

Crosstalk between Lipids and Non-Alcoholic Fatty Liver Disease

Subjects: **Biology**

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Non-alcoholic fatty liver disease (NAFLD), a complex liver disorder that can result in non-alcoholic steatohepatitis, cirrhosis, and liver cancer, is the accumulation of fat in the liver seen in people due to metabolic dysfunction. The pathophysiology of NAFLD is influenced by several variables, such as metabolic dysregulation, oxidative stress, inflammation, and genetic susceptibility. This illness seriously threatens global health because of its link to obesity, insulin resistance, type 2 diabetes, and other metabolic disorders. In recent years, lipid–NAFLD crosstalk has drawn a lot of interest. Through numerous methods, lipids have been connected to the onset and advancement of the illness.

liver

non-alcoholic fatty liver disease

lipid metabolism

1. Introduction

Lipids are the most abundant biomolecules in circulation and serve as an integral part of cell structure and function [1]. Research has shown that lipids play a crucial part in the development of non-alcoholic fatty liver disease (NAFLD) (currently known as non-metabolic-associated fatty liver disease (MAFLD)) [2] and they interact in a complicated manner [3]. In the early 2020s, an international panel of experts led a consensus-driven process to develop a more appropriate term for the disease. The proposed term was “metabolic dysfunction-association fatty liver disease” or MAFLD [4][5][6]. In addition to the name change, the consensus proposed a set of simple positive criteria to diagnose and evaluate individuals for the disease. In the case of NAFLD diagnosis, as published in the guidelines, it requires hepatic steatosis of $\geq 5\%$ without concurrent liver disease, including significant alcohol usage. The criterion of MAFLD utilizes the same standard for hepatic steatosis but identifies metabolic dysregulation factors as a pre-requisite for the diagnosis to be entertained [7]. Triglycerol (TG) accumulation in hepatocytes takes place due to an excessive intake of dietary fat and carbohydrates that leads to the development of hepatic steatosis [8]. Hepatocytes accumulate TG-containing lipid droplets, which further leads to the development of large lipid droplets that compress other organelles and harm and inflame the hepatocytes [8]. An imbalance in lipid production, export, and absorption results in the accumulation of TG and other neutral lipids in hepatocytes and is a characteristic feature of NAFLD [8][9]. The dysregulation of genes involved in fatty acid oxidation, such as peroxisome proliferator-activated receptor-alpha (PPAR- α) and sterol regulatory element binding protein-1c (SREBP-1c), and lipogenesis has been associated with AFLD [10][11]. The risk of AFLD has also been associated with mutations in lipid metabolism-related genes, such as Patatin-like phospholipase domain-containing protein 3 (PNPLA3) [12]. NAFLD encompasses a spectrum of conditions, ranging from simple steatosis to non-alcoholic

steatohepatitis (NASH), which may ultimately lead to hepatocellular carcinoma [13]. Recent studies suggest that NAFLD has become the most widespread liver disease globally [14], owing to its escalating incidence across various regions. The primary characteristic of NAFLD is the accumulation of neutral lipids in the liver, predominantly TG [15]. In MAFLD, individuals with significant alcohol intake or chronic viral hepatitis are included where these individuals have been excluded from the NAFLD criteria [5]. Hepatic lipid accumulation arises from a disparity between the uptake of lipids via circulation or de novo lipogenesis (DNL) and their disposal through free fatty acid oxidation or TG-rich lipoprotein secretion [9][13][15]. This imbalance ultimately culminates in lipoperoxidation stress and consequent hepatic impairment. The aforementioned stages are subject to modification by NAFLD, albeit to varying degrees [14]. The regulation of these pathways is meticulously controlled through the participation of membrane transport proteins, nuclear receptors, and cellular enzymes. According to a study on the relationship between lipid metabolism and inflammation in the development of NAFLD, hepatic fibrosis and steatosis can be caused by inflammatory pathways that are sparked by excessive amounts of free fatty acids (FFAs) in the liver [16].

2. Accumulation of Lipids Exacerbates NAFLD Progression

Lipids are crucial to NAFLD progression and development, and there are some lipids that promote the progression [17]. Lipids such as saturated fatty acid (SFA) have been linked to the development of NAFLD [18]. By increasing fatty acid intake and accumulation in the liver, SFA causes hepatic steatosis. In addition, SFA causes insulin resistance and inflammation, both of which are crucial to the pathogenesis of NAFLD [18][19]. SFA-rich diets have been proven in studies to exacerbate disease severity in animal models. To improve their stability and shelf life, trans fatty acids (TFAs) are unsaturated fatty acids that have undergone chemical modification [20]. TFAs have been linked to a higher risk of NAFLD and can be found in processed foods and dairy products. TFAs can also increase TG buildup in the liver and induce inflammation and insulin resistance [21]. NAFLD has been proven to benefit from omega-3 fatty acids (n-3), which are polyunsaturated fatty acids (PUFAs) [22]. Due to their anti-inflammatory and antioxidant effects, n-3 fatty acids can mitigate NAFLD development and progression [22]. In animal models, n-3 fatty acid-rich diets have been demonstrated to minimize hepatic steatosis and inflammation [23]. Sphingolipids are another group of lipids that have been investigated in relation to the development of NAFLD [24]. Sphingolipids are a class of complex lipids that are critical components of cellular signaling pathways. Multiple studies have demonstrated that dysregulated sphingolipid metabolism aids the disease's progression, but animal models show that inhibition of sphingolipid production slows the course of NAFLD [24].

3. Lipids Alleviate NAFLD and Decreased during Disease Progression

According to different studies, certain lipids may act as a barrier to the development of NAFLD. The following lipids have been demonstrated to downregulate the progression of NAFLD: In both animal models and human trials, n-3 PUFAs have been found to decrease hepatic steatosis, inflammation, and fibrosis [22][25]. They do this by raising anti-inflammatory cytokines and decreasing pro-inflammatory cytokines to achieve their positive effects [26].

Monounsaturated fatty acids (MUFAs) also have been proven to decrease hepatic steatosis and inflammation [27]. They reduce oxidative stress and regulate lipid metabolism to induce positive effects. Phospholipids are crucial components of cell membranes, and it has been demonstrated that they regulate hepatic lipid metabolism and inflammation [28]. Targeting phospholipid metabolism may be a viable therapeutic strategy for NAFLD because phospholipid levels are altered in NAFLD patients. Lysophospholipids (LysoPLs) are the deacylated products of phospholipids with a single fatty acid chain. Several types of LysoPLs were identified and quantified in biological samples and have been found to be decreased in NAFLD compared to those in the control [29].

4. Mechanism of Lipid Accumulation in NAFLD

Hepatic accumulation of fat is driven by an imbalance between the acquisition and disposal of lipids, which are controlled by four main pathways: circulating lipid intake, de novo lipogenesis (DNL), fatty acid oxidation (FAO), and export of lipids in very-low-density lipoproteins (VLDLs) [30]. The hepatic absorption of circulating fatty acids is mainly reliant on fatty acid transporters [30]. The transportation process is mainly facilitated by fatty acid transport proteins (FATP), CD36, and caveolins that are situated in the plasma membrane of the hepatocyte [2]. In mice, FATP2 knockdown reduces fatty acid uptake and alleviates hepatic steatosis driven by a high-fat diet [31]. Long-chain fatty acid transport is facilitated by the fatty acid translocase protein CD36, which is regulated by the peroxisome proliferator-activated receptor (PPAR), fetus X receptor, and liver X receptor [32]. Hepatic steatosis and elevated mRNA and protein expression of CD36 occur in mice fed a high-fat diet [33][34]. While liver-specific CD36 knockouts reduce hepatic lipid levels in both genetic and diet-induced steatosis, adenovirus-mediated overexpression of CD36 improves hepatic fatty acid intake and fat accumulation [33]. The significantly elevated CD36 levels in NAFLD patients support the idea that CD36 plays a causal role in steatosis. In the liver of mice with NAFLD, there was an increase in caveolin 1, one of the three membrane proteins belonging to the caveolins family that contribute to lipid trafficking and the development of lipid droplets [2][34].

In mice given a high-fat diet, a whole-body caveolin 1 deletion (cav1^{-/-}) reduced hepatic steatosis [35]. FABP1, the most prevalent FABP isoform in the liver [36], makes it easier for fatty acids and their acyl-CoA derivatives to be transported, stored, and used. FABP1 may also protect against lipotoxicity by binding otherwise cytotoxic FFAs and promoting their oxidation or incorporation into the triglycerides [37]. Following FABP1 ablation, hepatic triglycerides and lipid disposal pathways (fatty acid export and oxidation) are decreased in fasted mice. This finding suggests that decreased liver triglyceride levels are related to reduced hepatic lipid uptake, at least in a fasted state when lipid flux to the liver is increased [38][39]. As compared to controls, patients with NAFLD had higher levels of hepatic FABPs mRNA [40][41]. Therefore, increased intracellular trafficking of fatty acids in the lipid-rich liver of NAFLD patients may be diverting toxic fatty acids to storage, thereby encouraging steatosis. DNL enables the liver to convert acetyl-CoA into fresh fatty acids. Acetyl-CoA carboxylase (ACC) first transforms acetyl-CoA into malonyl-CoA, and fatty acid synthase (FAS) subsequently transforms malonyl-CoA into palmitate [42]. Before being eventually stored as triglycerides or exported as VLDL particles, new fatty acids may subsequently experience a variety of desaturation, elongation, and esterification stages. Increased DNL can therefore result in hepatic steatosis, hypertriglyceridemia, and/or steatohepatitis, but it can also do the opposite [43]. According to a study,

DNL was higher in NAFLD patients than in controls [44]. Two essential transcription factors, carbohydrate regulatory element binding protein (ChREBP) and SREBP1c, are primarily responsible for controlling the transcriptional regulation of DNL [10][42][45].

Hepatic triglyceride levels are higher in transgenic mice overexpressing SREBP1c, which is consistent with its lipogenic role, while SREBP1c knockout mice exhibit decreased expression of lipogenic enzymes [46][47]. SREBP1c expression is increased in patients with NAFLD. Compared to wild-type controls, ChREBP knockout mice have been shown to have a 65% reduction in hepatic fatty acid synthesis [48]. They also have increased insulin resistance, delayed glucose clearance, and severe intolerance to simple sugars like fructose and sucrose, which cause death in most mice. Adenovirus-mediated ChREBP overexpression in high-fat-fed mice led to hepatic steatosis and elevated DNL [49]. ChREBP was revealed to be one of the main regulators of DNL in NAFLD, upregulating genes coding for ACC1 and FAS [50], but SREBP1c was downregulated in patients with NAFLD compared to healthy controls. Both human patients and animal models of NAFLD showed increased expression of downstream targets ACC and FASN in response to high SREBP1c [46][47][50]. When taken as a whole, increased lipogenesis and lipid accumulation in NAFLD suggest that DNL may be a good therapeutic target. The majority of fatty acid oxidation takes place in the mitochondria and is regulated by PPAR α [51][52]. FAO is mediated by cytochromes, peroxisomes, and mitochondria in mammalian cells [52][53]. Fatty acids are processed mostly through peroxisomal β -oxidation since the mitochondria are unable to oxidize very-long-chain fatty acids [52]. However, in cases of lipid overload, such as in NAFLD, cytochrome ω -oxidation also plays a role [54]. However, these processes produce a significant quantity of reactive oxygen species (ROS), oxidative stress, and toxic dicarboxylic acids, which may promote inflammation and the development of disease [54]. Moreover, in comparison to patients with less severe steatosis or non-steatosis controls, patients with more severe steatosis had increased expression of genes involved in mitochondrial and peroxisomal β -oxidation [55]. According to several studies, activation of PPAR α causes the transcription of several FAO-related genes in the mitochondria, peroxisomes, and cytochromes, lowering the levels of hepatic lipids [51][52][55][56].

Hepatic steatosis is the outcome of PPAR α knockout in ob/ob mice, suggesting the significance of PPAR α in controlling hepatic lipid metabolism [57]. As a result of several studies, PPAR α was downregulated in NASH patients compared to steatosis patients and healthy controls [58][59] and PPAR α expression declined as the NAFLD activity score and fibrosis stage increased [58]. Thus, PPAR α expression may influence both inflammation and several features of NASH progression, in addition to regulating lipid homeostasis. Lipid oxidation and oxidative damage to mitochondrial DNA further reduce mitochondrial function, creating a self-reinforcing feedback loop that worsens oxidative stress and mitochondrial dysfunction [51]. The hepatic steatosis and compromised mitochondrial β -oxidation in mice heterozygous for mitochondrial trifunctional protein are accompanied by a compensatory increase in CYP2E1-facilitated FAO and oxidative stress [60][61]. Increased CYP4A11, a crucial fatty acid-metabolizing enzyme also found in the cytochromes, has been observed in NAFLD patients, which is consistent with increased cytochrome-mediated FAO [62]. Therefore, one crucial event in steatosis and NASH may be an increase in FAO in cytochromes, with the increased ROS produced by the CYP enzymes aggravating hepatic oxidative stress and, subsequently, worsening liver damage. Peroxisomes are the final of the three organelles crucial to fatty acid metabolism and hepatic lipid regulation. Targeting this system causes hepatic lipid accumulation and fibrosis,

oxidative stress, and inflammation, emphasizing the role of peroxisomal FAO in NAFLD and NASH [63]. This effect can also be caused by deficiencies in ACOX, the enzyme that catalyzes the first step in peroxisomal FAO. The peroxisomes produce ROS as they oxidize fatty acids, much like ω -oxidation in the cytochromes; similarly, the peroxisomes may cause oxidative stress and hasten the onset of disease [55]. The liver is not only the source of lipid imbalance, but low muscle function has been reported to influence NAFLD. Myokines are cytokines or peptides that are produced by muscle fibers and have been reported to have an influence on lipid metabolism and liver function in relation to exercise [64]. Some recent studies showed similar pathophysiological mechanisms between geriatric syndrome Sarcopenia and NAFLD. The skeletal muscle mass index (SMI) and hepatic steatosis have been negatively correlated among investigated type 2 diabetes patients and low SMI could increase the risk of NAFLD [65][66]. To address this issue, several nutritional strategies for improving muscle mass were investigated [67]. For example, adequate protein, vitamin D, alkaline diets, dairy, and omega-3 fatty acids shown to have positive impact on muscle strength in middle age to later life that could be able to help in reducing the risk of NAFLD. Further, a ketogenic diet was reported to help in the management of sarcopenic obesity, which has similar mechanisms to that of NAFLD [68].

5. Export of Lipids in Very-Low-Density Lipoprotein (VLDL)

Fatty acids can only be exported from the liver after being combined with cholesterol, phospholipids, and apolipoproteins in water-soluble VLDL particles since they are hydrophobic in nature [69][70]. Apolipoprotein B100 (apoB100) is lipidated in the endoplasmic reticulum by the enzyme microsomal triglyceride transfer protein (MTTP), which results in the formation of VLDL particles. The developing VLDL particle is subsequently transported to the Golgi apparatus, where it undergoes further lipidation until it becomes a mature VLDL particle [8]. The number of triglycerides in a VLDL particle can vary significantly, even though each VLDL particle relates to one apoB100 molecule, which is necessary for the VLDL export [69]. MTTP and apoB100 are therefore essential for regulating hepatic lipid homeostasis and hepatic VLDL secretion. As a result, patients with genetic abnormalities in the apoB or MTTP gene (i.e., hypobetalipoproteinemia and abeta proteinemia, respectively) are more likely to develop hepatic steatosis because of defective triglyceride export [71][72]. Although moderate exposure to fatty acids increased apoB100 secretion, prolonged exposure causes ER stress and apoB100 posttranslational degradation, which decreased apoB100 secretion both in vivo and in vitro [73][74]. As a result, ER stress is linked to the progression of NAFLD through apoB100 inhibition. If the diameter of the sinusoidal endothelial pores prevents the secretion of very big VLDL particles, this restriction may eventually lead to lipid retention and NAFLD [75]. While mRNA levels of apoB100 and MTTP were shown to be greater in patients with NAFLD compared to controls, failure to increase the amount of released VLDL particles could imply insufficient apoB100 levels as a precipitating factor in NAFLD [40][76]. MTTP levels were lower in NAFLD patients with more severe steatosis (>30%) compared to healthy controls, which raises the possibility that intracellular lipid accumulation may also directly impede lipid export [40].

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