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Hepatic Lipid Homeostasis in NAFLD

Shuo Zhang, Bing Ji, Changqing Yang and Li Yang

Abstract

Non-alcoholic fatty liver disease (NAFLD) is currently the most common liver disease, affecting 25% of world population. Hepatic steatosis has 60–90% prevalence among obese patients. It is also associated with multitude of detrimental effects and increased mortality. This narrative chapter investigates hepatic lipid homeostasis in NAFLD, focusing on the four molecular pathways of hepatic steatosis to lipid homeostasis in the liver. Hepatic steatosis is a consequence of lipid acquisition pathways exceeding lipid disposal pathways. In NAFLD, hepatic uptake of fatty acids and de novo lipogenesis surpass fatty acid oxidation and lipid export. The imbalance of the hepatic lipid may promote cellular damage by inducing oxidative stress in peroxisomes and cytochromes, especially with compromised mitochondrial function. Lipid export may even decrease with disease progression, sustaining the accumulation of lipids. NAFLD has a complex molecular mechanism regulating hepatic lipid homeostasis. Thus, as well as inter-individual differences, any intervention targeting one or more pathway is likely to have consequences on multiple cellular signaling pathways. We should be taken into careful consideration when developing future treatment options for NAFLD.

Keywords: non-alcoholic fatty liver disease, lipid metabolism, fatty acids uptake, de novo lipogenesis, triacylglycerol synthesis, lipophagy, very-low-density lipoprotein secretion

1. Introduction

Non-alcoholic fatty liver disease (NAFLD) is a spectrum of liver disorders defined by the presence of steatosis in more than 5% of hepatocytes with little or no alcohol consumption [1]. NAFLD is also associated with obesity, insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, hyperlipidemia, and metabolic syndrome. Currently, NAFLD is increasing at approximately to be 25% in the general adult population [2–4] and 10% among children [5]. It encompasses six histological subtypes: simple liver steatosis, non-alcoholic steatohepatitis (NASH), non-alcoholic fibrosis, cirrhosis, hepatocellular carcinoma (HCC), and liver transplantation [6]. The global prevalence of NASH has been estimated to range from 3–5%. NAFLD is also associated with increased mortality, particularly due to cardiovascular disease, hepatocellular carcinoma, and liver-related events [7].
All of these complications of NASH can put significant health, economic, and patient-experience burdens to the patients and the society [8].

Hepatic steatosis is the hallmark of NAFLD, which also encompasses hepatic inflammation, hepatocyte damage, and even fibrosis, highlighting the potentially progressive nature of the disease. Although fibrosis also occurs in patients with steatosis alone, NASH has even higher rates of progression and overall mortality in NAFLD [9]. Additionally, hepatic steatosis is associated with metabolic dysfunctions, such as obesity status, insulin resistance, dyslipidemia, and cardiovascular disease [10].

The liver is an essential central regulator of lipid homeostasis organ, which is keeping the balance between lipid acquisition and disposal [11]. The liver acquires lipids through the uptake of circulating fatty acids (FAs) and via de novo lipogenesis (DNL) and be disposed of through fatty acid oxidation (FAO) in the mitochondria, peroxisomes, and cytochromes and through export as very low density lipoprotein (VLDL) particles. Lipid accumulation is the result of lipid acquisition pathways exceeding disposal pathways consequently. The disruption of one or more of these pathways may precipitate the retention of fat within the liver and the subsequent development of NAFLD. These processes are closely regulated by complex interactions between hormones, nuclear receptors, and transcription factors, keeping hepatic lipid homeostasis under tight control [12].

However, molecular mechanisms of hepatic lipid homeostasis in NAFLD are not fully elucidated. This chapter explores current insights into these four pathways and the molecular mechanisms regulating the pathological aggregation of NAFLD, discussing processes that may be instrumental in the development and progression of hepatic steatosis.

2. Hepatic FAs uptake

2.1 Plasma non-esterified FAs

There are several sources of FAs, including uptake from the blood and DNL, of which uptake from the blood is the major source of FAs for esterification into triacylglycerol (TG) in most conditions (Figure 1). The intracellular hydrolysis of TG in the adipose tissue is the largest contribution of FAs uptake from the blood [13], which is under the control of insulin. Insulin inhibits the activity of the two major lipolytic enzymes, including adipose triglyceride lipase (ATGL) and hormone-sensitive lipase. This dynamic process of FA uptake is upregulated during fasting conditions or insulin resistance, while downregulated during post-prandial period [14]. Although plasma concentration of FAs is often elevated in obesity and NAFLD, indicated the effect of insulin resistance, the relationship between insulin resistance and lipolysis is complex. It is identified that FAs release per kilogram fat mass is reduced in obesity, which might be associated with the downregulation of ATGL and hormone-sensitive lipase in adipose tissue [15]. In addition, the elevated postprandial FAs concentration could also be explained that insulin resistance reduces the insulin-mediated inhibition of adipose tissue TG hydrolysis in obesity [16]. Except for the condition of the body itself, the type and amount of dietary fat are also associated with subcutaneous adipose tissue lipolysis. Study found that high-fat diet could reduce the post-prandial suppression of adipose tissue lipolysis compared with moderate-fat diet [17]. Similarly, another study demonstrated that compared with unsaturated fat or free
Hepatic Lipid Homeostasis in NAFLD
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Once flow to the hepatic vein, FAs are transported across the plasma membrane, mainly via transporter-mediated mechanisms, which is predominately mediated by fatty acid transport proteins (FATP), fatty acid translocase (FAT), also referred to as cluster of differentiation 36 (CD36), and caveolins located in the hepatocyte plasma membrane [19]. Studies found that the knockdown of FATP2 or FATP5, FATP isoforms primarily in the liver, reduces hepatocyte FAs uptake and further reverses steatosis [20, 21], indicating the FATP-mediated facilitation of steatosis. For CD36, it is regulated by peroxisome proliferator-activated receptor (PPAR) γ, pregnane X receptor, and liver X receptor (LXR) to facilitate long-chain FAs transportation. Studies identified that high-fat diet (HFD) upregulates mRNA and protein expression of CD36 and further aggravates hepatic steatosis, while liver-specific knockout of CD36 downregulates hepatic lipid levels and improves insulin resistance [22, 23]. CD36 is located in the hepatocyte plasma membrane in steatosis and NASH, while the expression of which is week in cytoplasm of hepatocytes in normal livers, which may indicate that the translocation of CD36 protein from cytoplasm to membrane could induce NAFLD progression (Figure 2) [24]. Caveolins are the third kind of transport-mediated protein, of which caveolin 1 is increased and mainly located in the centrilobular zone 3, the most severe part of sugar-enriched diet, diet enriched in saturated fat was associated with higher adipose tissue lipolysis [18].

Figure 1.
Hepatic lipid metabolism. The homeostasis of intrahepatic lipid is governed by the four major pathways. Fatty acids (FAs), derived from blood circulation or de novo lipogenesis, can be stored in the form of lipid droplets (LDs). Conversely, FAs could be oxidized into acetyl-CoA as a substrate of ketone bodies, cholesterol, or glucose. FAs can also be esterified into triglyceride, which could form very low-density lipoprotein (VLDL) via apolipoprotein (Apo) B100 and microsomal TG transfer protein (MTTP) and further excreted from the liver.
Non-alcoholic Fatty Liver Disease - New Insight and Glance into Disease Pathogenesis

steatosis in the liver with NAFLD. Study found that the upregulation of caveolin 1 might have clinical benefits in alleviating lipid accumulation in NAFLD [25, 26].

When uptake into cytoplasm, this hydrophobic FAs is binded with fatty acid-binding proteins (FABP) 1, the predominant isoform in the liver, to shuttle between different organelles. FABP1 could bind with cytotoxic-free FAs and promote its...

Figure 2.
Hepatic lipid metabolism in NAFLD. In NAFLD, cluster of differentiation 36 (CD36), fatty acid transport protein (FATP)-2 and -5 mediates uptake of circulating lipids increases. Fatty acid binding protein (FABP) 1 is increased in the early stage of disease and may decline with disease progression, which lead to lipotoxicity deterioration and disease progression. As for de novo lipogenesis, elevated sterol regulatory element-binding protein 1c (SREBP1c) and declined carbohydrate regulatory element-binding protein (ChREBP) enhance the downstream expression of acetyl-CoA carboxylase (ACC) and fatty acid synthase (FASN) in NAFLD. For lipid disposal, mitochondrial dysfunction may lead to increased generation of reactive oxygen species (ROS) and utilization of cytochrome- and peroxisomal-mediated oxidation. Meanwhile, lipid export compensates for increased hepatic triglyceride levels in the early stage of disease. While the levels of microsomal triglyceride transfer protein (MTPP) and apolipoprotein B100 (ApoB100) may be decreased, therefore limiting very low density lipoprotein (VLDL) export and facilitating lipid accumulation in NASH. Green arrow: Increased expression. Red arrow: Decreased expression. PPAR, peroxisome proliferator-activated receptor.
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oxidation and incorporation into TG, protecting the effect of lipotoxicity. In stage of
steatosis, overexpression of FABP1 protein might enhance lipid flux to compensate
lipotoxicity. While in the mid or late stage of NAFLD, presented as mild or advanced
fibrosis, the level of FABP1 protein undergoes a series of decline, which leads to
lipotoxicity deterioration and disease progression [27, 28].

2.2 Dietary chylomicrons

The contribution of dietary fat, in form of chylomicron remnants or chylomicron-
derived spillover non-esterified fatty acids (NEFA), to liver fat accumulation depends
on the amount and frequency of fat intake [29]. Chylomicron-derived TG is hydro-
lysed by lipoprotein lipase and mainly took up by adipose tissue, the rest of which is
absorbed into the liver either by the LDL receptor (LDLR) or by the LDLR-related
protein 1 (LRP1) [13, 30]. Once absorbed in the liver, chylomicron is hydrolysed by
hepatic lysosomes to release FAs. In both obesity and NAFLD, hepatic expression of
LDLR and LRP1 could be downregulated, which might be associated with the higher
plasma concentrations of TG in these patients. Therefore, hepatic expression of LDLR
and LRP1 participate in modulating the dyslipidemia and in preventing oxidized
LDL-mediated liver injury.

3. FAs and triacylglycerol synthesis

3.1 De novo lipogenesis

Except uptake of circulating FAs, DNL enables liver to synthesize FAs by
using non-lipid precursors (such as sugars and proteins) [31]. The production of
acetyl-CoA initially provides the substrate required for DNL, which is converted to
malonyl-CoA by acetyl-CoA carboxylase (ACC) and malonyl-CoA is then converted
to palmitate by fatty acid synthase (FASN) [32]. The transcriptional regulation of
DNL is mainly regulated by two transcription factors: sterol regulatory element-
binding protein 1c (SREBP1c) and carbohydrate regulatory element-binding
protein (ChREBP), which both stimulated by the activation of LXR and by nuclear
translocation to activate target gene transcription [33, 34]. Studies identified that in
NAFLD, SREBP1c expression is elevated, which is in agreement with hepatic TG lev-
els, while SREBP1c knockout decreases the expression of lipogenic enzymes [33]. In
addition, SREBP1c induces lipogenesis elevation and harmful lipid species accumu-
lation, which might interfere with insulin signaling and therefore indirectly leads to
the development of hepatic insulin resistance. When SREBP1c elevated, the expres-
sion of downstream targets ACC and FASN is accordingly increased in NAFLD [33,
35]. Although study demonstrated that knockout ACC1 could decrease hepatic lipid
accumulation and inhibit DNL process, it may reactivity increase the expression of
ACC2, which inhibits mitochondrial β-oxidation and leads to hepatic steatosis [36].
ACC1/2 inhibition could be a new option to improve hepatic steatosis in NAFLD
[33]. As for another transcription factors, ChREBP participates in fructolysis, gly-
colysis, gluconeogenesis, and DNL pathways could mediate carbohydrate-associated
DNL rather than induced by HFD [37]. Study found that high-fructose feeding could
increase hepatocellular carbohydrate metabolites, expression of ChREBP target
genes, and hepatic steatosis [38]. Inhibiting ChREBP expression could downregulate
glucose-induced lipogenesis, which further reduces hepatic TG content and protect
steatosis [39]. On the other hand, ChREBP knockout enhances cholesterol synthesis and its lipotoxicity and therefore induces hepatic steatosis, which may indicate the hepatoprotective effect of ChREBP [40].

Synthesized FAs may undergo a series of steps including desaturation, elongation, and esterification, and therefore ultimately being stored as a form of TG or exported in the form of VLDL particles. DNL was independently associated with intrahepatic TG levels [29]. Abnormally elevated DNL, occurred in NAFLD, could lead to the excessive production of saturated FAs (like palmitate), which induces steatohepatitis [41]. Besides, elevated DNL might also lead malonyl-CoA to inhibit the activity of carnitine palmitoyl transferase 1 (CPT1) suppressing hepatic FAs oxidation and increase ceramide synthesis from palmitoyl-CoA causing mitochondrial dysfunction, oxidative stress, and cell death. The above three effects may indirectly induce intrahepatic TG accumulation. Therefore, inadequate suppression of DNL is a feature of liver lipid accumulation in NAFLD.

3.2 Triacylglycerol synthesis

TG, synthesized by glycerol-3-phosphate acyltransferase (GPAT) or monoacylglycerol pathway via esterify fatty acyl-CoAs, is the major form of fat accumulated in the liver with NAFLD. The accumulation of TG in the liver, proved to be related to insulin resistance, is due to the abnormal balance between the hepatic DNL, TG synthesis, hepatic lipolysis, and lipid secretion. Although TG synthesis primarily occurs at the endoplasmic reticulum (ER), it can also occur at lipid droplets (LDs), mitochondria, and the nuclear envelope [42]. Several studies indicate that mitochondrial GPAT1 occupies 30–50% of the total GPAT activity in the liver, participating in hepatic steatosis [42]. The overexpression of GPAT1 in the rat liver was reported causing hepatic steatosis and insulin resistance in the absence of obesity or high-fat feeding [43]. In contrast, GPAT1 knockout mice showed remarkably lower hepatic TG concentrations and were prevented from hepatic steatosis and hepatic insulin resistance induced by HFD [44]. Inhibiting the activation of GPAT-1 might mitigate the progression of NAFLD.

4. Formation of hepatic LDs

LDs are specialized and dynamic cytosolic organelles, which mainly consist of a phospholipid monolayer with a core of neutral hydrophobic lipids (mostly TG and cholesterol ester, CE) [45]. As lipid storage reservoirs, LDs regulate the in- and out-flux of lipids, controlled by protein targeting process to prevent their accumulation and conversion to a toxic species. The most frequent proteins found in LDs are PLINs, especially PLIN2 and PLIN3 [21], which are involved in the formation of the LDs, during which enzymes including diacylglycerol O-acyltransferase 1, 2 (DGAT1, 2) and glycerol-3-phosphate acyltransferase 4 (GPAT4) localize around the droplet surface and further synthesize TG to store in the LDs. Researches hypothesized that LDs are formed when neutral lipids accumulate on the membranes of the ER, during which a lens is initially formed and then transforms into a budding LDs, and eventually buds off into the cytoplasm [46, 47].

The initial size of the LDs, fusion of cytoplasmic LDs, and in situ TG synthesis contributed to LDs growth. LDs form in the ER, where neutral lipids accumulate within the leaflet of the membrane bilayer. Once formed, small nascent LDs could be
mediated by cell death-inducing DFFA-like effector proteins (CIDE), which lead to the fusion and formation of the large LD [45]. Under fasting or steatosis conditions, CIDEA and CIDEC could be induced to promote LD fusion [48, 49]. In addition to LDs fusion, there exists a potential phenomenon that lipid synthesis directly occurred on the surface of LDs or at newly formed LD-ER membrane bridges, which may also result in LDs expansion. Besides, TG synthesis such as acyl-CoA synthetases as well as the acyltransferases GPAT4 and DGAT2 could expand LD monolayer membrane by inducing excessive TG into the LD core [47, 50]. Once reaching critical concentration, LDs are budded and excreted into the cytoplasm, referred to as a phase separation of the bilayer, and continue to grow the size of LDs. As for LDs budding, in vitro studies recently found that several factors could drive the differences in the phospholipid composition between the two leaflets, result in tension asymmetry, which therefore favor budding toward the side with lower monolayer tension [51]. Fat storage-inducing transmembrane protein 2 (FIT2), an integral endoplasmic reticulum membrane protein with lipid-phosphate phosphatase activity, is required for correct budding of nascent LDs, which might promote LDs budding by inducing membrane asymmetries between the ER bilayers. Besides, other factors, including the asymmetric insertion of proteins at the bilayer, the asymmetric acting of lipid-modifying enzymes on leaflets of the bilayer, or an asymmetric refill of newly synthesized phospholipids, may also lead to the asymmetric surface tension of the leaflets.

5. Lipid mobilization and degradation

5.1 Lipolysis

In hepatocytes, lipolysis and lipophagy together participate in lipids mobilization, which are further degraded by β-oxidation. The lipolysis of LDs involves the coordinated response of surface proteins and corresponding enzymes. Intracellular lipolysis can be divided into neutral and acid lipolysis, depending on the pH value and the corresponding subcellular location.

Neutral lipolysis of TG occurs in the cytoplasm with neutral pH, during which the TG and CE stored in LDs are directly degraded by the consecutive action of the three neutral lipases, including patatin-like phospholipase domain-containing protein 2 (PNPLA2), LIPE/HSL (lipase E, hormone-sensitive type), and monoglyceride lipase (MGL) [52]. Studies found that ATGL encoded by the patatin-like phospholipase domain-containing protein 2 (PNPLA2) gene may participate in NAFLD, of which ATGL knockout leads to LDs accumulation, while overexpression of ATGL could alleviate hepatic steatosis and increase FAs oxidation [53, 54]. Recent study identified that despite enhancing hepatic steatosis, ATGL/PNPLA2 deficiency may decrease hepatic lipolysis and increase PPARδ, which protects hepatocyte from inflammation and ER stress [55]. HSL was considered a rate-limiting enzyme for TG hydrolysis. HSL deficiency, characterized by relatively mild forms of dyslipidemia and hepatic steatosis, manifests in a more benign phenotype than does ATGL deficiency [56]. Besides, HSL could bind to CHREBP to prevent its translocation into the nucleus and downregulate its transcriptional activity of CHREBP [57]. MGL is the rate-limiting enzyme of monoacylglycerol (MG) degradation that derives from phospholipids or TG. Study found that MGL deficiency in mice leads to MG accumulation, minor changes of plasma VLDL metabolism, and a moderate protection from diet-induced hepatic steatosis [58]. Besides, MGL inhibition could attenuate LPS-induced
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inflammation in liver [59]. Hypoxia training may induce MGL expression and amelio-
rate hepatic steatosis [60].

Acid lipolysis, mediated by lipases such as the lipase A and lysosomal acid (LIPA/ LAL), occurs in acidic pH inside lysosome, which could hydrolyze lipids delivered into lysosomes through receptor-mediated endocytosis of lipoproteins and lipophagy and further produce free cholesterol and FAs [61]. The reduction of LAL activity causes intra-lysosomal CE accumulation and lowers free cholesterol in cytosol, which could induce transcription factor promoting lipogenesis and synthesis of cholesterol and of VLDL [62]. Clinical study has demonstrated that blood LAL levels at different stages of NAFLD evolution are gradually declined [63]. In addition, impaired LAL activity appears specific to NAFLD in the context of liver disease.

5.2 Lipophagy

In addition to the actions of lipolysis, lipophagy plays a role in lipid mobilization and degradation in hepatocytes (Figure 3). Lipophagy could act as the downstream of lipolysis, since large LDs could produce small LDs by re-esterification via ATGL that can subsequently be targeted by lipophagy [64]. Depending on the manner of LDs transportation into lysosomes and vacuoles, lipophagy could be divided into macro- and microautophagy [52]. Macrolipophagy involves the autophagosome-mediated LDs sequestration and their subsequent delivery to lysosomes/vacuole for degradation by lysosomal acid lipase, while microlipophagy is the process through which LDs and lysosomes take place direct physical interaction and transferation of lipids [65]. Inhibition of lipophagy could lead to TG and LDs accumulation in vitro and in vivo, a decrease in TG breakdown and a colocalization between TG components and TG or LDs proteins [52, 66]. Dysregulation of lipophagy may induce hepatic lipid accumulation and therefore lead to NAFLD.

Increasing evidence supports the ATGL-mediated interplay between lipolysis and lipophagy for different size of LDs [66]. Lysosomal inhibition has been shown to lead to the accumulation of small LDs within autophagosomes, which demonstrated that macrolipophagy primarily targets small LDs. Study identifies that ATGL participates in neutral lipolysis to decrease the size of large LDs and create small newly LDs, accessible for sequestration of macrolipophagy, via FAs re-esterification [67]. ATGL may also activate sirtuin 1 (SIRT1) to promote LDs degradation by macrolipophagy [68]. Besides, ER stress inhibits macrolipophagy by downregulating the fusion between the autophagosome and the lysosome, which could lead to accumulation of ubiqui-
tinated proteins and LDs that in turn increase ER stress and reactive oxygen species (ROS) production. HFD-induced mice liver may lead to the altered lipid composition of autophagosomes and/or lysosomes, which in turn affects their fusion and impaired lipophagy [69]. In addition, excess nutrient supply may alter the upstream kinase pathways of lipophagy and impair its function. The MAP3K5/ASK1 (mitogen-activated protein kinase 5), a regulator of the MAPK signaling cascades, negatively correlates with hepatic lipids accumulation and NASH scores, and positively correlates with TG level, suggesting its macroautophagy-related protective role [70], on the other hand MAP3K5 inhibition is reported to reduce hepatic lipid accumulation and inflammation [71]. The effect of MAP3K5 on NAFLD may need to be further investigated.

In some cases, lysosomes can directly engulf one relatively large LD, supporting the existence of microlipophagy in hepatocytes. Compared with macroautophagy, microlipophagy may be a more efficient pathway for small LDs degradation without
Figure 3.
A scheme of the lipophagy process. Lipophagy caused by nutrient deficiency can be divided into five main stages: (1) initiation, (2) nucleation, (3) extension, (4) fusion, and (5) degradation. The increase of cAMP/ATP ratio can activate AMPK, which inhibits mTORCs and activates ULK1/2 through direct or indirect phosphorylation. The formed ULK1/2-ATG13-ATG101-focal adhesion kinase family interacting protein of 200 KD (FIP200) complex activates Beclin 1 and interacts with UVRAG, autophagy, and Beclin 1 regulator 1 (AMBRA1), VPS34 phosphoinositide 3-kinase regulatory subunit 4 (PI3KR4, such as VPS15) binds to form phosphatidylinositol 3-phosphate (PI3P) and connects with WD repeat protein interacting with phosphoinositides (WIPIs) to participate in the nucleation and elongation. In the elongation stage, ATG7 and ATG10 ligases connect ATG12 with ATG5 and combine with polyprotein ATG4 to form a complex by promoting ATG7 (E1) and ATG10 (E2). Pro-LC3-I is combined with phosphatidylethanolamine (PE) through ATG4, ATG7, and ATG3 to form LC3-II. LC3-II binds to the expanding autophagy membrane, recruits transporters such as P62/SQSTM1, and selects and wraps components such as cytoplasm or organelles in cells. Closed autophagosomes fuse with lysosomes to produce autophagy lysosomes, causing lumen acidification, hydrolase activation, and content degradation.
using autophagosomes [52]. Studies have reported that the process of microlipophagy needs the core TG machinery [72, 73], while others demonstrate that microlipophagy does not require core TG proteins [74]. At present, there is insufficient research on the correlation between microlipophagy and NAFLD, and studies are needed to unveil its precise mechanism.

5.3 Hepatic FAs oxidation

Hepatic FAs oxidation (FAO), commonly induced by low-circulating glucose concentrations, occurs mainly in the mitochondria to provide energy, which is controlled by PPARα [75]. FAs are transported into the mitochondria via CPT1 situated in the outer mitochondrial membrane and preferably metabolized via peroxisomal β-oxidation.

The action of PPARα is upregulated by FAs and glucagon and suppressed by insulin. PPARα activation could induce the transcription of FAO-related genes in the mitochondria, peroxisomes, and cytochromes, which therefore reduces the level of hepatic lipids [76]. PPARα knockout could lead to hepatic steatosis in mice, emphasizing the critical role of PPARα in promoting FAO and preventing hepatic lipid accumulation [77]. However, studies of FAO are conflicting in patients with NAFLD. Increased FAO might be a compensatory response in NAFLD to reduce the lipids accumulation and lipotoxicity, which could also produce ROS to induce oxidative stress. Compared to patients with less severe steatosis or non-steatotic controls, the expression of β-oxidation-related genes was higher in patients with more severe steatosis [78]. Combination of stable isotope-labeled tracers identified that fasting mitochondrial oxidation was twice as high in patients with NAFLD than in those without NAFLD [79]. FAs oxidation and its oxidative damage to mitochondrial DNA occur in NAFLD, which could further impair mitochondrial function, resulting in a vicious cycle and alteration of mitochondrial ultrastructure [79]. Study found that FAO and the rate-limiting enzyme in β-oxidation of hepatic mitochondrial were reduced in definite NASH compared with no disease controls [80]. In addition, FAs-metabolizing enzyme located in the cytochromes such as CYP2E1 and CYP4A11 elevates in the context of NAFLD. Increased FAO in cytochromes may induce excess accumulation of ROS and exacerbation of hepatic oxidative stress, which could lead to hepatic steatosis.

6. Hepatic FAs secretion

Except FAO, non-oxidized FAs in the liver could be esterified into TG and then used for VLDL secretion. During this time, circulating lipids could undergo a series of process, including internalization, procession and incorporation into TG, CE and membrane lipids, and TG secretion, by which hydrophobic FAs are released into the blood stream as the form of VLDL [81]. VLDL is initially formed with the transfer of a apolipoprotein B100 (ApoB100) from the rough to the smooth ER, in which a primordial VLDL particle is form by the addition of TG via microsomal TG transfer protein (MTTP). Then, the nascent VLDL particle is transferred to the Golgi apparatus and further forms a mature VLDL particle [82].

The link has been established between increased VLDL secretion and metabolic diseases [81, 82]. Although studies found that the greater availability of TG and higher MTTP activity could promote VLDL particle production and plasma TG
concentrations [82, 83], there do not exist a definite positive correlation between plasma TG concentrations and the hepatic steatosis. In response to excess hepatic fat, NAFLD patients actually secrete more VLDL-TG than do subjects without NAFLD. ApoB100 and MTTP are associated with VLDL secretion, and serve as key components in hepatic VLDL secretion and in maintaining hepatic lipid homeostasis. The transcription of MTTP could be upregulated by PPARα and its expression parallels with ApoB100 secretion, while insulin could reduce hepatic lipid secretion by inducing ApoB100 degradation and suppressing MTTP synthesis, which downregulates both ApoB100 and MTTP [83, 84]. In normal liver, high level of insulin levels during post-prandial state facilitates the mobilization of dietary lipids rather than hepatic VLDL, while the selective hepatic insulin resistance in NAFLD may induce insulin to stimulate DNL without inhibiting VLDL production, indirectly increasing the secretion of VLDL. Although VLDL particles overproduction has been reported in patients with NAFLD, ApoB100 secretion is unchanged. Further study demonstrated that VLDL particles secreted as a more TG-rich and larger form than those in normal people [85]. Notably, while intrahepatic lipid accumulation increases VLDL-TG secretion, when hepatic fat content exceeded 10%, the capacity of VLDL-TG secretion is unable to compensate the lipid metabolic homeostasis. Besides, compared to no disease controls, NAFLD patients with more advanced steatosis had lower MTTP levels, which indicate that lipids accumulation may impair lipid secretion [81].

The association between dietary structure and VLDL secretion has been identified in several studies, which suggest the more significant effect of sugar than that of fat and carbohydrate on VLDL secretion. A study compared the influence of sugar-enriched diet and less sugar diet, which found that the former could significantly increase the VLDL1-TG production rate in patients with or without NAFLD [86], while the VLDL2 production rate increased only after the high sugar diet in NAFLD [86]. While for dietary fat, study found that the level of monounsaturated FAs in the diet may not affect the production of VLDL1 and VLDL2 in patients with mild hypercholesterolemia [87]. Moreover, study demonstrated that although high-carbohydrate diet could induce higher VLDL-TG concentrations and a lower VLDL-TG uptake than control diet in normal or hypertriglyceridemia individuals, two groups did not have different responses [88].

7. Diagnosis and management of NAFLD

Liver biopsy is the gold standard to diagnose NAFLD. However, this procedure is invasive, expensive, and time-consuming, which limits its clinical application [89, 90]. MRI is highly sensitive and offers the possibility to quantitate fat tissue, which might be limited by high costs. Elastography could determine the elastic properties of liver; however, the thickness of peripheral tissue contributes as limiting factor. As for serological method, although ALT shows a low specificity for NAFLD, it still be the most common diagnostic biomarker. Besides, cytokeratin-18 (CK18) could be used to diagnose NASH. Lipidomics serves as a new method and could utilize the specific signature of various lipids to identify NAFLD, of which studies found that lysosphospholipids (LPLs), TG, bis-(monoacylglycerol)-phosphate (BMP), 5-, 8-, 11-hydroxyeicosatetraenoic acids (5-,8-,11-HETEs), 9-,13-hydroxyoctadecadienoic acids (9-,13-HODEs), and short- and medium-chain TG are elevated, while phosphoinositols (PI), phosphatidylethanolamines (PE), and phosphatidylcholines (PC) are reduced [91-94].
Decreasing the synthesis and/or increasing the disposal of intrahepatic FAs has been suggested to attenuate the risk of NAFLD. Lifestyle interventions composing of diet, exercise, and weight loss remain the optimal therapeutic strategy, of which general caloric restriction is one of the most effective ways to reduce liver FAs uptake. While, compared with general caloric restriction, studies indicated the additional metabolic benefits of intermittent fasting, including a reduction of hepatic steatosis, inflammation and PKCe activation, and increased insulin sensitivity [95, 96]. A meta-analysis found that people lose at least 5% of body weight could improve hepatic steatosis and lose at least 7% of body weight could improve NASH [97]. Therefore, caloric restriction and loss weight are the important measures to relieve NAFLD.

For patients failed to achieve lifestyle modification, pharmacological medication may be needed to reduce FAs accumulation. Several studies target to inhibit either ACC or DGAT2, which could reduce DNL and therefore lower the concentration of TG [98, 99]. Meanwhile, pathways associated with insulin resistance have been demonstrated as a therapeutic target of NAFLD, including bile acid-based insulin sensitization, peroxisome proliferator-activator receptors, FGF21, and metformin. Obeticholic acid (OCA), a selective farnesoid X receptor (FXR) agonist, is the first synthetic bile acid for the treatment of NASH that showed the potential anti-inflammatory and anti-fibrotic effects in the liver [100]. Thiazolidinedione, a selective ligand of the PPARs, seems to decrease HfTAg content [101]. Additionally, saroglitazar was demonstrated lowering steatosis and ALT in mouse with NASH [102]. Moreover, supplementation with n-3 polyunsaturated fatty acid (PUFA) could also reduce the concentration of TG [103].

8. Conclusion

NAFLD is the pathological state co-mediated by several stages, involving hepatic FAs uptake, FAs and TG synthesis, hepatic LDs formation, lipid mobilization and degradation, and FAs secretion. Current studies suggest that dietary structure and genetic variants are likely to alter metabolic pathways that lead to the imbalance of hepatic FAs uptake and utilization. There exist complex mechanisms to maintain hepatic lipid homeostasis and prevent chronic lipid overload, which may indicate any intervention on lipid metabolic pathway lead to significant consequences on lipid homeostasis. Therefore, the effect of individual differences on disease occurrence and prognosis need to be awarded in further research and treatment of NAFLD.

Conflict of interest

The authors declare no conflict of interest.
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Hepatic Lipid Homeostasis in NAFLD
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21


