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Review

Non-alcoholic fatty liver disease: A poorly known pandemic☆

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ABSTRACT

Non-alcoholic fatty liver disease (NAFLD) consists of an excessive depositing of fat in the liver, which can end up by causing inflammation, fibrosis and also cirrhosis with the corresponding complications including liver cancer. NAFLD has become the most common liver disease worldwide. The incidence has increased in parallel with the obesity, diabetes and metabolic syndrome epidemic, thus resulting in becoming one of the main indications for liver transplant. The diagnosis has principally been through histology but with the development of non-invasive methods, these have helped in simplifying the management of these patients in clinical practice. The only therapeutic strategies currently available are focused on weight loss (lifestyle changes or bariatric surgery). There is still no approved pharmacological option for the treatment of NAFLD, however there are a number of molecular studies in advanced stages of development.

Hígado graso no alcohólico: una pandemia poco conocida

Palabras clave:
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Esteatohepatitis
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RESUMEN

El hígado graso no alcohólico (HGNA, *Nonalcoholic Fatty Liver Disease* [NAFLD]) consiste en el depósito excesivo de grasa en el hígado que puede acabar generando inflamación, fibrosis e incluso cirrosis y sus complicaciones, incluido el carcinoma hepatocelular. El HGNA se ha convertido en la enfermedad hepática crónica más prevalente del mundo. Su incidencia ha ido aumentando en paralelo con la epidemia de obesidad, diabetes y síndrome metabólico, siendo además una de las principales causas de indicación de trasplante hepático. Su diagnóstico ha sido clásicamente histológico, pero el desarrollo de métodos no invasivos está ayudando a simplificar el manejo de estos pacientes en la práctica clínica. Las únicas estrategias terapéuticas disponibles son las enfocadas en la pérdida de peso (cambios de estilo de vida y/o cirugía bariátrica). Todavía no hay fármacos aprobados para el tratamiento del HGNA, pero existen numerosas moléculas en fases avanzadas de desarrollo.

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Introduction

The term non-alcoholic fatty liver disease (NAFLD) encompasses a broad spectrum of lesions associated with liver fat deposition of metabolic origin. The most benign and prevalent form of NAFLD is called simple steatosis, defined by the presence of fat in the liver, without fibrosis and with mild or non-existent inflammation. The histological definition of simple steatosis requires that at least 5% of hepatocytes per field have cytoplasmic lipid deposits.[1]

In a variable percentage of patients (15–25% according to the series)[1–6] the presence of steatosis may be associated with the development of inflammation, predominantly lobular, and signs of hepatocellular degeneration, among which hepatocyte ballooning stands out. The concurrence of steatosis, hepatocyte ballooning and lobular inflammation in the biopsy define non-alcoholic steatohepatitis (NASH).[1–3] NASH is considered the progressive form of NAFLD. The spectrum of NASH ranges from initial non-fibrotic forms with inflammation and ballooning to cirrhosis. The cirrhotic forms of NASH are in most cases difficult to distinguish from other aetiologies. In this sense, given the high prevalence of NAFLD and the fact that histological signs of NASH tend to disappear as fibrosis progresses, cryptogenic cirrhosis in patients with NAFLD risk factors tends to be attributed to this entity.

The current definitions of NAFLD and NASH require ruling out the presence of several intercurrent conditions.[2,3] On the one hand, non-metabolic steatosis, also called "secondary" steatosis, among which alcohol and various drugs stand out (Table 1) must also be ruled out. On the other hand, the presence of other causes of liver disease (alcohol, viruses or cholestatic forms, among others) should be ruled out.

Etiopathogenesis and natural history

The diagnosis of NAFLD is much more likely in the presence of certain pathophysiological conditions. The presence of obesity, diabetes and other comorbidities that make up the metabolic syndrome significantly increase the risk of NAFLD and NASH.[1–3,5–8] However, the exact mechanisms that determine fat deposition in the hepatocyte, and especially those that determine the onset of inflammation and fibrosis and the progression of the disease, are not yet accurately known. There is now widespread consensus on the fact that liver and peripheral resistance to insulin is a determining factor in the development of NAFLD.[7,9] Such insulin resistance would determine a greater flow of lipids through the hepatocyte, which could not oxidize an excess of free fatty acids. The resulting metabolic stress would eventually trigger apoptosis and hepatocellular degeneration phenomena that would activate mechanisms of repair through inflammation and fibrogenesis in the liver. Such intrahepatic phenomena appear to be closely regulated also from other organs and tissues. Changes in adipose tissue would determine a quantitative and qualitative alteration of lipid secretion towards the hepatocyte as well as endocrine signals (adipokines) that would induce metabolic and inflammatory changes in the liver, what is known as "lipotoxicity".[7] The role of intestinal microbiota is increasingly evident as a modulator of the onset and progression of NASH.[10] Individual genetic and epigenetic susceptibility factors have an impact in the presentation and progression of the disease.[11] Among the genetic susceptibility factors, the polymorphisms of the PNPLA3 and TM6SF2 genes should be highlighted.

The complex pathophysiology of NASH determines that the natural history of the disease is highly variable, as shown by recent studies based on the analysis of paired biopsies.[12,13] Steatosis is the initial and necessary step for the development of NAFLD. Most patients with steatosis at the time of diagnosis will not develop inflammation or fibrosis. It is estimated that 20–30% of patients with NAFLD will progress to NASH with different degrees of fibrosis, and that 10–20% of these will eventually develop cirrhosis. In general, the risk of progression from one stage of fibrosis to the next is estimated to be 7 years. However, paired biopsy studies also show that there are 10–20% of patients who may experience a progression of 2–3 degrees of fibrosis in less than 6 years.[12] The identification of risk factors for rapid progression represents a major challenge that can help guide the screening, diagnosis and follow-up efforts in patients with NAFLD. Finally, these longitudinal cohort studies also show that fibrosis, rather than signs of activity such as inflammation and ballooning, is the main prognostic factor for progression to cirrhosis and mortality in both hepatic and extrahepatic causes.[2,14]

Table 1
Most frequent causes of 'secondary' liver steatosis (non-NAFLD).

Macrovesicular steatosis
Excessive consumption of alcohol (>40 g/day in males and 30 g/day in women)
Drugs: amiodarone, tamoxifen, methotrexate, glucocorticoids
Hepatitis C (genotype 3)
Wilson's disease
Lipodystrophies
Parenteral nutrition
Severe subacute or chronic calorie loss
Microvesicular steatosis
Reye's syndrome
Drugs: valproate, antiretrovirals
Steatosis associated with pregnancy
HELLP syndrome
Inborn errors of metabolism: deficits of lysosomal acid lipase (Wolman disease in children, cholesteryl ester storage disease in adults), others

NAFLD, non-alcoholic fatty liver disease.

Epidemiology

Prevalence and incidence

NAFLD is the most prevalent chronic liver disease in the world. The overall prevalence in adult subjects is estimated at around 20–30%, but there are significant variations according to geography, the age group of the population studied and diagnostic methods used.[2,15] In the United States, where the prevalence of risk factors for NAFLD is higher, large sample cohort studies estimate an overall prevalence of NAFLD of 30–46% (with significant variations within the US territory itself).[15,16] In Europe, the prevalence is somewhat lower than in the United States, around 25–30%.[2,15,16] In Spain, related epidemiological data is scarce. A study published in 2011 in the area of Barcelona among a primary care population and with ultrasound-based NAFLD diagnosis estimated a prevalence of 25%.[17] More recent studies based on more sensitive techniques (such as liver elastography) suggest that the prevalence may be even greater.

Prevalence increases significantly when specific populations with a high prevalence of traditional NAFLD risk factors are studied. Thus, in adult population with obesity, the prevalence is in the range of 50–70%.[5] In the diabetic population, recent cohort studies have shown that the prevalence of NAFLD in type-2 diabetes is 60–80%.[5,8,18,19] In patients with more than one risk factor (e.g., obesity and diabetes) the prevalence is almost universal (80–100%, depending on the series).[2,5] Similar figures have been obtained in populations made up of candidates for bariatric surgery.[2,5,15,16]

A particularly worrisome epidemiological aspect is the progressive increase of NAFLD cases in paediatric patients and adolescents. Recent studies suggest that in the United States the prevalence of NAFLD at these ages is around 10–15%. The cases of advanced fibrosis and even cirrhosis at these ages are no longer a rarity.[20,21]