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Fatty liver: Role of inflammation and fatty acid nutrition

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A B S T R A C T

Nonalcoholic fatty liver disease (NAFLD) refers to a wide spectrum of liver damage, ranging from simple steatosis to nonalcoholic steatohepatitis (NASH), advanced fibrosis, and cirrhosis. NAFLD is strongly associated with insulin resistance and is defined by accumulation of liver fat $>5\%$ per liver weight in the presence of <10 g of daily alcohol consumption. The exact prevalence of NAFLD is uncertain because of the absence of simple noninvasive diagnostic tests to facilitate an estimate of prevalence but in subgroups of people such as those with type 2 diabetes, the prevalence may be as high as 70%. NASH is an important subgroup within the spectrum of NAFLD that progresses over time with worsening fibrosis and cirrhosis, and NASH is associated with increased risk for cardiovascular disease. It is, therefore, important to understand the pathogenesis of NASH specifically, to develop strategies for interventions to treat this condition. The purpose of this review is to discuss the roles of inflammation, fatty acids and fatty acids in nutrition, in the pathogenesis and potential treatment of NAFLD.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) refers to a wide spectrum of liver damage, ranging from simple steatosis to steatohepatitis, advanced fibrosis, and cirrhosis. NAFLD is strongly associated with insulin resistance and is defined by accumulation of liver fat $>5\%$ per liver weight, in the presence of <10 g of daily alcohol consumption [1] (see Box 1). NAFLD is a hepatic component of the metabolic syndrome and is an independent risk factor for cardiovascular disease (CVD). NAFLD is associated with an increased risk of all-cause death and predicts future CVD events, independently of age, sex, LDL-cholesterol, smoking and the cluster of features of metabolic syndrome. To date there are no licensed treatments for NAFLD but currently, treatments such as bariatric surgery for the obese person with NAFLD, and glitazones in people with type 2 diabetes have shown promising results. Treatments are needed that will target not only hepatic fat accumulation, but also inflammation and fibrosis in people with the varying spectrum of liver conditions comprising NAFLD. The purpose of this review is to focus on the roles of inflammation, fatty acids and fatty acids in nutrition, in the pathogenesis and potential treatment of NAFLD. This review contains information published in a detailed recent review of the extra- and intra-hepatic mechanisms contributing to the pathogenesis of NAFLD [2].

2. Pathogenesis

NAFLD represents a heterogeneous cluster of conditions from simple accumulation of hepatic fat (steatosis), hepatic fat accumulation with inflammation [steatohepatitis or nonalcoholic steatohepatitis, (NASH)] to NASH with extensive fibrosis and finally to cirrhosis. People developing cirrhosis, with regenerating nodules, have an increased risk of developing hepatocellular carcinoma. Evidence suggests from the long-term follow-up of patients with NAFLD and elevated liver enzymes that the liver condition does not progress in all subjects with liver steatosis on initial liver biopsy [3]. Mortality is probably not increased in patients with steatosis. In contrast survival of patients with NASH is reduced and these subjects often die from cardiovascular as well as liver-related causes. Therefore, it is important not only to elucidate the mechanisms contributing to hepatic steatosis but also mechanisms contributing to NASH. Crucial to an understanding of the mechanisms contributing to NASH is to elucidate pathways leading to inflammation and fibrosis. This is an area of considerable research interest and it was postulated several years ago that there was most likely a 'second hit' or insult that

Abbreviations: NEFA, nonesterified fatty acid; HSL, hormone sensitive lipase; LPL, lipoprotein lipase; VLDL, very-low density lipoprotein; n-3 PUFA, omega – 3 polyunsaturated fatty acid; SREBP-1c, sterol regulatory element binding protein–1c; ACC, acetyl CoA carboxylase; FAS, fatty acid synthentase; mGAT, mitochondrial glycerol 3 phosphate acyltransferase; aGPAT, acylglycerol-sn-3-phosphate acyltransferase; PAP, phosphatidic acid phosphatase; DGAT2, diacyl glycerol acyltransferase–2; CCT–CTP, phosphocholine cytidylyltransferase; CPT–CDP-choline, 1,2 diacylglycerol choline phosphotransferase; PEMT, phosphatidylethanolamine N-methyltransferase; ChREBP, carbohydrate response element binding protein; LXR, liver X receptor; SCD-1, stearoyl CoA desaturase–1; CPT-1, carnitine palmitoyl transferase–1; UCP-2, uncoupling protein – 2; NADPH, nicotinamide adenine dinucleotide phosphate (reduced form)

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prompted disease progression [4] (Fig. 1). The severity of the liver condition in NAFLD can be quantitated with a simple histopathogical scoring system that assesses severity of steatosis, ballooning of hepatocytes, lobular inflammation and fibrosis [5] (Table 1).

There is a strong link between insulin resistance and excessive deposition of triglyceride in the hepatocytes, which is the hallmark for diagnosis for NAFLD. The excessive/ectopic fat deposition in the liver could be initiated by (a) increased fatty acid delivery from extra hepatic sources such as adipose tissue, (b) increased synthesis of fatty acid via the de novo pathway, (c) increased dietary fat, (d) decreased mitochondrial β oxidation, (e) decreased clearance of VLDL particles, or several of these factors in combination.

It is still a matter of debate as to whether insulin resistance causes NAFLD or, whether excessive accumulation of triglyceride, or precursors on the synthetic pathway precede and then cause insulin resistance [6]. Regardless of which comes first, it is likely that hepatic insulin sensitivity deteriorates with increasing hepatic fat accumulation, resulting in increased hepatic gluconeogenesis and increased hepatic glucose output.

Box 1–Nonalcoholic fatty liver disease definition.

NAFLD definition

- Liver injury–fat accumulation exceeding 5–10% by weight–fat laden hepatocytes identified by light microscopy
- Similar to alcohol-induced liver injury
- NAFLD
  - Steatosis
  - Steatohepatitis (NASH)
  - NASH+extensive fibrosis
  - NASH-induced cirrhosis

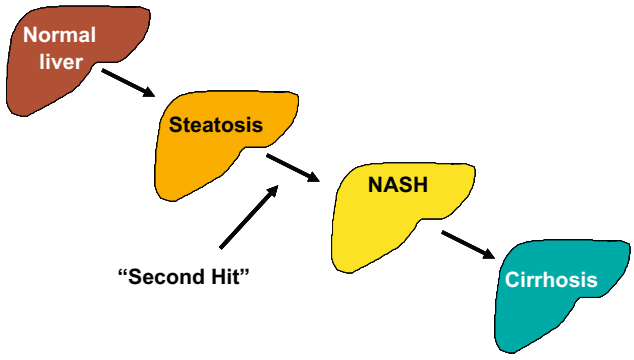

Fig. 1. Nonalcoholic fatty liver disease represents a spectrum of liver disease. Hepatic fat accumulation begins with the development of simple hepatic steatosis that is probably associated with no increase in liver-related morbidity and no increase in cardiovascular disease. In some individuals there is a subsequent 'second hit' or insult that causes disease progression to a more florid form of the disease that may result in cirrhosis and even hepatocellular carcinoma.

Table 1
Histological (Kleiner) scoring system for nonalcoholic fatty liver disease [5].

Feature	Criteria	Score
Steatosis	< 5%	0
	5–33%	1
	33–66%	2
	> 66%	3
Ballooning	None	0
	Few	1
	Promonant	2
Lobullar inflammation	None	0
	< 2 foci/200x field	1
	2–4 foci/200x field	2
	> 4 foci/200x field	3
Fibrosis	No fibrosis	0
	Zone 3 pericellular fibrosis	1a/b
	Zone 1 fibrosis	1c
	Zone 1 and zone 3 pericellular fibrosis	2
	Bridging fibrosis	3
	Cirrhosis	4

2.1. *The contribution of extra-hepatic fatty acid supply to the liver to cause hepatic steatosis*

Increased delivery of non-esterified fatty acids (NEFAs) to the liver from adipose tissue is important to the development of NAFLD, particularly if increased hepatic fatty acid uptake is not balanced by increased utilisation and export of lipids as lipoprotein from the liver. Recent studies in humans and rodents have shown that increased NEFA delivery from adipose tissue is a significant source of fat accumulation in the hepatocytes and approximately 60% of fat accumulating in hepatocytes is derived from adipose tissue sources [7]. In insulin resistant subjects, there is failure of insulin-mediated suppression of hormone sensitive lipase, resulting in uncontrolled lipolysis in the adipose tissue [8,9]. Hormone sensitive lipase knockout mice have reduced plasma NEFA and triglyceride concentrations and show increased hepatic insulin sensitivity [10,11]. Peripheral (subcutaneous) fat constitutes a major proportion of the fat mass; however, it is not an absolute requirement for developing fatty liver. Patients with lipodystrophy, who are also insulin resistant with no peripheral and intra-abdominal fat, develop fatty liver and severe hepatic insulin resistance [12]. In this situation the stimulus for fatty liver may be increased free fatty acid flux to the liver stimulating lipogenesis, combined with inadequate compensatory fat oxidation, leading to fat accumulation over time. Furthermore, there is some contribution to free fatty acid flux to the liver from intra-abdominal fat in insulin resistant subjects [13]. Intra-abdominal fat is strongly associated with reduced insulin sensitivity even in lean subjects [14] and, has been shown to correlate positively with hepatic fat and hepatic insulin resistance.

The role of diet in the pathogenesis of NAFLD has recently been investigated in humans and animal models and it is plausible that the relative impacts of different fatty acids may produce differential impacts on the liver, according to the timing of their delivery during development and ageing. However, although little is known about this, a high fat diet in adulthood can lead to development of fatty liver. A low fat/high carbohydrate diet also induces fatty liver via increased de novo fatty acid synthesis [15]. In addition to the above effect, high dietary fat intake is associated with obesity and insulin resistance. As a consequence of insulin resistance, there is impaired suppression of lipolysis by insulin leading to increased NEFA delivery to the liver. There is also reduced glucose uptake in the fed state by adipose tissue and skeletal muscle resulting in hyperglycaemia and diversion of glucose to the hepatic de novo lipogenesis pathway [16]. In another recent study [17], the relationship between dietary profile and markers of visceral and somatic obesity in NAFLD has been studied. In liver biopsy proven individuals, the investigators showed that dietary intake of fat was higher in patients with NASH, particularly in those people who did not have diabetes. These data suggest that lipid intake may play a greater role in NASH, than has been previously suspected.