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ISSN 2959-409X

Dysregulated Lipid Metabolism in Non-alcoholic Fatty Liver Disease

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Abstract:

Non-alcoholic fatty liver disease (NAFLD) is a global health concern and a clinicopathological syndrome characterized by excessive fat deposition in hepatocytes. It develops in the absence of alcohol intake or other established liver-damaging factors, encompassing a spectrum from simple hepatic steatosis to non-alcoholic steatohepatitis (NASH), which may or may not progress to cirrhosis. Abnormal lipid metabolism plays a central role in NAFLD progression, driven by genetic mutations, dysregulation of transcription factors, and altered lipid species. This review introduces key genetic factors, such as TM6SF2, PNPLA3, and MBOAT7, which contribute to lipid accumulation and liver inflammation, and discusses transcription factors like SREBP1c and PPARγ that promote lipogenesis, exacerbating hepatic fat buildup. This review also explores Lipid species like triglycerides, free fatty acids, and ceramides act as signaling molecules, influencing metabolic pathways and contributing to insulin resistance, inflammation, and fibrosis. Additionally, this review discusses signaling pathways such as mTOR and AMPK modulate lipid metabolism and impact NAFLD progression. Understanding these molecular mechanisms offers potential therapeutic targets to mitigate the metabolic disturbances in NAFLD and develop effective treatments for this increasingly prevalent disease.

Keywords: NAFLD; NASH; lipid metabolism; fatty acid.

1. Introduction

Nonalcoholic fatty liver disease (NAFLD) has emerged as one of the most widespread liver disorders worldwide, with its prevalence rising significantly across various populations. Notably, its occurrence has surged in regions such as Asia and South America, where it now exceeds the rates observed in the United States and Europe [1]. The spectrum of NAFLD extends from simple steatosis to more severe stages, such as nonalcoholic steatohepatitis (NASH), and can even progress to cancer like hepatocellular carcinoma (HCC) [2]. These conditions generally result from an excessive caloric intake without

substantial alcohol consumption, differentiating them from alcohol-related liver diseases. NASH is marked by chronic inflammation and varying levels of fibrosis, with studies indicating that approximately 20% of patients with NASH may advance to cirrhosis [3]. Alarmingly, NASH can progress to HCC even in the absence of significant cirrhosis, underscoring the need for effective diagnostic and therapeutic strategies [4].

Previous research has extensively explored the complex interplay between non-alcoholic fatty liver disease (NAFLD) and lipid metabolism, underscoring the critical role that lipid homeostasis dysregulation plays in the disease's progression. Aberrations in hepatic lipid metabolism lead to excessive lipid accumulation, which induces hepatotoxic effects and contributes to the onset of NAFLD [5,6]. Dyslipidemia, typified by elevated oxidized low-density lipoprotein (ox-LDL), plasma free fatty acids (FFAs), and triglycerides (TGs), further exacerbates liver inflammation, oxidative stress, and lipotoxicity, driving disease progression [6]. Notably, these dyslipidemic changes can manifest at all stages of NAFLD, aggravating its progression and complicating treatment efforts.

Given the increasing prevalence of nonalcoholic fatty liver disease (NAFLD) and its associated severe complications, the exploration of innovative therapeutic approaches focused on lipid metabolism has become imperative. A comprehensive understanding of the metabolic pathways involved in the pathogenesis of NAFLD is essential for devising targeted and effective interventions. This review introduces the current literature on lipid metabolism in NAFLD, focusing on the roles of genetic mutation (TM6SF2, PNPLA3, and MBOAT7), transcription factors (SREBP1c and PPARγ), lipids and signaling pathways (mTOR and AMPK). It also examines the mechanisms of lipid uptake and the potential therapeutic implications of modulating lipid metabolism in NAFLD. By integrating findings from recent research, this review seeks to offer a thorough analysis of the relationship between lipid metabolism and NAFLD. It highlights the critical need for additional studies to clarify the distinct functions of various lipid species in the progression of the disease. Ultimately, the findings may inform the development of more effective, targeted therapies that address the underlying metabolic disturbances associated with NAFLD, paving the way for improved patient outcomes and reduced burden of liver-related diseases in the population.

2. Dysregulated Lipid Metabolism in NAFLD

The complex interaction between genetic factors, lipid species, and signaling pathways regulates disruptions in lipid metabolism, contributing to the advancement of NAFLD and its potential transition into more severe hepatic conditions, including NASH, cirrhosis, and HCC [2].

2.1 Effects of Gene Mutations and Transcription factors on the Dysregulated Lipid Metabolism in NAFLD

In the context of NAFLD, the lipid metabolism is significantly influenced by various genetic factors that drive disease progression. Genetic mutations in transmembrane 6 superfamily member 2 (TM6SF2), patatin-like phospholipase domain-containing protein 3 (PNPLA3), and membrane-bound O-acyltransferase domain-containing 7 (MBOAT7) are identified as three crucial contributors to lipid dysregulation in NAFLD [7]. Each of them contributes to the NAFLD through distinct mechanisms.

The TM6SF2 gene, located on chromosome 19 (19p12), contains a nonsynonymous variant (E167K, rs58542926) that significantly influences lipid metabolism by modulating the hepatic secretion of very-low-density lipoproteins (VLDL) [8]. The 19p12 locus, encompassing this particular variant, has been linked to levels of plasma triglycerides (TG) and total cholesterol (TC), and its relation to NAFLD has been established [9,10]. Initial studies suggested that TM6SF2, showing high expression in the liver, could be a key player in NAFLD [11]. Research has identified the TM6SF2 E167K variant as an independent risk factor for hepatic steatosis, frequently leading to heightened liver fat accumulation and elevated liver enzyme levels. Nevertheless, its correlation with the progression of NAFLD, including fibrosis, cirrhosis, and HCC, remains less consistently established.

The PNPLA3 gene is located on chromosome 22 (22q13.31). Of the 34 identified single nucleotide polymorphisms (SNPs) within this gene, three have been significantly associated with traits related to nonalcoholic fatty liver disease (NAFLD). Among these, the rs738409 variant is recognized as a crucial determinant in the genetic predisposition to fatty liver disease [12]. The rs6006460 (S453I) variant has been linked to reduced hepatic fat content, particularly in African American populations, whereas rs2294918 (Lys434Glu) is associated with increased alanine aminotransferase (ALT) levels [13]. In addition, I148M variant, linked to rs738409, affects lipid metabolism by altering the activity of its lipase function [7]. Normally, PNPLA3 is localized on the lipid droplet (LD) surface, functioning as a triacylglycerol (TAG) lipase. The genetic variant results in impaired lipase activity, which is essential for breaking down triglycerides in lipid droplets. Consequently, the I148M variant results in larger and more stable lipid droplets, exacerbating triglyceride accumulation and contributing to hepatic steatosis.

ISSN 2959-409X

MBOAT7 gene is located on chromosome 19(19q13.42). It influences lipid metabolism through its role in phospholipid remodeling, particularly in the acylation of lysophosphatidylinositol (LPI) [7]. The rs641738 variant in MBOAT7 results in reduced gene expression and enzymatic activity, thereby disrupting the phospholipid composition within the liver [14]. This change affects membrane dynamics and lipid droplet formation, contributing to increased lipid storage within hepatocytes [14]. Moreover, MBOAT7 deficiency has been linked to a heightened inflammation and fibrosis, as the disrupted lipid signaling exacerbates inflammatory pathways and promotes fibrotic responses [7].

Morover, numerous transcription factors involved in lipid metabolism pathways are crucial in the onset and progression of NAFLD. Among these, sterol regulatory element-binding protein 1c (SREBP1c) and peroxisome proliferator-activated receptor gamma (PPARγ) are two prominent pro-adipogenic regulators [7]. SREBP1c, part of the basic helix-loop-helix leucine zipper (bHLH-Zip) transcription factor family, operates at the intersection of sterol and fatty acid metabolism [15]. It enhances fatty acid and triglyceride synthesis by inducing the expression of key lipogenic enzymes such as acetyl CoA carboxylase, fatty acid synthase (FAS), and stearoyl CoA desaturase-1 (SCD-1), among others [15]. In NAFLD, liver X receptor activation significantly elevates SREBP1c expression, and dysregulated SREBP1c-driven hepatic lipogenesis has been observed in patients with NAFLD [16]. PPARγ, a nuclear receptor superfamily member, exists in two isoforms, PPARγ1 and PPARγ2, which bind to DNA alongside retinoid X receptor (RXR) and are activated by fatty acids and their derivatives [7]. PPARγ is involved in lipid storage. It can enhance the expression of lipid droplet (LD) proteins to boost the cell‘s capacity for lipid storage. Additionally, when PPARγ is specifically deleted in hepatocytes, it mitigates high-fat diet (HFD)-induced hepatic steatosis.

2.2 Effect of Lipids on Dysregulated Lipid Metabolism in NAFLD

Lipids are critically involved in the metabolic dysregulation associated with NAFLD, functioning as signaling molecules that modulate various metabolic pathways [17]. NAFLD is distinguished by an abnormal accumulation of lipids, especially triglycerides, within the liver, resulting in hepatic steatosis. Several specific lipids have been identified as key regulators in the abnormal hepatic lipid metabolism, contributing to the disease's pathophysiology.

One of the primary lipid species implicated in NAFLD is triglycerides (TGs). Triglycerides (TGs) typically function as the main storage and transport medium for fatty acids within the liver. Hepatic steatosis, a defining feature of NAFLD, results from the excessive buildup of triglycerides in hepatocytes. This accumulation is driven by an imbalance between lipid availability—encompassing fatty acid uptake and de novo lipogenesis —and lipid utilization, which includes fatty acid β-oxidation and very low-density lipoprotein (VLDL) secretion. Triglycerides, although initially stored as relatively inert molecules in lipid droplets, serve as a marker of dysregulated lipid metabolism. Their accumulation reflects the liver's altered capacity to process fatty acids, contributing to hepatocellular stress and downstream metabolic consequences.

Another lipid of significance in NAFLD is free fatty acids (FFAs). Insulin resistance, a key characteristic of NAFLD, may impair insulin's capacity to regulate lipolysis, leading to increased circulating free fatty acids (FFAs) [18]. These elevated FFAs are absorbed by the liver. Within adipose tissue, the surplus FFAs are esterified into triglycerides, leading to their intracellular accumulation. Additionally, elevated levels of free fatty acids (FFAs) contribute to lipotoxicity, leading to mitochondrial impairment, heightened oxidative stress, and inflammation. These factors synergistically worsen hepatic metabolic imbalances, promoting the transition from non-alcoholic fatty liver (NAFL) to NASH.

Cholesterol is another lipid that plays a significant role in NAFLD progression. The excessive accumulation of cholesterol in hepatocytes has been shown to induce endoplasmic reticulum (ER) stress, a key factor in the dysregulated metabolism of the liver.10 This ER stress leads to the activation of inflammatory pathways and promotes hepatocyte apoptosis, contributing to disease progression [19].

In addition to triglycerides, FFAs, and cholesterol, other lipid species, such as ceramides, are also involved in the deranged lipid metabolism in NAFLD. Ceramides, a class of sphingolipids, have been identified as key mediators of insulin resistance and lipotoxicity in the liver [20]. Elevated ceramide levels in NAFLD impair insulin signaling pathways, thereby worsening hepatic insulin resistance [21]. Ceramides also promote the activation of inflammatory pathways, further contributing to hepatic inflammation and fibrosis [22]. The role of ceramides in altering lipid metabolism underscores their contribution to the development of steatohepatitis and liver fibrosis, key features of advanced NAFLD. Additionally, ceramide is the precursor of S1P. S1P, a multifunctional bioactive signaling molecule produced by sphingosine kinases 1 and 2 (SPHK1 and SPHK2), interacts with five distinct sphingosine-1-phosphate receptors (S1PR1–5), thereby regulating various cellular processes, including cell growth, survival, differentiation, migration, maintenance of vascu-

lar integrity, lymphocyte trafficking, and immune function [23]. Elevated ceramide levels indicate that S1P could be significantly involved in the pathophysiology of NAFLD.

2.3 Effects of Signaling Pathways in the Dysregulated Lipid Metabolism in NAFLD

The deranged lipid metabolism in NAFLD is also modulated by various signaling pathways, which play crucial roles in preventing or promoting disease progression. AMP-activated protein kinase (AMPK) serves as a crucial regulator of cellular energy balance and plays a significant role in the dysregulation of lipid metabolism associated with NAFLD [24]. The suppression of AMPK, an essential energy sensor, is widely recognized as a primary contributor to the development of fatty liver disease and is regarded as both a cause and consequence of hepatic steatosis in NAFLD [25]. AMPK activation is integral to preserving lipid homeostasis by inhibiting fatty acid and cholesterol synthesis while promoting fatty acid oxidation (FAO) and lipid catabolism [26]. These pathways work together to prevent excessive hepatic lipid accumulation, a key feature of NAFLD, and thus help to slow disease progression [26]. AMPK confers its hepatoprotective effects through multiple mechanisms. Primarily, it suppresses lipogenesis by downregulating key lipogenic genes, including fatty acid synthase (FAS), sterol regulatory element-binding protein-1c (SREBP-1c), acetyl-CoA carboxylase (ACC), and 3-hydroxy-3-methylglutaryl-CoA reductase (HMGCR) [24]. Through the phosphorylation of ACC, AMPK reduces malonyl-CoA levels, thereby inhibiting fatty acid synthesis and promoting a metabolic shift towards FAO [24]. Additionally, AMPK upregulates the expression of carnitine palmitoyltransferase 1 (CPT1) and peroxisome proliferator-activated receptor gamma co-activator 1 (PGC1), both of which are crucial for mitochondrial FAO [24,27]. Hence, it promotes the catabolism of fatty acids, aiding in the prevention of lipid buildup. In addition to this, AMPK supports mitochondrial functional integrity, which is crucial for efficient FAO and energy production [28]. Mitochondrial dysfunction, commonly observed in NAFLD, leads to an imbalance between pro-oxidant and antioxidant systems, which exacerbates lipid peroxidation and contributes to liver damage [29]. By maintaining mitochondrial health, AMPK helps mitigate these damaging effects. Multiple signaling pathways involved in NAFLD pathogenesis interact with AMPK to regulate lipid metabolism. One such pathway is the liver kinase B1 (LKB1)-AMPK axis. LKB1 acts as an upstream kinase that activates AMPK, playing a critical role in inhibiting lipogenesis and enhancing FAO [24]. Another important pathway is the Keap1-Nrf2 axis. Using the AMPK-ULK1 (UNC-51-like kinase 1) signaling axis, AMPK induces autophagy, resulting in the degradation of KEAP1 and the consequent activation of the dysregulated Keap1-Nrf2 signaling pathway [30]. This protective signaling cascade helps shield the liver from lipotoxicity and oxidative stress, further underscoring the vital role of AMPK in combating NAFLD progression.

While AMPK primarily functions to suppress lipid synthesis and promote FAO, another pathway called rapamycin (mTOR) pathway exerts contrasting effects, particularly by promoting lipogenesis and facilitating the progression of NAFLD [31]. The mechanistic target of mTOR pathway plays a pivotal role in the abnormalities of lipid metabolism in NAFLD. In response to diverse stimuli, including high-fat diets, excessive refined carbohydrate intake, and elevated insulin production, the mTOR pathway becomes activated [32]. By activating mTOR complexes (mTORC1 and mTORC2), the pathway modulates cellular processes, including lipogenesis, nutrient absorption, and metabolism [32]. In NAFLD, the mTOR pathway promotes DNL and lipid accumulation in the liver, contributing to disease pathogenesis. mTORC1, in particular, is instrumental in regulating nutrient signaling and lipid metabolism. It enhances the expression of SREBP1. mTORC1 increases SREBP1 transcription, thereby facilitating DNL and resulting in the accumulation of TAG within the liver [33]. This process is particularly pronounced during overnutrition when the liver is unable to fully oxidize excess nutrients, further exacerbating lipid accumulation [34]. Furthermore, mTORC2 modulates the activity of carbohydrate-responsive element-binding protein 1 (ChREBP1), which plays a significant role in the development of hepatic insulin resistance and lipid accumulation - key characteristics of NAFLD [35].

Autophagy, a cellular degradation process essential for maintaining liver homeostasis, is tightly regulated by the AMPK/mTOR pathway. mTORC1 inhibits autophagy, while AMPK activation promotes autophagy, particularly under conditions of energy depletion [32]. In NAFLD, the dysregulation of autophagy may contribute to lipid accumulation and steatosis. Hence, the balance between AMPK and mTORC1 plays a vital role in the regulation of lipid metabolism and in the prevention of the progression of NAFLD.

3 Therapeutic Strategies Targeting Abnormal Lipid Metabolism in NAFLD

A key factor in the pathogenesis of NAFLD is the disruption of lipid metabolism, with particular emphasis on pathways such as FAO, de novo lipogenesis (DNL), and cholesterol synthesis. These strategies encompass pharmacological treatments and lifestyle interventions aimed at

ISSN 2959-409X

restoring hepatic lipid homeostasis.

3.1 Pharmacological Targeting of Lipid Metabolism Pathways

De novo lipogenesis refers to the hepatic synthesis of fatty acids derived from carbohydrates, playing a significant role in the development of hepatic steatosis associated with NAFLD. Therapeutic strategies aimed at inhibiting DNL have shown potential in reducing lipid accumulation. Among the most notable is the inhibition of Acetyl-CoA Carboxylase (ACC), a key enzyme in this pathway.1 The ACC inhibitor firsocostat has demonstrated promising results, especially in phase II clinical trials, where it demonstrated a notable reduction in liver steatosis among patients diagnosed with NAFLD [36]. By inhibiting ACC, firsocostat decreases the conversion of acetyl-CoA to malonyl-CoA, thereby limiting fatty acid synthesis. In addition, inhibitors of fatty acid synthase (FASN), such as TVB-2640, have also shown potential by reducing hepatic fat content in patients with NAFLD. Preclinical studies with cerulenin, another FASN inhibitor, have demonstrated similar effects in mice models. These therapies aim to halt lipid accumulation at the source, targeting the overproduction of fatty acids within the liver.

Enhancing FAO represents another critical approach to deranged lipid metabolism in NAFLD. Peroxisome proliferator-activated receptor alpha (PPAR-α) is key regulator of FAO and have been targeted by pharmacological agents to treat NAFLD [37]. Agonists of PPAR-α, such as pioglitazone, can improve insulin sensitivity and thus offer therapeutic benefits for patients with NASH [38]. These agents have been particularly effective in elderly patients with advanced fibrosis, underscoring their value in managing severe cases of NAFLD [39]. Additionally, carnitine palmitoyltransferase 1 (CPT1) inhibitors, such as etomoxir, enhance FAO and reduce hepatic lipid content, contributing to the improvement of NAFLD-associated metabolic abnormalities [40].

Modulating cholesterol metabolism is another promising avenue for NAFLD treatment. Farnesoid X receptor (FXR) agonists, including obeticholic acid (OCA), are crucial in the regulation of bile acid and cholesterol metabolism [41]. Studies have demonstrated that FXR activation can mitigate hepatic inflammation, enhance insulin sensitivity, and alleviate liver fibrosis in animal models of NAFLD [42,43]. OCA, in particular, has demonstrated efficacy in resolving NASH and improving liver histology, as evidenced by the results of the FXR Ligand Obeticholic Acid in NASH Treatment (FLINT) trial, where OCA significantly outperformed placebo in achieving NASH remission [44].

3.2 Targeted Therapies

CD36, an important fatty acid transporter involved in hepatic lipid accumulation and inflammation, has been identified as a promising therapeutic target for the treatment of NAFLD. Elevated CD36 expression has been associated with increased fatty acid uptake, insulin resistance, and steatosis in human studies [45]. Targeting CD36 expression has the potential to enhance insulin sensitivity and alleviate hepatic steatosis, making it a promising therapeutic strategy. Studies in mice have shown that CD36 inhibition not only reduces liver fat content but also improves markers of systemic inflammation, highlighting its potential to mitigate NAFLD progression [44].

3.3 Lifestyle Changes

Nutrition-based strategies continue to play a pivotal role in the treatment and management of NAFLD.. Both the Mediterranean and ketogenic diets have shown significant promise in improving lipid metabolism and reducing hepatic steatosis [46]. The Mediterranean diet, characterized by a lower intake of sugars and refined carbohydrates and a higher consumption of monounsaturated fats and omega-3 polyunsaturated fatty acids (n-3 PUFAs), provides significant anti-inflammatory effects, making it an essential dietary approach for treating NAFLD [46]. Omega-3 polyunsaturated fatty acids (PUFAs), including eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA), have been shown to decrease hepatic fat accumulation, enhance liver enzyme levels, and mitigate inflammation. These effects establish a robust theoretical foundation for their application in the treatment of NASH. On the other hand, the ketogenic diet, characterized by a reduction in carbohydrate intake alongside an increase in fat and protein consumption, has demonstrated efficacy in decreasing intrahepatic triglyceride levels and enhancing metabolic parameters in the short term [47]. However, prolonged compliance with a ketogenic diet may increase glucose intolerance in mouse models, highlighting the need for careful monitoring when considering this approach [48].

In addition, physical activity (PA) is a vital aspect of managing non-alcoholic fatty liver disease (NAFLD) and significantly contributes to the prevention of disease progression. Multiple studies have demonstrated that PA, independent of weight loss, can promote the remission of NAFLD, particularly when combined with dietary modifications [49]. Encouraging moderate exercise regimens can help reverse metabolic abnormalities associated with NAFLD and should be integrated into treatment plans.

4. Conclusion

Despite being a significant public health concern, less

approved pharmacological treatment exists for NAFLD, primarily due to its complex pathogenesis, leaving non-pharmacological interventions as the primary treatment approach. This review highlights the critical role of lipid metabolism in the development and progression of NAFLD, which may provide potential targets for pharmacotherapy. This review also highlights the intricate mechanisms underlying dysregulated lipid metabolism in NAFLD, focusing on the interplay between genetic mutations, lipid species, and signaling pathways. Genetic factors, particularly mutations in TM6SF2, PNPLA3, and MBOAT7, are critical drivers of lipid dysregulation, influencing metabolism by altering lipoprotein secretion, impairing lipase activity, and affecting phospholipid composition, thereby contributing to disease progression. Additionally, transcription factors such as SREBP1c and PPARγ significantly influence lipid metabolism, promoting lipogenesis and lipid storage, respectively. Specific lipids, including triglycerides, free fatty acids, cholesterol and ceramides, act as key mediators in the pathophysiology of NAFLD, with elevated levels initiating inflammatory responses that exacerbate liver damage. Signaling pathways involving AMPK and mTOR are crucial in regulating lipid metabolism, with AMPK serving as a protective factor against lipid accumulation while mTOR promotes lipogenesis. The implications of this research extend to potential therapeutic strategies targeting these pathways, with pharmacological interventions like ACC inhibitors and PPAR-α agonists showing promise in mitigating lipid accumulation and improving insulin sensitivity. Furthermore, lifestyle modifications, such as alterations in diet and increased physical activity, play a crucial role in the management of NAFLD. Future research should aim to clarify the molecular mechanisms underlying lipid metabolism and exploring novel therapeutic targets to enhance liver health, which could lead to more effective treatments for patients with NAFLD and its related complications.

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