Nutrition, Metabolism & Cardiovascular Diseases (2009) 19, 291–302

available at www.sciencedirect.com

ScienceDirect

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

Nutrition, Metabolism & Cardiovascular Diseases

REVIEW

Hepatic lipid metabolism and non-alcoholic fatty liver disease☆

P. Tessari*, **A. Coracina**, **A. Cosma**, **A. Tiengo**

Dept. of Clinical and Experimental Medicine, Chair of Metabolism, University of Padova, Italy

Received 22 April 2008; received in revised form 10 December 2008; accepted 29 December 2008

KEYWORDS
Fatty liver;
Insulin;
Metabolic syndrome;
Hepatic lipid metabolism;
Microsome;
Peroxidation;
Gene expression;
Lipoprotein export;
Metformin;
Apoptosis

Abstract Non-alcoholic fatty liver disease (NAFLD) is an increasingly recognized pathology with a high prevalence and a possible evolution to its inflammatory counterpart (non-alcoholic steatohepatitis, or NASH). The pathophysiology of NAFLD and NASH has many links with the metabolic syndrome, sharing a causative factor in insulin resistance. According to a two-hit hypothesis, increased intrahepatic triglyceride accumulation (due to increased synthesis, decreased export, or both) is followed by a second step (or ''hit''), which may lead to NASH. The latter likely involves oxidative stress, cytochrome P450 activation, lipid peroxidation, increased inflammatory cytokine production, activation of hepatic stellate cells and apoptosis. However, both ''hits'' may be caused by the same factors. The aim of this article is to overview the biochemical steps of fat regulation in the liver and the alterations occurring in the pathogenesis of NAFLD and NASH.

Introduction

Non-alcoholic fatty liver disease (NAFLD), the most common liver disease, is defined by a hepatic triglyceride content exceeding 5% of liver weight [1], although a ''normal'' triglyceride liver content in healthy, lean and middle-aged humans with low transaminase concentrations has been recently set to 1.9% of organ weight and to 3.9% in the ''general'' population [2]. NAFLD may also have a genetic predisposition [3].

NAFLD prevalence is 10–24%, increasing to 25–75% in obesity and type II diabetes mellitus [4,5]. NAFLD is associated with insulin resistance, hypertriglyceridemia and, more generally, to the metabolic syndrome [6]. In non-diabetic subjects, there is a correlation between body mass index and liver fat [7]. Fatty liver disease is a major contributor to cardiovascular and overall obesity-related morbidity and mortality [8,9].

NAFLD accounts for ≈90% of cases of asymptomatic elevation of transaminases when other causes of liver

☆ Disclosure Statement: The authors have nothing to disclose.

* Corresponding author. Dept. of Clinical and Experimental Medicine, Chair of Metabolism, Policlinico Universitario, via Giustiniani 2, 35128 Padova, Italy. Tel.: +39 049 8211748; fax: +39 049 8754179.
E-mail address: paolo.tessari@unipd.it (P. Tessari).

0939-4753/$ - see front matter © 2009 Elsevier B.V. All rights reserved.
doi:10.1016/j.numecd.2008.12.015

disease are excluded [5]. Nonetheless, transaminases are normal in >80% of subjects with NAFLD [10]. Although a ''benign'' condition, NAFLD is a risk factor for more serious liver alterations (necroinflammation, hepatocyte ballooning, Mallory bodies formation, enlargement and dysfunction of mitochondria), eventually leading to fibrosis and to non-alcoholic steatohepatitis (NASH). NASH in turn affects ≈3% of the general lean population, ≈20% of obese subjects and ≈50% of morbidly obese subjects [5]. About 10% of NAFLD patients eventually progress to NASH. This rate represents the net balance between 12 and 40% of NAFLD converted to NASH and 16–28% of NASH reverted to NAFLD. NASH may progress to cirrhosis and to liver-related death (mostly hepatocellular carcinoma) in ≈25% and ≈10% of cases, respectively [4].

Two steps (or ''hits'') have been proposed for the pathophysiology of NAFLD and NASH [4,11], although this theory has recently been challenged. The first ''hit'' is insulin resistance leading to NAFLD. The second is oxidative stress, determining lipid peroxidation, increased cytokine production and inflammation, ultimately resulting in NASH [12].

Dietary factors may modulate liver steatosis: a diet high in saturated fat increases liver lipids and plasma insulin levels, inducing insulin resistance [13,14], and affecting mitochondrial function. Inflammatory stimuli play a role in the progression of NAFLD to NASH through the activation of nuclear receptors.

Liver cells are involved in many pathways of lipid metabolism (Table 1) and also according to their location within the lobule. The aim of this review is to provide a concise update on fatty acid and lipoprotein metabolism in the liver particularly in relationship to NAFLD and NASH, in the context of other causative factors.

Hepatic zonation of lipid metabolic activities

On the basis of enzyme and metabolite distributions in selected cell cultures of either *periportal* (i.e. afferent) - or *perivenous* - (i.e. efferent)-enriched hepatocyte populations, and using the isolated liver following orthograde vs. retrograde perfusion [15], two functionally-specialized zones have been proposed. The *periportal* zone is the site of oxidative energy metabolism, fatty acid β-oxidation, amino acid catabolism, ureagenesis, gluconeogenesis, cholesterol synthesis and degradation [16], bile formation and detoxifying metabolic pathways. Conversely, the *perivenous zone* is the site of glycolysis, glycogen synthesis from glucose, *de novo* lipid synthesis, ketogenesis, glutamine formation, and xenobiotic metabolism. These zones are characterized by differences in blood flow and innervation, which determine concentration gradients of oxygen, substrates and hormones, as well as by differences in nerve density. The differential gene expression in upstream and downstream hepatocytes can also be caused by the zonal gradients of oxygen and hormone concentrations.

Table 1 Liver metabolic activities related to lipid metabolism.

- hepatic zonation of lipid metabolism
- liposynthesis
- *de novo* lipogenesis
- fatty acid β-oxidation
- lipolysis
- lipoprotein synthesis and export

Fatty acid oxidation occurs in the mitochondria, and in the cytosol in peroxisomes and microsomes. The distribution of palmitate oxidation in rat mitochondria within the acinar cells is flexible, and changes markedly with the physiological status [17]. The [periportal/perivenous] ratio of oxidation was 1.5, 2.0, 1.0 and 0.4 in fed, starved, refed and cold-exposed rats, respectively [17], and it was paralleled by zonation of the carnitine palmitoyltransferase-1 (CPT-1) activity (in fed and in cold-exposed animals), as well as of the mitochondrial 3-hydroxy-3-methyl-glutaryl-CoA synthase activity (in starved animals). In contrast, no differences as regards sensitivity of CPT-1 to malonyl-CoA, the intracellular concentration of malonyl-CoA, fatty acid synthase [FAS] activity, acetyl-CoA carboxylase activity, and the relative content of the two hepatic acetyl-CoA carboxylase isoforms, were detected [17]. However, peroxisomes palmitate oxidation was always preferentially located in the perivenous hepatic areas, irrespective of the physiological status of the animal. Thus, the changes in the acinar distribution of mitochondrial long-chain fatty acid oxidation involve specific mechanisms under different physiological conditions.

Liposynthesis and *de novo* lipogenesis

The esterification of free fatty acids (activated as acyl-CoA) with glycerol (activated as alpha-glycerophosphate [α-GP]) (i.e. *liposynthesis*) is driven by the key enzymes glycerophosphate acyltransferase (GPAT). Both the nutritional status and insulin activate GPAT gene transcription and/or activity [18]. Glucagon inhibits GPAT [19]. An overflow of FFA to the liver stimulates both esterification and lipoprotein synthesis [20]

The synthesis of FFA from acetyl-CoA (*de novo lipogenesis*) is stimulated by insulin first through glucokinase activation and increased glucose metabolism, then through activation of the transcription factor sterol regulatory element-binding protein-1c (SREBP-1c) [21,22] (Fig. 1). SREBP-1 in turn stimulates several lipogenic enzymes, such as liver pyruvate kinase (L-PK), acetyl-CoA carboxylase (ACC), fatty acid synthase (FAS), stearyl-CoA desaturase (SCD) and the recently discovered enzyme Spot 14 (S14) [22]. L-PK is activated first to produce acetyl-CoA. In the liver, pyruvate is phosphorylated predominantly for lipogenesis. Subsequently, insulin stimulates acetyl-CoA carboxylation to malonyl-CoA through the activation of the cytosolic enzyme acetyl-CoA carboxylase (ACC), independently of FFA levels [23]. Malonyl-CoA is a key regulator of the partitioning of FFA between esterification and oxidation [23]. A high malonyl-CoA concentration, a reflection of active *de novo* lipogenesis, spares the FFAs from oxidation and directs them to esterification to produce triglycerides. Conversely, a low malonyl-CoA enhances CPT-1 activity favoring fatty acid transport into the mitochondria and β-oxidation. Glucagon enhances CPT-1 activity and