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Review

Crosstalk between Lipids and Non-Alcoholic Fatty Liver Disease

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Abstract: 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. The connection between lipids and NAFLD is the main topic of the current review, along with the various therapeutic targets and currently available drugs. The importance of hepatic lipid metabolism in the progression of NAFLD is summarized with the latest results in the field.

Keywords: liver; non-alcoholic fatty liver disease; lipid metabolism; fatty acids

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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 [4–6]. 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]. One of the key mechanisms linking lipids and NAFLD hepatic lipid metabolism is shown in Figure 1. 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]. With this background, in this review we aim to cover importance of liver lipid metabolism on the progression of NAFLD.

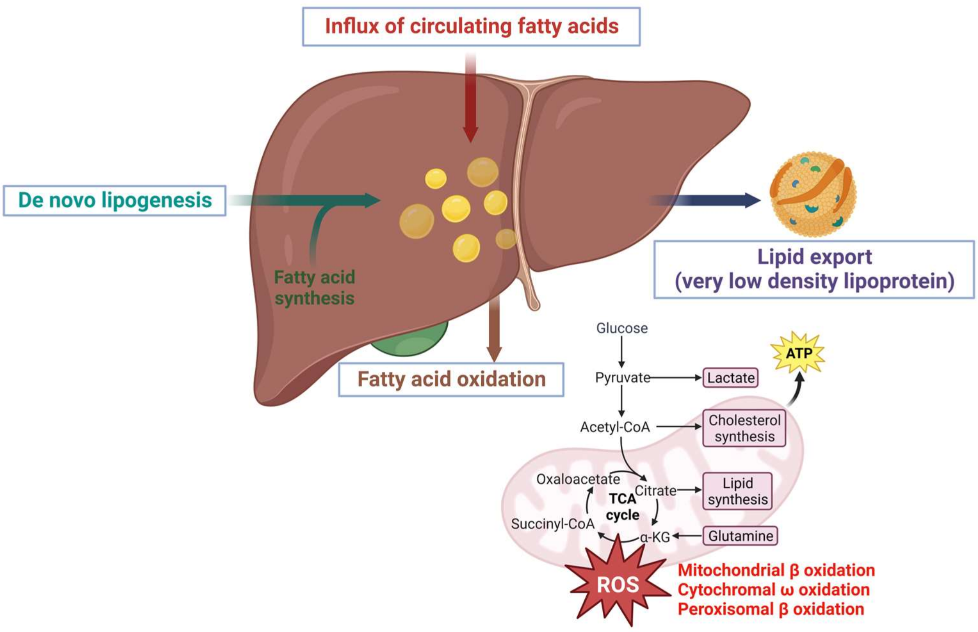

Figure 1. Key mechanisms linking lipids and NAFLD hepatic lipid metabolism (circulating lipid intake, de novo lipogenesis (DNL), fatty acid oxidation (FAO), and export of lipids as very-low-density lipoproteins (VLDLs) are the four primary mechanisms that regulate the acquisition and disposal of lipids). Created with BioRender.com. https://app.biorender.com/illustrations/64913003fa97ac5897c2774f (accessed on 18 September 2023).

2. Experimental and Clinical Technologies for Studying NAFLD Progression

The excessive lipid accumulation of the liver leads to inflammation and hepatocellular injury [16]. Comprehending lipid dysregulation in NAFLD is crucial for deciphering the intricate interplays among lipids, metabolism, and liver pathology [8]. The progressive condition of non-alcoholic steatohepatitis (NASH) can lead to the development of fibrosis, cirrhosis, and hepatocellular carcinoma in individuals with NAFLD [9]. However, currently there are no medically sanctioned therapies available for the management of NASH [17]. The lack of reliable preclinical models for prediction, the intricate nature of disease pathogenesis, and insufficient validation of pharmacological targets in humans have impeded the progress of developing efficacious treatments. The development of clinically relevant in vitro models of the disease will pave the way toward surmounting these challenges. The utilization of advanced technologies and control engineering methodologies holds the potential to reveal the underlying biology of NAFLD and provide viable therapeutic interventions [18]. At present, the integration of novel technologies such as transcriptomics, organ-on-a-chip, and micro-physiological systems, along with control engineering methodologies, holds significant potential for elucidating the underlying mechanisms of NAFLD and identifying viable therapeutic options [19,20].

The utilization of a multi-disciplinary methodology in the creation of in vitro models has resulted in the development of solutions that are considerably more intricate than conventional 2D cultures [21]. Examples of such solutions include liver-on-a-chip platforms and 3D models [22,23]. These models have the potential to serve as dependable drug screening platforms, while also facilitating a more comprehensive understanding of the disease. To better understand NAFLD, 2D (monocultures and co-cultures) and 3D cultures (liver-on-a-chip, spheroids, organoids, or collagen gel sandwiches) have recently been presented [20–23]. Their development can rely on bio-printing technology (3D bio-printed liver-like tissues) [24]. Hepatocyte cell lines and primary hepatocytes have been used in several in vitro studies to investigate how lipid metabolism is altered in NAFLD, where these investigations revealed increased DNL, decreased fatty acid oxidation (FAO), and altered lipid droplet dynamics [20]. Lipid accumulation has been linked to dysregulated lipid transporters such as the cluster of differentiation 36 (CD36) and fatty acid binding proteins (FABP) [25,26]. In this way, in vitro studies can advance our understanding of NAFLD by offering fresh perspectives on intricate physiological systems and potential treatment targets [20]. Additionally, they serve as an efficient alternative for in vivo models in the initial stages of drug development [22,27].

Using animal models in in vivo investigations, the pathophysiology of NAFLD has been thoroughly investigated [27,28]. Table 1 presents some of the reported biomarkers of NAFLD.

Table 1. Biomarkers associated with nonalcoholic fatty liver disease (NAFLD).

Samples	Biomarkers	References
Serum miRNAs	miR-122 5p, miR-1290, miR-37 3p, miR192 5p	[29]
Serum and DNA samples	ALT alanine aminotransferase	[30]
Serum and DNA samples	AST aspartate aminotransferase	[31]
Serum and plasma	CK-18 cytokeratin-18 fragments (M30, M65)	[32]
Liver	DHEA-S dehydroepiandrosterone sulfate	[33]
Serum	ELF-enhanced liver fibrosis	[34,35]
Serum	FGF-21 fibroblast growth factor 21	[36]
Liver	PIIINP N-terminal propeptide of procollagen type III	[37]
Serum	PRO-C3 N-protease cleavage site of the N-terminal propeptide of procollagen III	[38]
Serum samples	RBP4 retinol-binding protein 4	[39]
Plasma samples	Adiponectin	[40]
Serum	Ferritin	[41]
Liver	FIB-4 fibrosis-4	[42]

Hepatic lipid dysregulation has been seen in several rodent models, including genetic and high-fat diet-induced models. Recent studies have found that dysregulation of lipid metabolism pathways has been implicated in alterations in lipid synthesis, impaired β-oxidation, and altered lipoprotein metabolism [43]. Additionally, the progression of NAFLD has been linked to disruptions in gut–liver axis signaling [44]. In vivo, models remain to be an essential tool for investigating NAFLD before clinical trials [20]. Despite being closer to humans, larger animal models like rabbits [45], monkeys [27], or minipigs [46] can bring ethical challenges, be more challenging to handle, and need more money and time. In vivo modeling has demonstrated increased human translatability in investigations of NAFLD pathogenesis and evaluations of prospective therapeutic targets, while primarily employing rodents [27,47]. Human lipid dysregulation has been studied through liver biopsy samples from patients with NAFLD [48]. Studies have revealed increased levels of hepatic TG, altered lipid compositions, and diacylglycerol (DG) and ceramide accumulation. Human NAFLD has also been linked to the dysregulation of lipid metabolism genes, including SREBP-1c and PPAR-α [48–50], as described below.

A transcriptomics study found a variety of alterations in gene expression as NAFLD progressed, including several that might be helpful for prognostication and diagnosis. For instance, early NAFLD displayed minor but functionally significant alterations in gene expression [51]. Additionally, investigators verified that AKR1B10 and GDF15 are valid biomarkers of NAFLD development [51]. According to recent research, such as the function of HSD17B13 in NAFLD genetic susceptibility, retinoic acid homeostasis, which may be influenced by AKR1B10 and HSD17B14, seems significant to both carcinogenesis and the progression of NAFLD [52]. These transcriptome data from a significant number of NAFLD patients with histologically characterized ailments provide insights into the pathogenesis of the condition by finding both established and dynamic variations in gene expression that arise as syndrome advances [51]. Another transcriptomics investigation identified SREBF1, a transcription factor involved in lipid homeostasis, as a principal upstream regulator [19]. Fatty acid binding protein 5, paternally expressed imprinted gene 10, HMGCR, HMGCS1, CXCL10, and insulin-like growth factor 1 were all upregulated, whereas sex hormone-binding globulin and insulin-like growth factor 1 were found downregulated, downstream of SREBF. These molecular alterations are a result of low-grade inflammation caused by the liver's fatty acid accumulation.

Cholesterol synthesis, lipid metabolism, adipogenesis, and metabolic disease are identified among the most canonical pathways, disease networks, and disease functions. The pro-inflammatory cytokines tumor necrosis factor and IL1B, platelet-derived growth factor (PDGF BB), and beta-estradiol were identified among the most prominent upstream regulators [19]. Several cellular downstream functions, including metabolism, extracellular matrix deposition, and tumor suppression, have been found to be affected by beta-estradiol inhibition. Additionally, triciribine, an AKT inhibitor, and ZSTK-474, a PI3K inhibitor, were identified as potential drug targets that aimed to affect gene expression in the same study. Another study compared the hepatic transcriptome dynamics of healthy, normal weight and obese people with those of patients with NAFLD and NASH [53]. The most obvious pathway disruptions seen in both conditions were found linked to indicators for lipid metabolism, immunomodulation, remodeling of the extracellular matrix, and cell cycle control [8,13,16,53].

Further, mitochondrial oxidative function plays a crucial role in NAFLD progression. Mitochondrial dysfunction was often observed in NAFLD. Past studies showed an ambiguous result that either increased or decreased mitochondrial energy metabolism during NAFLD progression, which was extensively reviewed by Shum M et al. [54]. More commonly, accumulation of fat in the liver is due to insufficient mitochondrial oxidation of fatty acids due to a decrease in mitochondrial ATP-synthesizing respiration or mitochondrial fragmentation induced by c-Jun-N terminal kinase (JNK) in mouse models with steatosis or NASH. Several studies were conducted to reveal the effect of a ketogenic diet (KD) on mitochondrial function and oxidative stress associated with NAFLD. A KD forces the body to use the accumulated fat for energy and tends to increase the level of several proteins involved in oxidative phosphorylation and mitochondrial bioenergetics (ex: uncoupling proteins). A KD can also improve mitochondrial morphology by balancing the mitochondrial dynamics and reduces the reactive oxygen species. The effect of a KD on liver lipid metabolism and mitochondrial function has been recently well reviewed by

Paoli A et al. [55]. Overall, several mechanisms were proposed to address progression of NAFLD and to suggest the potential target pathways.

3. Dysregulated Lipid Metabolism and NAFLD Progression

3.1. Accumulation of Lipids Exacerbates NAFLD Progression

Lipids are crucial to NAFLD progression and development, and there are some lipids that promote the progression [51]. Lipids such as saturated fatty acid (SFA) have been linked to the development of NAFLD [56]. 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 [56,57]. 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 [58]. 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 [59]. NAFLD has been proven to benefit from omega-3 fatty acids (n-3), which are polyunsaturated fatty acids (PUFAs) [60]. Due to their anti-inflammatory and antioxidant effects, n-3 fatty acids can mitigate NAFLD development and progression [60]. In animal models, n-3 fatty acid-rich diets have been demonstrated to minimize hepatic steatosis and inflammation [61]. Sphingolipids are another group of lipids that have been investigated in relation to the development of NAFLD [62]. 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 [62].

3.2. 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 [60,63]. They do this by raising anti-inflammatory cytokines and decreasing pro-inflammatory cytokines to achieve their positive effects [64]. Monounsaturated fatty acids (MUFAs) also have been proven to decrease hepatic steatosis and inflammation [65]. 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 [66]. 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 [67]. A summary of lipids dysregulated in the progression of NAFLD is listed in Table 2.

Table 2. Summary of lipids that are dysregulated in NAFLD.

Lipids That Upregulate the NAFLD Progression	Significance in NAFLD	References
Saturated Fatty Acids (SFAs)	Lipidomic studies of liver tissues have reported a lipid imbalance characterized by elevated levels of SFAs.	[56,57]
Trans Fatty Acids (TFAs)	TFAs can increase triglyceride buildup in the liver and induce inflammation and insulin resistance	[58]
Sphingolipids	Sphingolipid metabolism is dysregulated in NAFLD, which promotes the disease's progression. Inhibition of sphingolipid pathway slows the progression of NAFLD.	[62]

Table 2. *Cont.*

Lipids That Upregulate the NAFLD Progression	Significance in NAFLD	References
Diacylglycerols (DGs)	DG species are crucial lipid signaling molecules in the development of NAFLD, where their elevation contributes to altered triglyceride, phosphatidylcholine (PC), and phosphatidylethanolamine (PE) levels characteristic of the disease.	[43]
Triacylglycerols (TGs)	Increased accumulation of TGs in hepatocytes, insulin resistance, inflammation, cell death, and fibrosis are signs of liver damage that progresses during NAFLD.	[3]
Free fatty acid (FFA)	FFA levels increased significantly and were found accompanied by an increase in oxidative stress at the onset of AFLD.	[16]
Lipids that downregulate NAFLD progression		
Omega-3 polyunsaturated fatty acids (PUFAs)	Omega-3 PUFAs have been shown in both animal and human studies to reduce hepatic steatosis, inflammation, and fibrosis by increasing anti-inflammatory cytokines and lowering pro-inflammatory cytokines to produce their beneficial effects. They reduced liver fat in NAFLD patients.	[60,61]
Monounsaturated fatty acids (MUFAs)	In both animal and human trials, MUFAs have been proven to decrease hepatic steatosis and inflammation by reducing oxidative stress and regulating lipid metabolism to produce positive effects.	[65]
Phospholipids	Phospholipids have been demonstrated to regulate hepatic lipid metabolism and inflammation. Targeting phospholipid metabolism may be a viable therapeutic strategy for NAFLD.	[66]
Long-chain polyunsaturated FA (LCPUFA)	Supplementation with n-3 LCPUFA appears to reduce nutritional hepatic steatosis in adults.	[60]
Lysophospholipids	Lysophospholipids, such as sphingosine 1-phosphate (S1P), lysophosphatidylcholine (LPC), lysophosphatidic acid (LPA), lysophosphatidylinositol (LPI), and lysophosphatidylethanolamine (LPE) have emerged as potential contributors to NAFLD/NASH.	[67]
Phosphatidylcholine (PC) and phosphatidylethanolamine (PE)	A decreased PC/PE ratio has been found in the liver, erythrocytes, and plasma of patients with NAFLD and NASH in relation to healthy individuals.	[67]

3.3. 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) [68]. The hepatic absorption of circulating fatty acids is mainly reliant on fatty acid transporters [68]. 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 [69]. 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 [70]. Hepatic steatosis and elevated mRNA and protein expression of CD36 occur in mice fed a high-fat diet [71,72]. 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 [71]. 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 [2,72]. Summary of lipid target pathways in NAFLD and clinical trial status are shown in Table 3.

Table 3. Summary of lipid target pathways in NAFLD and clinical trial status.

Drug	Clinical Trial Status *	Action	References
SREBP1-c inhibitors			
Oltipraz (OPZ)	Phase 2	Antisteatotic effect by inhibiting the activity of liver X receptor-α, thereby suppressing SREBP-1c activity	[73]
Statins (HMG-CoA reductase inhibitors)	Phase 3	Restrict cholesterol synthesis. Examples: simvastatin, atorvastatin	[74,75]
ATP-citrate lyase (ACLY) inhibitors			
Bempedoic acid	Phase 3	Decreases low-density lipoprotein and cholesterol levels	[76]
Hydroxy citric acid	-	Reduce fatty acid synthesis	[77]
Acetyl-CoA carboxylase (ACC) inhibitors			
GS-0976	Phase 2	Reduces hepatic de novo lipogenesis and steatosis	[78]
MK-4074	Phase 1	Suppresses de novo lipogenesis and enhances liver fatty acid oxidation	[79]
PF-05221304	Phase 2	Inhibits de novo lipogenesis	[80]
NDI-010976	Phase 1	Inhibits de novo lipogenesis	[81]
Fatty acid synthase (FAS) inhibitors			
TVB-2640	Phase 2	Reduces excess liver fat and directly inhibits inflammatory and fibrogenic pathways	[35]
Orlistat	Phase 4	Decreases free fatty-acid flux into the liver and improves insulin sensitivity	[82]
FT-4101	Phase 1/2	Reduces hepatic de novo lipogenesis	[83]
Stearoyl-CoA desaturase 1 (SCD1) inhibitors			
Aramchol	Phase 3	Reduced fibrogenic gene expression	[84]
PPAR α/δ/γ agonists			
Pioglitazone (PPARγ agonist)	Phase 4	Reduces liver fibrosis and adipose tissue insulin sensitivity	[85]
Elafibranor (GFT505) (PPARα/δ agonist)	Phase 3	Protective effects on steatosis, inflammation, and fibrosis	[86]
Triazolone derivatives (PPARα/δ agonist)	Phase 3	A potential therapeutic target for NASH	[87]
Saroglitazar (PPARα/γ agonist)	Phase 2	Improves insulin sensitivity and lipid and glycemic parameters	[88]
Lanifibranor (pan-PPAR agonist)	Phase 2	Improves both hepatic and peripheral insulin sensitivity	[89]
Bezafibrate (PPARα agonist)	Phase 3	Inhibits the accumulation of visceral fat, following amelioration of hyperlipidemia	[90]
Gemcabene (PPARα agonist)	Phase 2	Reduces the mRNA expression levels of metabolic genes linked to lipogenesis and lipid modulation	[91]
Seladelpar (PPARδ agonist)	Phase 3	Improves insulin sensitivity and reverses dyslipidemia	[92]

* Information collected from https://clinicaltrials.gov/ct2/ (accessed on 17 May 2023). ClinicalTrials.gov is a resource provided by the U.S. National Library of Medicine.

In mice given a high-fat diet, a whole-body caveolin 1 deletion (cav1−/−) reduced hepatic steatosis [93]. FABP1, the most prevalent FABP isoform in the liver [94], 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 [95]. 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 [96,97]. As compared to controls, patients with NAFLD had higher levels of hepatic FABPs mRNA [98,99]. 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, as shown in Figure 1. 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 [100]. 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 [101]. According to a study, DNL was higher in NAFLD patients than in controls [102]. Two essential transcription factors, carbohydrate regulatory element binding protein (ChREBP) and SREBP1c, are primarily responsible for controlling the transcriptional regulation of DNL [10,100,103].

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 [104,105]. 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 [106]. 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 [107]. ChREBP was revealed to be one of the main regulators of DNL in NAFLD, upregulating genes coding for ACC1 and FAS [108], 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 [104,105,108]. 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 PPARα [109,110]. FAO is mediated by cytochromes, peroxisomes, and mitochondria in mammalian cells [110,111]. Fatty acids are processed mostly through peroxisomal β-oxidation since the mitochondria are unable to oxidize very-long-chain fatty acids [110]. However, in cases of lipid overload, such as in NAFLD, cytochrome ω-oxidation also plays a role [112]. 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 [112]. 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 [113]. According to several studies, activation of PPARα causes the transcription of several FAO-related genes in the mitochondria, peroxisomes, and cytochromes, lowering the levels of hepatic lipids [109,110,113,114].

Hepatic steatosis is the outcome of PPARα knockout in ob/ob mice, suggesting the significance of PPARα in controlling hepatic lipid metabolism [115]. As a result of several studies, PPARα was downregulated in NASH patients compared to steatosis patients and healthy controls [116,117] and PPARα expression declined as the NAFLD activity score and fibrosis stage increased [116]. Thus, PPARα 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 [109]. 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 [118,119]. 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 [120]. 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 [121]. 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 [113]. 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 [122]. 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 [123,124]. To address this issue, several nutritional strategies for improving muscle mass were investigated [125]. 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 [126].

3.4. 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 [127,128]. Apolipoprotein B100 (apoB100) is lapidated 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 [127]. 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 [129,130]. 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 [131,132]. 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 [133]. 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 [98,134]. 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 [98].

4. Lipid Target Pathways in NAFLD for Drug Discovery

The global prevalence of NAFLD and its tight association with insulin resistance, obesity, and type 2 diabetes make it a significant contributor to chronic liver disease including steatosis, liver inflammation, hepatocellular damage, and increasing fibrosis, which are recognized as the hallmarks of NAFLD. Due to the prevalence of NAFLD and the possibility that it may also progress to more serious liver disease, effective pharmaceutical treatments are urgently required; however, despite the advancements, there are presently no cures for NAFLD. Both ongoing research on potential new treatment targets and recognized molecular pathways implicated in the pathophysiology of NAFLD depend heavily on lipids [135]. Targeting abnormal fatty acid and glucose metabolism to stop liver fat accumulation and the creation of a profibrotic environment appear to be promising therapeutic strategies [136,137]. Metabolic disorders, such as steatosis, are considered essential steps in the pathogenesis of NAFLD/NASH. One potential strategy for the creation of new NAFLD therapeutics is the targeting of the lipid metabolism pathways in the liver [75]. A summary of key targets and their clinical trial status are shown in Table 3. As mentioned, some of the lipid metabolic processes associated with the onset and progression of NAFLD include DNL, FAO, and triglyceride secretion [75,138]. For the treatment of NAFLD, several medicines that target enzymes are currently being developed associated with these, such as acetyl-CoA carboxylase and FAS for DNL; PPAR agonists for fatty acid oxidation; and MTTP inhibitors for triglyceride secretion.

4.1. Hepatic Lipid Metabolism-Based Targets

High glucose availability triggers the activation of the lipogenesis mechanism, which transforms extra carbohydrates into lipids [100,103,139]. Glycolysis transforms glucose into pyruvate in the postprandial state, which is then transported into the mitochondria to participate in the TCA cycle. The ATP-citrate lyase in the cytosol converts the citrate produced during the TCA cycle into acetyl-CoA. ACC-1 starts de novo fatty acid synthesis by ATP-dependent carboxylation of acetyl-CoA to malonyl-CoA. FAS, a multifunctional enzyme complex, adds malonyl-CoA, a 2-carbon donor, to the acetyl-CoA primer [135].

The main fatty acid produced by lipogenesis is palmitic acid, an SFA. Palmitic acid can be converted to long-chain fatty acids after being elongated by members of the fatty acyl-CoA elongase family. Stearoyl-CoA desaturase-1 (SCD1) may also desaturate palmitic acid into palmitoleic acid or elongate it into stearic acid. Stearoyl-CoA is converted to oleoyl-CoA by SCD1, which is a crucial metabolite in the synthesis of triglycerides [140], as described in Figure 2. β-oxidation of fatty acids takes place within the mitochondrial matrix [100]. The mitochondrial matrix can freely accept short and medium-chain fatty acids; however, on the other hand, the carnitine shuttle is required to carry long-chain fatty acids into the mitochondria [100]. The process of β-oxidation entails the successive removal of 2-carbon segments in the form of acetyl-CoA and the synthesis of shorter acyl-CoA, as well as a simultaneous reduction in 1 FAD and 1 NAD+ [135]. In contrast to acetyl-CoA, which enters the TCA cycle, the electrons transported by NADH+, H+, and FADH2 enter the electron transfer chain (ETC) promptly during oxidative phosphorylation. Understanding the interaction between DNL and β-oxidation is crucial to comprehending NAFLD [135], as shown in Figure 2. The development of hepatic steatosis is facilitated by the interaction of increased plasma glucose (hyperglycemia) and insulin concentrations (hyperinsulinemia), which stimulate de novo fatty acid production (lipogenesis) and impair the β-oxidation [141]. Following the esterification process, which turns FAs into triglycerides, triglycerides can either be retained as lipid droplets inside hepatocytes or released into circulation as VLDLs [135].

DNL is mainly regulated by two key transcription factors: SREBP-1c (activated by insulin) and ChREBP (activated by elevated glucose) [100]. Four crucial enzymes regulate DNL: ATP-citrate lyase (ACLY), ACC, FAS, and SCD1 [Figure 2]. ChREBP (a carbohydrate sensor of de novo lipogenesis) has been identified as a master regulator of lipid metabolism and is more prevalent in the active areas of DNL [139]. ChREBP is increased at the transcriptional, translational, and post-translational levels after a meal high in carbohydrates. Under a high-carbohydrate diet, global ChREBP-deficient (ChREBPKO) mice exhibit lower hepatic glycolytic and lipogenic gene expression and triglyceride synthesis [106]. Interestingly, endoplasmic reticulum stress causes substantial liver damage in ChREBPKO animals fed an HFD [50]. SREBP1-c (an insulin-sensitive regulator of de novo lipogenesis) is directly activated by insulin through increased gene expression and enhanced proteolytic processing [49]. As a result, SREBP1-c expression and activity are lowered in the presence of the insulin receptor in hepatocytes, which influences triglyceride formation [142]. SREBP1-c is activated in hepatic steatosis, just like ChREBP, and its hyperactivation causes an accumulation of triglycerides in the liver [143]. Furthermore, SREBP1-c activity is completely blocked by hepatocyte-specific deletion of SCAP (SREBF chaperone), the protein that escorts SREBP1-c into the nucleus and prevents hepatic steatosis [143], indicating that hepatic steatosis is driven by elevated nuclear SREBP-1c levels [144]. According to other studies, SREBP-1c hyperactivation encourages the accumulation of hepatic TG [145,146]. This suggests that targeting SREBP-1c for its role in regulating hepatic lipid metabolism may be an effective approach for treating NASH/NAFLD. The synthetic dithiolethione oltipraz (OPZ) has an antisteatotic action that reduces SREBP-1c activity [73]. The mTOR complex 1 (mTORC1) inhibitor rapamycin prevents the nuclear accumulation of mature versions of SREBP-1c and the expression of its target genes [147].

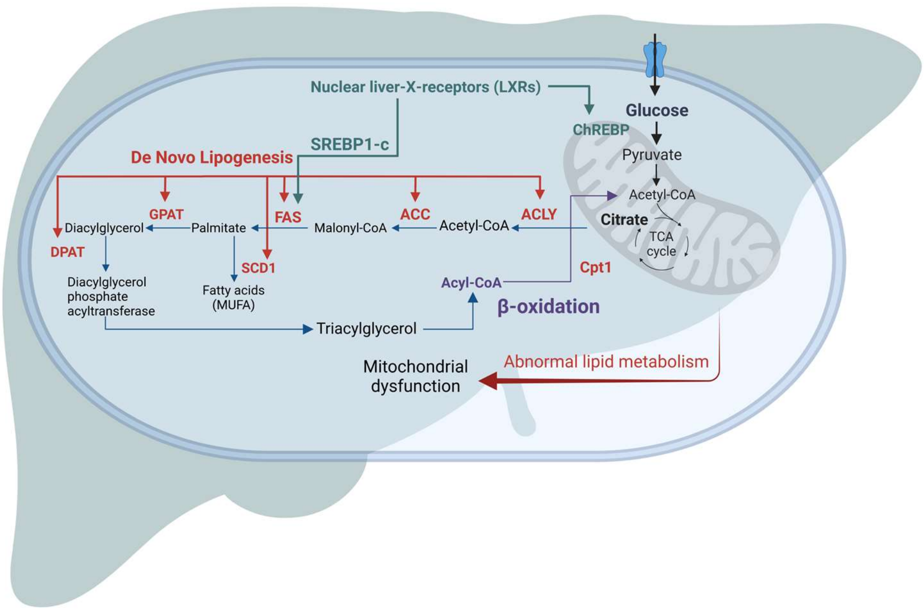

Figure 2. Lipid target pathways in NAFLD for drug discovery (created with BioRender.com). https://app.biorender.com/illustrations/6490a7446fdc02e8667d3a2e (accessed on 18 September 2023).

According to a recent study, Flcn deletion in the liver prevented mTORC1 signaling to enhance TFE3 nuclear translocation, which in turn activated the genes for lipid catabolism and decreased the genes for DNL. SREBP-1c activation was prevented by this particular ablation of hepatic Flcn [148]. 3-hydroxy-3-methyglutaryl-coenzyme A (HMG-CoA) reductase, a crucial enzyme in cholesterol synthesis and ketogenesis that is strongly linked to the emergence of fatty liver disease, is controlled by SREBP2 transcriptionally [149,150]. Statins, or HMG-CoA reductase inhibitors, limit the production of cholesterol and are typically prescribed as hypolipidemic medications. It has been demonstrated that statins inhibited the development of MCD-induced NAFLD in mice and enhanced the FAO capacity of the liver by activating the PPAR [74]. According to studies, statins can potentially be used as a treatment approach for NAFLD [151]. The gene expression of ATP-citrate lyase (ACLY) was found to increase in patients with NAFLD [152]. Bempedoic acid, an ACLY inhibitor, alleviated high-fat-diet-induced NASH in mice, improved glycemic control, reduced hepatic TG and total cholesterol (TC), and significantly reduced low-density lipoprotein cholesterol (LDL-C) levels [75,76]. Additionally, hydroxy citric acid, another competitive inhibitor of

ACLY, dramatically decreased the levels of liver damage markers and fatty acid production in rats receiving HFDs [153].

Acetyl-CoA is transformed by ACC into malonyl-CoA, which is a rate-limiting step in DNL. Inhibition of ACC was shown to lessen liver fibrosis in an HFD model in preclinical research [154]. According to Loomba et al., the ACC inhibitor GS-0976 reduced liver biochemistry, hepatic steatosis, hepatic DNL, and several fibrosis indicators [78]. Administration of MK-4074 demonstrated lowered DNL and improved liver FAO, which resulted in significantly lower hepatic TG levels in preclinical animal models and clinical investigations [79]. Malonyl-CoA is changed during DNL into palmitic acid by the rate-regulating enzyme fatty acid synthase (FAS) [75]. Patients with NAFLD/NASH exhibit considerably greater levels of FAS mRNA expression in the liver than healthy individuals [155]. In adult NASH patients with 8% liver fat and liver fibrosis, TVB-2640 can act as an FAS inhibitor [35]. Stearoyl-CoA desaturase 1 (SCD1) is an enzyme that catalyzes the rate-limiting step in the formation of MUFAs, particularly oleate and palmitoleate from stearoyl-CoA and palmitoyl-CoA [156]. The expression of SCD1 in the liver was increased both in patients with NAFLD and ob/ob mice [157]. Aramchol is an inhibitor of SCD1, which is one of the key enzymes of DNL. It showed an inhibitory effect on SCD1 activity to reduce liver fat content in patients with NASH [158].

4.2. Targeting β Oxidation/Mitochondrial Dysfunction

Energy homeostasis in hepatocytes is primarily controlled by oxidative mitochondrial metabolism, which includes the formation of ROS, ATP synthesis, and the β-oxidation of FFAs and the TCA cycle [159–161]. Ineffective β-oxidation of fatty acids causes a buildup of harmful lipids, such as hepatic diacylglycerols, ceramides, and long-chain acylcarnitines, which hastens the NAFLD process and increases inflammation [162]. When NAFLD develops, FFAs overwhelm the ETC's mitochondria, FAO, and electron flux, increasing and disrupting mitochondrial homeostasis. This causes an excessive amount of ROS to be produced because the ETC's complex activity is not upregulated, which causes "electron leakage" and exacerbates the accumulation of lipids in hepatocytes [111,163]. Additionally, the liver with NAFLD showed a reduced ability to remove ROS. Increased lipid peroxidation and ROS production are also caused by an increase in mitochondrial cytochrome P450 2E1 (CYP2E1) expression, which is associated with the development of NAFLD in the NASH [164]. CYP2E1 has recently come to be recognized as an additional potential significant cause of ROS overproduction, in addition to the mitochondrial respiratory chain [164]. As a matter of fact, increased hepatic CYP2E1 expression and activity have frequently been identified in correlation with obesity and NAFLD. Higher levels of CYP2E1 in NAFLD may also negatively affect mitochondrial function because a significant amount of CYP2E1 can be found within liver mitochondria. Moreover, elevated CYP2E1 activity caused by NAFLD could render some patients more susceptible to the hepatotoxicity of various xenobiotics by causing the production of hazardous reactive metabolites [75,164].

In general, PPARs have a role in the metabolism of glucose and lipids in a variety of organs and support the anti-inflammatory response in NAFLD [75,135]. Three distinct isotypes of PPARs have been found (α, β/δ, and γ), and each is important in lipid metabolism and glucose homeostasis in NAFL/NASH [165]. A transcription factor known as PPARα is highly expressed in hepatocytes [116] and is an essential regulator of lipid transport and metabolism, particularly through activation of the mitochondrial and peroxisomal fatty acid β-oxidation pathways [166]. PPARα could potentially provide protection against steatosis and inflammation, according to some studies in mice [167,168]. PPARα deletion in mice demonstrated enhanced NAFLD/NASH and hepatic inflammation [168]. These results suggest that PPARα is an intriguing target for NAFLD as it controls important metabolic pathways in the liver and negatively correlates with human liver disorders. In order to treat dyslipidemia and hypertriglyceridemia in humans, fibrates, which are pharmacological ligands of PPARα and are known as lipid-lowering medicines, are currently being used [169].

Numerous hepatic advantages have been shown in preclinical trials (for improvement of hepatic steatosis, inflammation, and fibrosis) [170,171]. There are numerous drugs (PPAR agonists) being studied in both preclinical and clinical settings that target various PPAR subtypes [75]. PPARβ/δ usually has higher expression levels than PPARα and PPARγ. According to the transcriptomic analysis of liver tissue, PPARβ/δ deletion elevated genes related to innate immunity and inflammation while downregulating pathways such as lipoprotein metabolism and glucose utilization [172]. To maintain metabolic balance, activated PPARβ/δ decreases hepatic glucose production and increases β-oxidation in muscle [173]. Multiple animal models of NAFLD/NASH showed liver-protective effects of elafibranor (GFT505), a dual PPARα/δ agonist [86,174], on steatosis, inflammation, and fibrosis. A phase 4 clinical trial is now being conducted on the potential PPARγ agonist pioglitazone. In patients with type 2 diabetes, pioglitazone significantly increased insulin sensitivity in adipose tissue while reducing liver fibrosis. The enzyme Carnitine palmitoyltransferase (CPT1) controls the mitochondrial long-chain FAO [85]. Malonyl-CoA, an intermediary in the de novo synthesis of fatty acids obtained from glucose, physiologically inhibits this enzyme. Malonyl-CoA levels rise due to increased glucose metabolism, which then inhibit CPT1 and prevent FAO, causing lipids to partition and be stored. Potential lipid biomarkers for human NAFLD are highlighted by liver CPT1A gene therapy's ability to attenuate diet-induced hepatic steatosis in rats [85].

4.3. Future Challenges in Controlling NAFLD

To control NAFLD, numerous obstacles must be overcome, including the absence of efficient pharmacological treatments and the requirement for lifestyle changes [175]. There are presently no officially licensed medications to prevent, treat, or reverse NASH, and developing them has been difficult despite a significant unmet medical need [17,176]. Although several drugs showed potential in clinical trials, many have not yet received approval due to safety concerns or poor efficacy [177,178]. The development of safer, more potent drugs that specifically address NAFLD's underlying causes should be the main goal of future research. The pathogenesis of NAFLD is complex as well as multifactorial, involving a number of genetic, environmental, and lifestyle variables [15,175]. To create more specialized therapies, it is necessary to better understand the molecular mechanisms involved in the onset and progression of NAFLD. Liver biopsy, which is invasive and unsuitable for routine screening, is currently the gold standard for diagnosing NAFLD [179]. Biomarkers capable of reliably diagnosing and monitoring NAFLD are required, especially in patients with advanced disease who are more likely to experience consequences [85,138].

Biological markers may provide prognostic or diagnostic information about the manifestation or progression of diseases [180]. A wide variety of serum biomarkers have been used for many years, including total cholesterol, triglycerides, insulin resistance, and C-peptide [32]. It has been proposed that emerging biomarkers, such as apolipoprotein A1, apolipoprotein B, leptin, adiponectin, FFAs, ghrelin, and tumor necrosis factor-alpha, can provide complementary information to traditional biomarkers [32]. Additionally, cytokeratin's markers of mitochondrial malfunction and cell death represent significant risk indicators [181]. Additionally, lifestyle changes like weight loss, exercise, and dietary adjustments are beneficial for treating NAFLD [15]. Motivating patients to make these changes and maintaining compliance, however, can be difficult. Moreover, it has become possible to identify therapeutic targets by understanding lipid dysregulation in NAFLD [75,135]. There is potential for future therapeutic interventions to alter lipid metabolism pathways, such as inhibiting DNL, activating FAO, and enhancing lipid export [68]. In addition, new approaches to treating NAFLD are being developed that target the gut microbiota, bile acid metabolism, and hepatic lipid droplet dynamics [20,68,75,135].

5. Conclusions

In general, lipids have complex interactions with NAFLD development; as well as studies that demonstrate this crosstalk, research and innovation are necessary to overcome the challenges associated with NAFLD control. Several factors contribute to the development of this disease, including dysregulation of lipid metabolism, inflammation, cholesterol metabolism, and ceramide metabolism. To effectively manage NAFLD, it may be necessary to use a multidisciplinary approach, targeting multiple pathways involved in disease pathogenesis. A detailed understanding of the mechanisms behind NAFLD progression can be gained by discovering the specific lipids that are upregulated in NASH and their associations with inflammatory pathways and insulin resistance. There is a need for further research on the complex interaction between lipid metabolism, inflammation, and insulin resistance in NAFLD. For treating and preventing NAFLD, it is crucial to develop effective pharmacological therapies, identify biomarkers, address comorbidities, and promote lifestyle modifications. In doing so, novel therapeutic strategies can be developed to treat this prevalent liver disease.

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