoholic fatty liver disease in patients with psoriasis confirm the impression that dermatologists have had for some time, namely that these patients experience more complications when using hepatotoxic drugs such as methotrexate than patients with other pathologies such as rheumatoid arthritis. Our protocols for the use of methotrexate are different from those of other specialties, such as rheumatology, which are much less concerned about the liver than we are. Further research is required to confirm these results in other countries, such as Spain. To date, with the information we have, it is advisable to include liver ultrasound in the diagnostic work-up of patients with moderate-to-severe psoriasis because of the high frequency of fatty liver disease in this group of patients and the implications for prognosis and treatment.

It is also important to know whether new biologic therapies can alter the course of fatty liver disease. Many diseases found in association with psoriasis are believed to share pathogenic mechanisms with this skin disease. A degree of persistent inflammation, with secretion of proinflammatory cytokines such as tumor necrosis factor (TNF) α or interleukin (IL) 17/23, favors the development of insulin resistance and metabolic syndrome. Macrophages in adipose tissue can also release TNF α, the cytokine implicated in psoriasis and metabolic syndrome.[10] Higher levels of IL 17/23 have also been observed in obese women.[11] If we manage to inhibit TNF-α or IL 23 through new treatments and reduce the weight of obese patients, both their psoriasis and their associated conditions will improve. If TNF-α is implicated in metabolic syndrome and nonalcoholic fatty liver disease is an expression of this syndrome in the liver, then by blocking this cytokine we can also expect a patient's liver condition to improve. Furthermore, if IL 17 and IL 23 induce insulin resistance in human endothelial cells[12] and one of the first steps in the development of nonalcoholic fatty liver disease is insulin resistance, we could also improve this condition by inhibiting these cytokines, although this remains to be demonstrated.

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