International Journal of Cardiology 167 (2013) 1109–1117

Contents lists available at SciVerse ScienceDirect

International Journal of Cardiology

journal homepage: www.elsevier.com/locate/ijcard

Review

Non-alcoholic fatty liver disease and cardiovascular risk

Angel Brea [a], José Puzo [b,*]

[a] Unidad de Lípidos, Servicio de Medicina Interna, Hospital San Pedro, Logroño, Spain
[b] Unidad de Lípidos, Bioquímica Clínica, Hospital San Jorge, Huesca, Spain

ARTICLE INFO

Article history:
Received 12 January 2012
Received in revised form 26 May 2012
Accepted 15 September 2012
Available online 9 November 2012

Keywords:
Fatty liver
Cardiovascular disease
Alcohol
Non-alcoholic fatty liver disease

ABSTRACT

The term "Non-alcoholic fatty liver disease" (NAFLD) covers a series of liver lesions similar to those induced by alcohol, but not caused by alcohol use. The importance of NAFLD lies in the high prevalence in Western societies and, from the point of view of the liver, in its progression from steatosis to cirrhosis and liver cancer. More recently, NAFLD has been found to be associated with lipid metabolism disorders, the deposition of fat outside of the adipocytes, insulin resistance and Metabolic Syndrome. Also attributed to NAFLD is a heightened systemic pro-inflammatory state, which accelerates arteriosclerosis, thereby increasing cardiovascular risk and associated cardiovascular events. Here we provide an update to the etiopathogenesis of NAFLD, its influence on cardiovascular disease, and the treatment options.

1. Introduction

The term "Non-alcoholic fatty liver disease" (NAFLD) is used to describe a wide range of liver disorders which, histologically, are very similar to those caused by alcohol. NAFLD develops in patients who do not drink alcohol, or who drink less than 20 g/day, which is the figure considered being the limit above which alcohol can cause liver damage [1].

NAFLD was first described almost 60 years ago [2], although it would be another thirty years before it was recognised as such by pathologist Jurgen Ludwig [3]. NAFLD refers to a series of liver conditions that range from simple fatty infiltration of the hepatocytes (steatosis) to inflammation and the development of fibrosis: "Non-alcoholic steatohepatitis" (NASH), with potential for progression to cirrhosis and liver cancer [4]. The high prevalence of NAFLD in Western societies was described at the end of the last century, but more recently it has been confirmed that not only can it be fatal due to development of chronic liver disease, but that it may also be associated with lipid metabolism disorders and increased cardiovascular risk.

This review provides an update to available literature on etiopathogenesis of NAFLD, its influence on development of cardiovascular disease (CVD), and current treatment options.

2. Epidemiology

NAFLD is an asymptomatic disease, which does not cause significant changes in transaminase levels in two thirds of those who suffer it. Its prevalence is determined through abdominal ultrasound, although this technique requires at least a fatty infiltration of a third of the liver parenchyma to detecting steatosis. Even with these limitations, it is estimated that NAFLD affects 20–30% of the population in the West [5]. NASH, diagnosed by liver biopsy would then affect 2–3% of the population [6]. The prevalence of NAFLD varies according to race, ranging from 45% in Hispanics to 33% in Caucasian Americans, 24% in African Americans [7] and 25% in Asians [8]. It tends to be more frequent in men than in women (42% versus 24% respectively), although may be higher among postmenopausal women [9]. The prevalence of NAFLD increases with age, from less than 20% in people under the age of 20 to more than 40% in over 60s. Nevertheless, NAFLD has also been described in the paediatric population with a prevalence of 2.6%, which may rise to anywhere in the range of 10–80% in obese children [10]. NAFLD is more prevalent in patients with diabetes mellitus type 2 (40–75%) or obesity (33–76%) and affects 99% of people undergoing bariatric surgery [11].

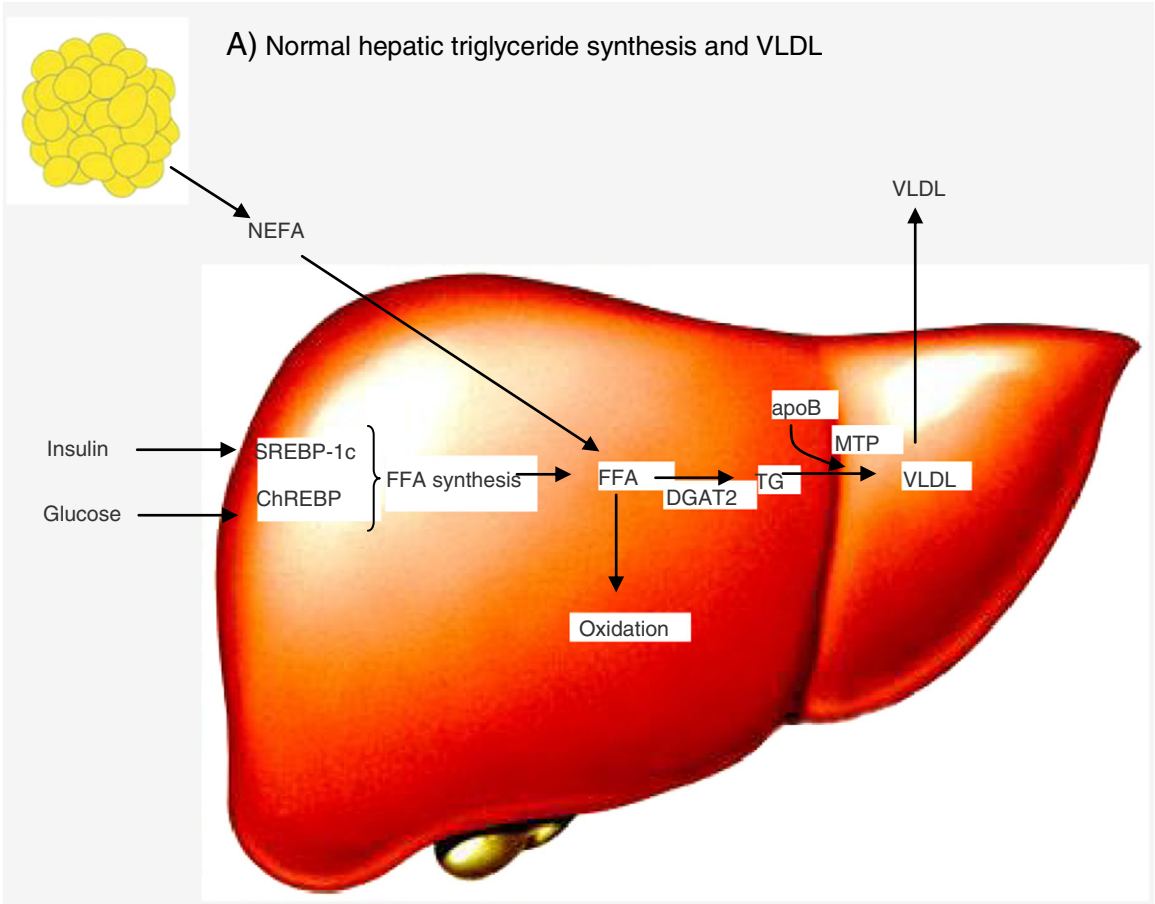
3. Pathogenesis

The liver plays a central role in lipid metabolism with the uptake of free fatty acids (FFAs) from the plasma. If the FFAs are not oxidised and used as a source of energy, after the synthesis of lipids and lipoproteins, they are stored or exported. A series of abnormalities in local and systemic factors which control the balance between flow, oxidation and export of lipids leads to the accumulation of triglycerides (TG) in the liver.

* Corresponding author at: Hospital General San Jorge, Unidad de Lípidos, Bioquímica Clínica, Pº Martinez de Velasco 36, Huesca 22004, Spain. Tel.: +34 974247078; fax: +34 974247099.
E-mail address: jpuzo@unizar.es (J. Puzo).

0167-5273/$ – see front matter © 2012 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.ijcard.2012.09.085

Insulin resistance (IR) [12] and obesity [13] are two important elements in the pathogenesis of NAFLD. Both increase the inflow of FFAs to the liver from subcutaneous and visceral fat and "de novo" intrahepatic synthesis of FFAs – de novo lipogenesis (DNL) – by overexpressing of lipogenic transcription factors such as protein-bound sterol regulatory element (SREBP-1c) or the bound protein response element to carbohydrates [14,15]. In NAFLD, DNL is a key factor in TG formation as, in contrast to what happens in healthy subjects, it is even activated during fasting periods, contributing 26% to TG synthesis [16]. After a diet high in sugars, in the IR state associated with NAFLD, the uptake of glucose by the muscles ends up being diverted towards the liver where it then contributes to DNL [16]. This is known as partial or selective IR, with dissociation between gluconeogenesis (cancelled out) and lipogenesis (stimulated). The hyperinsulinaemia then activates the mechanisms which desensitize hepatocytes to the effects of insulin. Postprandial gluconeogenesis is not suppressed and the postprandial hyperglycaemia typical of a pre-diabetic state occurs. At the same time, lipogenesis is promoted, causing these cells to become filled with fat [17]. The FFAs, which are not incorporated into the TG, are metabolised by oxidation in mitochondria, peroxisomes and microsomes (Fig. 1A). However, activation of SREBP-1c increases malonyl-CoA, which inhibits oxidation of the FFAs, thereby halting the activity of carnitine palmitoyltransferase-1, the gateway into mitochondria for the Acyl-CoA, in order to be oxidised. The net result of these three changes – greater supply of FFAs, increased intrahepatic synthesis and reduction in mitochondrial activity – is a greater availability of FFAs in the liver as substrate for TG synthesis [18]. In obese patients with NAFLD, adipocytes secrete less adiponectin. This leads to greater production of pro-inflammatory factors, i.e. tumour necrosis factor alpha (TNF-α) and interleukin-6 (IL-6) [19], which can contribute to IR and accumulation of fat in hepatocytes. In intrahepatic synthesis of TG, enzyme Acyl-CoA:diacylglycerol acyltransferase (DGAT) catalyses esterification from FFAs to TG. DGAT is composed of two



The liver lipid content is determined by the balance of several processes: a) Import of non-esterified fatty acids (NEFA) from adipose tissue, b) de novo synthesis of NEFA in hepatocytes, c) Beta-oxidation of NEFA, d) esterification of FFA-mediated TG DAGT2 e) Export of triglycerides and VLDL

Abbreviations: VLDL, very low density lipoproteins, FFA free fatty acids or NEFA non-esterified fatty acids, SREBP-1c: protein attached to the sterol regulatory element; ChREBP: protein response element linked to carbohydrates, TG: triglycerides, ApoB: apolipoprotein B, MTP: microsomal triglyceride transfer protein

Fig. 1. A. Normal hepatic triglyceride synthesis and VLDL. The liver lipid content is determined by the balance of several processes: a) import of non-esterified fatty acids (NEFA) from adipose tissue, b) de novo synthesis of NEFA in hepatocytes, c) beta-oxidation of NEFA, d) esterification of FFA-mediated TG DAGT2, and e) export of triglycerides and VLDL. Abbreviations: VLDL: very low density lipoproteins, FFA: free fatty acids or NEFA: non-esterified fatty acids, SREBP-1c: protein attached to the sterol regulatory element, ChREBP: protein response element linked to carbohydrates, TG: triglycerides, Apo B: apolipoprotein B, and MTP: microsomal triglyceride transfer protein. B. Pathophysiology of NAFLD. Influence of insulin resistance in NAFLD. Abbreviations: ↑ = increased, ↓ = decreased; NAFLD: non-alcoholic fatty liver disease, NASH: non-alcoholic steatohepatitis, FFA: free fatty acids, SREBP-1c: protein attached to the sterol regulatory element; ChREBP: element binding protein response to carbohydrates, TG: triglycerides, VLDL: very low density lipoproteins, Apo B: apolipoprotein B; MTTP: microsomal triglyceride transfer protein, and VLDL: very low density lipoprotein.