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EDITORIAL

Nonalcoholic steatohepatitis and diabetes☆

Esteatohepatitis no alcohólica y diabetes

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Non-alcoholic fatty liver disease (NAFLD) or fatty liver disease is the most common current cause of liver disease, occurring in approximately 30% of the adult population.[1] Although it is often a benign disease, in an increasing number of cases it may progress to steatohepatitis with a greater or lesser degree of fibrosis, cirrhosis, and hepatocellular carcinoma. The number of patients with this condition who require a liver transplant is also increasing.[2] The prevalence of NAFLD is difficult to establish because most patients have no symptoms and its estimation depends on the diagnostic method, laboratory test changes, imaging tests, or liver biopsy, but rates ranging from 1.5% to 3% have been estimated. NAFLD is closely related to metabolic syndrome, and especially to obesity, insulin resistance, and type 2 diabetes mellitus (T2DM), so that 90% of obese subjects and 70% of patients with T2DM have a greater or lesser degree of liver steatosis. Some studies also show that up to 20% of patients with T2DM and normal liver function tests have histological lesions of steatohepatitis,[3] and 5–7% of these show significant fibrosis.[4] Because of the increased obesity and overweight and T2DM occurring in 30% and 8% of the population respectively, an increased prevalence of NAFLD can also be expected. There are several recent reviews of the relationship between non-alcoholic steatohepatitis and diabetes.[5–7]

Although the pathogenesis of NAFLD and its progression to steatohepatitis are not fully known, the condition shares a number of common mechanisms with T2DM, including changes in glucose and lipid metabolism, insulin resistance, and genetic and environmental factors.[8] In both conditions there is an increase in insulin resistance in the liver, muscle, and adipose tissue that results in the secretion of proinflammatory cytokines. Environmental factors such as diet, sedentary lifestyles, microbiota composition, and exposure to some chemical compounds are associated with obesity, T2DM, and NAFLD. A number of genes related to a greater risk of the development of steatohepatitis have been reported, some of which are also associated with the risk of developing T2DM.[9] These genes include adiponutrin and transcription factor 7-like 2, although the influence of genes related to glucose metabolism and insulin resistance, lipid metabolism, oxidative stress, inflammation, and fibrosis has been reported.[9]

Besides the greater risk of patients with T2DM experiencing NAFLD, there is evidence showing that NAFLD may be a risk factor for T2DM. In this regard, a study that compared subjects with NAFLD and control, both with no diabetes, showed a greater prevalence of T2DM and metabolic syndrome in subjects with NAFLD when they were re-evaluated after 11 years.[10] On the other hand, when diabetes occurs

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in subjects with insulin resistance and obesity, diabetes is an independent factor for the progression of NAFLD and the development of cirrhosis. Thus, when the association of T2DM and NAFLD is studied, not only should NAFLD prevalence be considered, but also the impact of diabetes on the progression to steatohepatitis. It may be stated, following the definition of Loria et al.,[11] that there is a vicious cycle between fatty liver and diabetes, with insulin resistance leading initially to fatty liver and T2DM in predisposed subjects, and diabetes in turn promoting its progression to fibrosis and the eventual development of cirrhosis and hepatocellular carcinoma. There is clear evidence showing that NAFLD is an independent risk factor for the development of cardiovascular diseases in patients with T2DM, and also with type 1 diabetes mellitus.[12] There are also some data showing that NAFLD may be a risk factor for the development of long-term complications of diabetes such as retinopathy and renal failure, but additional studies are needed on this subject.[13]

In all patients with T2DM, as in subjects with other risk factors, the presence of fatty liver should be ruled out, an attempt should be made to establish the grade of the disease, and patient referral to a specialist should be considered. Liver biopsy is still considered the best test for diagnosis, because it allows us to differentiate between simple steatosis and steatohepatitis and to establish the grade of the lesion and the severity of the fibrosis. Biopsy is, however, an invasive test which is not free of risks, is costly, and has a non-negligible chance of sampling errors. Because of this, a number of noninvasive methods, including both laboratory and imaging tests, have been developed in recent years.[14] Laboratory methods include various indices that combine liver function biochemical parameters with clinical data such as age, the body mass index, abdominal circumference, the presence of T2DM and/or other components of metabolic syndrome. The most widely available of the radiographic methods is ultrasonography, which makes it possible for the presence of fat to be detected and for a semiquantitative grading to be established, although not for the presence of fibrosis to be detected, unless it is quite advanced. Magnetic resonance imaging is a more precise technique, but is also more expensive. Liver elastography and acoustic radiation force impulse are procedures that allow for the quantification of fibrosis. In practice, according to the recommendations of an expert panel, all patients with T2DM, especially if they have other components of metabolic syndrome such as obesity, dyslipidemia, or hypertension, should be given liver function tests and abdominal ultrasonography. If patients have moderate increases in transaminases and/or ultrasonographic evidence of steatosis, they should be referred to a hepatologist, especially if changes persist after one month despite lifestyle changes and improved control of diabetes.[15]

If the pathogenesis of NAFLD and that of T2DM have many points in common, the same applies to their treatment. In both conditions, lifestyle changes including adequate diet and aerobic physical exercise facilitate weight decrease and improvements in fatty liver and diabetes control.[16] Lifestyle changes are, therefore, the first therapeutic measure. The problem is that only a small percentage of patients follow these recommendations, especially over a long period of time. In morbid obesity, weight loss after bariatric surgery causes significant improvements in steatosis and fibrosis, as well as in blood glucose levels.

There is currently no approved treatment for NAFLD. However, improved understanding of the pathophysiology of this disease has led to new treatments being proposed, among which special mention should be made of those that improve insulin resistance, antioxidants, and treatments with antifibrogenic action.[16,17] Among the antidiabetics, metformin has improved liver enzyme levels and fat contents of the liver in some studies, but without modifying histological lesions. PPAR-gamma agonists, especially pioglitazone, improve liver histology, but have a number of side effects such as weight increase, heart failure, and the risk of fracture, so should be used with caution. New antidiabetic drugs, including glucagon-like peptide 1 receptor agonists such as liraglutide and exenatide, and dipeptidyl-peptidase 4 inhibitors such as sitagliptin, appear more promising. The experimental results and clinical data suggest that these drugs decrease liver inflammation and steatosis.[18,19] However, large treatment studies are needed before these treatments can be recommended.

Current clinical guidelines do not recommend that the presence of NAFLD should be routinely ruled out in diabetic patients unless they have elevated transaminase levels or some other sign suggesting liver disease. This is due, at least partly, to the fact that noninvasive diagnostic methods are not well established and no effective treatment is available. Given that many patients with NAFLD are stable and do not progress to steatohepatitis, some authors also question the cost-benefit of routinely ruling out NAFLD. However, as previously discussed, NAFLD is highly prevalent in patients with T2DM, and both conditions mutually reinforce each other, so that patients with NAFLD, especially obese patients, are more prone to developing T2DM, and T2DM promotes the progression of lesions in fatty liver. On the other hand, both NAFLD and T2DM predispose to the development of cardiovascular complications. Therefore, it is desirable to promote the collaboration of endocrinologists and hepatologists in the control of patients with T2DM and fatty liver. Such collaboration has recently resulted in the publication of clinical guidelines for the control and treatment of NAFLD, jointly prepared by the European Association for the Study of the Liver (EASL), the European Association for the Study of Diabetes (EASD), and the European Association for the Study of Obesity (EASO).[20]

References

1. Caballeria L, Pera G, Auladell MA, Toran P, Muñoz L, Miranda D, et al. Prevalence and factors associated with the presence of nonalcoholic fatty liver disease in an adult population in Spain. Eur J Gastroenterol Hepatol. 2010;22:24–32.
2. Satapathy SK, Sanyal AJ. Epidemiology and natural history of nonalcoholic fatty liver disease. Sem Liver Dis. 2015;35:221–35.
3. Portillo-Sanchez P, Bril F, Maximos M, Lomonaco R, Biernacki D, Orsak B, et al. High prevalence of nonalcoholic fatty liver disease in patients with type 2 diabetes mellitus and normal plasma aminotransferase levels. J Clin Endocrinol Metab. 2015;100:2231–8.
4. Armstrong MJ, Hazlehurst JM, Parker R, Koushiappi E, Mann J, Khan S, et al. Severe asymptomatic non-alcoholic fatty

liver disease in routine diabetes care: a multidisciplinary team approach. QJM. 2014;107:33–41.
5. Pappachan JM, Antonio FA, Edavalath M, Mukherjee A. Non-alcoholic fatty liver disease: a diabetologist's perspective. Endocrine. 2014;45:344–53.
6. Bhatt HB, Smith RJ. Fatty liver disease in diabetes mellitus. Hepato Biliary Surg Nutr. 2015;4:101–8.
7. Hazlehurst JM, Woods C, Marjot T, Cobbold JF, Tomlinson JW. Non-alcoholic fatty liver disease and diabetes. Metabolism. 2016;65:1096–108, http://dx.doi.org/10.1016/j.metabol.2016.01.2016.001.
8. Saponaro C, Gaggini M, Gastaldelli A. Nonalcoholic fatty liver disease and type 2 diabetes: common pathophysiologic mechanisms. Curr Diab Rep. 2015;15:607.
9. Anstee QM, Day CP. The genetics of NAFLD. Nat Rev Gastroenterol Hepatol. 2013;10:645–55.
10. Adams LA, Waters OR, Knuiman MW, Elliot RR, Olynyk JK. NAFLD as a risk factor for the development of diabetes and the metabolic syndrome: an eleven-year follow-up study. Am J Gastroenterol. 2009;104:861–7.
11. Loria P, Lonardo A, Anania F. Liver and diabetes a vicious circle. Hepatol Res. 2013;43:51–64.
12. Targher G, Bertolini L, Rodella S, Tessari R, Zenari L, Lippi G, et al. Nonalcoholic fatty liver disease is independently associated with an increased incidence of cardiovascular events in type 2 diabetic patients. Diabetes Care. 2007;30:2119–21.
13. Targher G, Bertolini L, Chonchol M, Rodella S, Zoppini G, Lippi G, et al. Nonalcoholic fatty liver disease is independently associated with an increased prevalence of chronic kidney disease and retinopathy in type 1 diabetic patients. Diabetologia. 2010;53:1341–8.
14. Chalasani N, Younossi Z, Lavine JE, Diehk AM, Brunt EM, Cusi K, et al. The diagnosis and management of non-alcoholic fatty liver disease: practical guide-line by the American Association for the Study of Liver Diseases, American College of Gastroenterology and the American Gastroenterological Association. Hepatology. 2012;55:2005–23.
15. Caballeria L, Saló J, Berzigotti A, Planas R, Vila C, Huertas C, et al. Hígado graso no alcohólico. Documento de posicionamiento de la Sociedad Catalana de Digestología. Gastroenterol Hepatol. 2014;37:372–83.
16. Rinella ME, Sanyal AJ. Management of NAFLD: a stage-based approach. Nat Rev Gastroenterol Hepatol. 2016;13:196–205.
17. Gawrieh S, Chalasani N. Pharmacotherapy for nonalcoholic fatty liver disease. Sem Liver Dis. 2015;35:338–48.
18. Amstrong MJ, Houlihan DD, Rowe IA, Clausen VH, Elbrond B, Gough SC, et al. Safety and efficacy of liraglutide in patients with type 2 diabetes and elevated liver enzymes: individual patient data meta-analysis of the LEAD program. Aliment Pharmacol Ther. 2013;37:234–42.
19. Arase Y, Kawamura Y, Seko Y, Kobayashi M, Suzuki F, Suzuki Y, et al. Efficacy and safety of sitagliptin therapy for diabetes complicated with non-alcoholic fatty liver disease. Hepatol Res. 2013;43:1163–8.
20. EASL-EASD-EASO. Clinical practice guidelines for the management of non-alcoholic fatty liver disease. Diabetologia. 2016;59:1121–40.