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#### **REVIEW ARTICLE**

Nonalcoholic fatty liver disease, association with cardiovascular disease and treatment. (1). Nonalcoholic fatty liver disease and its association with cardiovascular disease

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#### **KEYWORDS**

Non-alcoholic fatty liver disease;

**Abstract** Non-alcoholic fatty liver disease (NAFLD) comprises a series of histologically lesions similar to those induced by alcohol consumption in people with very little or no liver damage. The importance of NAFLD is its high prevalence in the Western world and, from the point of view of the liver, in its gradual progression from steatosis to steatohepatitis, cirrhosis, and

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2 Á. Brea et al.

Non-alcoholic steatohepatitis; Cardiovascular risk; Cardiovascular diseases; Atherosclerosis; Treatment liver cancer. During the last decade it has been observed that NAFLD leads to an increased cardiovascular risk with acceleration of arteriosclerosis and events related to it, being the main cause of its morbidity and mortality. This review, updated to January 2016, consists of two parts, with the first part analysing the association of NAFLD with cardiovascular disease. © 2016 Published by Elsevier España, S.L.U. on behalf of Sociedad Española de Arteriosclerosis.

#### PALABRAS CLAVE

Enfermedad del hígado graso no alcohólica; Esteatohepatitis no alcohólica; Riesgo cardiovascular; Enfermedades cardiovasculares; Arteriosclerosis; Tratamiento Enfermedad del hígado graso no alcohólico, asociación con la enfermedad cardiovascular y tratamiento (I). Enfermedad del hígado graso no alcohólico y su asociación con la enfermedad cardiovascular

Resumen La enfermedad del hígado graso no alcohólico (EHGNA) comprende una serie de lesiones hepáticas histológicamente similares a las inducidas por el alcohol, en personas con un consumo del mismo muy escaso o nulo. La importancia de la EHGNA radica en su alta prevalencia en el mundo occidental y, desde el punto de vista hepático, en su progresiva evolución desde esteatosis a esteatohepatitis, cirrosis y cáncer de hígado. Durante la última década se ha observado que la EHGNA da lugar a un incremento del riesgo cardiovascular con aceleración de la arteriosclerosis y de los eventos a ella vinculados, principal causa de su morbimortalidad. Esta revisión actualizada a enero de 2016 consta de dos partes, analizando en esta primera parte la asociación de la EHGNA con la enfermedad cardiovascular.

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#### Introduction

Non-alcoholic fatty liver disease (NAFLD) covers a variety of histological lesions similar to those caused by alcohol abuse but without the consumption of alcohol, or with a consumption of less than 30-40 mg/day for men, and less than 20 mg/day for women. Simple steatosis is defined as a triglyceride deposit in the hepatocytes that is greater than 5% of the cellular weight, although from a practical point of view this diagnosis is made if more than 5% of the hepatocytes contain typically macrovesicular fat. 1 If the disease progresses, the phenomena of hepatocellular ballooning and necrosis, as well as infiltration by inflammatory cells and fibrosis of the hepatic tissue are included in the histological spectrum, giving rise to non-alcoholic steatohepatitis (NASH). While only a small percentage of simple steatosis evolves into more severe advanced forms, the cirrhosis conversion rate for patients suffering from NASH is 25-30% within 4 years.<sup>2</sup> Likewise, between 7% and 15% of those suffering from NASH or cirrhosis develop hepatocellular carcinoma.<sup>3,4</sup>

In the last decade, numerous tests in which NAFLD is linked with a greater risk of cardiovascular disease (CVD), which is the main cause of death in patients with NAFLD, have been added to the current evidence, displacing the old idea that hepatic steatosis is an innocuous disease (Table 1). It is estimated that in Europe the prevalence of NAFLD is between 2% and 44% of the general population<sup>5,6</sup> and 26% in Spain.<sup>7</sup> Given its association with excess weight and metabolic syndrome, growing problems that have reached epidemic proportions worldwide, it is expected that NAFLD will be an urgent public health issue in the not-too-distant future. This review will closely examine the relationship between NAFLD and CVD.

## Non-alcoholic fatty liver disease and atherosclerosis markers

The surrogate markers of atherosclerosis include arterial damage and the possibility of it developing into a symptomatic cardiovascular event. We will review the influence of NAFLD on these markers below.

#### Carotid ultrasound

NAFLD is associated with an early increase in the carotid intima-media thickness (IMT) and a greater prevalence of plaques, as was initially demonstrated by our group in patients of both sexes. Other cohort and population studies have ratified these findings. In a meta-analysis of all these studies, it was found that NAFLD is linked to an increase of 51–144% in the carotid IMT and that the presence of atheromatous plaques is 2–3 times greater. It was concluded that all patients with NAFLD should be evaluated using a carotid ultrasound. Another meta-analysis confirmed that NAFLD diagnosed using an ultrasound is associated with the presence of 2.8 times more carotid plaques, and 4.41 times more if diagnosed through a biopsy.

The severity of the histologic lesion is correlated with the increase in the IMT, which is concordant with the fact that the patients with NASH have an increased cardiovascular risk (CVR) than those with simple steatosis. <sup>10</sup> In fact, with hepatic fibrosis the IMT is much greater. <sup>14</sup> Fracanzani et al. evaluated the risk factors that affect the progression of the IMT in patients with NAFLD and the CVD rate after more than 10 years of follow-up. In this period, the IMT of the patients with fatty liver was greater than that of the controls and the development of plaques progressed faster. A higher

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