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Review

Disturbed Vitamin A Metabolism in Non-Alcoholic Fatty Liver Disease (NAFLD)

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Abstract: Vitamin A is required for important physiological processes, including embryogenesis, vision, cell proliferation and differentiation, immune regulation, and glucose and lipid metabolism. Many of vitamin A's functions are executed through retinoic acids that activate transcriptional networks controlled by retinoic acid receptors (RARs) and retinoid X receptors (RXRs). The liver plays a central role in vitamin A metabolism: (1) it produces bile supporting efficient intestinal absorption of fat-soluble nutrients like vitamin A; (2) it produces retinol binding protein 4 (RBP4) that distributes vitamin A, as retinol, to peripheral tissues; and (3) it harbors the largest body supply of vitamin A, mostly as retinyl esters, in hepatic stellate cells (HSCs). In times of inadequate dietary intake, the liver maintains stable circulating retinol levels of approximately 2 $\mu\text{mol/L}$, sufficient to provide the body with this vitamin for months. Liver diseases, in particular those leading to fibrosis and cirrhosis, are associated with impaired vitamin A homeostasis and may lead to vitamin A deficiency. Liver injury triggers HSCs to transdifferentiate to myofibroblasts that produce excessive amounts of extracellular matrix, leading to fibrosis. HSCs lose the retinyl ester stores in this process, ultimately leading to vitamin A deficiency. Non-alcoholic fatty liver disease (NAFLD) is the hepatic manifestation of metabolic syndrome and is a spectrum of conditions ranging from benign hepatic steatosis to non-alcoholic steatohepatitis (NASH); it may progress to cirrhosis and liver cancer. NASH is projected to be the main cause of liver failure in the near future. Retinoic acids are key regulators of glucose and lipid metabolism in the liver and adipose tissue, but it is unknown whether impaired vitamin A homeostasis contributes to or suppresses the development of NAFLD. A genetic variant of patatin-like phospholipase domain-containing 3 (PNPLA3-I148M) is the most prominent heritable factor associated with NAFLD. Interestingly, PNPLA3 harbors retinyl ester hydrolase activity and PNPLA3-I148M is associated with low serum retinol level, but enhanced retinyl esters in the liver of NAFLD patients. Low circulating retinol in NAFLD may therefore not reflect true "vitamin A deficiency", but rather disturbed vitamin A metabolism. Here, we summarize current knowledge about vitamin A metabolism in NAFLD and its putative role in the progression of liver disease, as well as the therapeutic potential of vitamin A metabolites.

Keywords: non-alcoholic fatty liver disease; metabolic syndrome; vitamin A; retinyl esters; retinol; retinoic acid; retinol binding protein 4; hepatic stellate cells; nuclear receptors; lipid metabolism

1. Vitamin A, Its Active Metabolites, and Dietary Causes of Vitamin A Deficiency

The generic term “Vitamin A” is used for compounds having the biological activity of retinol or its metabolic products, such as all-trans retinoic acid (atRA), 9-cis retinoic acid (9cRA), and 9-cis-13,14 dihydroretinoic acid (9cDHRA). Mammals cannot synthesize retinol themselves, so depend on the diet to acquire sufficient amounts of this micronutrient. Dietary sources of vitamin A are carotenoids, such as β -carotene (rich plant sources are sweet potatoes, carrots, and dark green leafy vegetables like spinach) and retinyl esters (rich animal sources are liver, eggs, and fish) [1]. Vitamin A is an essential fat-soluble vitamin and adequate daily intake (~ 700 – 900 μg for humans) and hepatic storage ($\sim 80\%$ in a healthy individual) are required to maintain plasma retinol levels around 2 $\mu\text{mol/L}$ in humans (1 – 2 $\mu\text{mol/L}$ in rodents) [2,3]. Vitamin A plays important physiological roles in vision, reproduction, growth, development, immunity, and metabolic programs [4–10]. Most functions of vitamin A are mediated through the activation of ligand-activated transcription factors. For example, atRA is a high-affinity ligand for retinoic acid receptors (RAR α , β and γ), while 9cRA and 9cDHRA activate retinoid X receptors (RXR α , β , and γ). The ligand-dependent activation and the physiological roles of RAR and RXR have been extensively reviewed in recent years [10–12].

Vitamin A deficiency (VAD) is common in low-income countries. According to the World Health Organization (WHO) an estimated 250 million preschool children in these countries have VAD and are predisposed to developmental and immune disorders, preventable (night) blindness, and infection-associated morbidity and mortality. Moreover, VAD in pregnant women increases the risk for maternal mortality, though high doses of vitamin A supplementation in pregnant women are contraindicated as they are associated with teratogenicity for the fetus [6,13]. The liver plays a central role in controlling vitamin A metabolism and chronic liver diseases, like biliary atresia [14,15], primary biliary cholangitis (PBC) [16–18], primary sclerosing cholangitis (PSC) [19], viral hepatitis [20], alcoholic liver disease (ALD) [21,22], and non-alcoholic fatty liver disease (NAFLD, NASH) [23–25] are associated with VAD. Moreover, VAD in hepatitis C virus (HCV)-infected patients is associated with a lack of response to interferon-based antiviral therapy [20]. Thus, VAD is also a highly relevant condition in high-income countries given the increased incidence of liver diseases associated with a Western lifestyle, e.g., 20–30% of the population of industrialized countries is suspected of having NAFLD [26–28]. Many epidemiological studies have reported VAD in liver diseases, including NAFLD, where the golden standard for assessing the vitamin A status is measuring serum retinol levels (<0.7 $\mu\text{mol/L}$ is considered VAD) [29]. Moreover, serum retinol levels are inversely associated with disease progression [11,24,25,30,31]. Oral vitamin A supplements are often not very effective in restoring adequate serum retinol levels in NAFLD patients, indicating a fundamentally impaired vitamin A metabolism. Animal studies have shown the beneficial effects of therapeutic use of vitamin A derivatives, e.g., retinoic acids or pharmacological modulators of RARs and RXRs. Relatively little is known, however, about changes in vitamin A metabolism in liver disease, including possible changes in storage (retinyl esters) vs. circulating (retinol, RA) forms and possible redirection of vitamin A pools within the liver (hepatocytes vs. hepatic stellate cells) and/or to extrahepatic tissues. Insight into these processes is needed to get a better view of the possible therapeutic application of vitamin A and/or its derivatives (retinoids acting on RARs and retinoids acting on RXRs) in liver diseases. This review aims to give an overview of vitamin A metabolism in patients and animal models of NAFLD and associated obesity, as well as the possible therapeutic value of vitamin A and its metabolites in NAFLD.

2. Vitamin A Uptake, Storage, and Metabolism

A schematic representation of vitamin A uptake, transport, storage, and metabolism is given in Figure 1. Plant-derived carotenes and animal-derived retinyl esters are the main sources of vitamin A in the diet. Bile salts produced by the liver are important to keep these fat-soluble compounds in solution in the digestive tract and make them available for absorption in the proximal part of the small intestine [32,33]. Retinyl ester hydrolases (REH) in the gut lumen release retinol from retinyl esters, after which it is absorbed by enterocytes by a yet to-be-characterized mechanism. Carotenes are taken

up by membrane-bound transporters, including fatty acid translocase (FAT/CD36), Niemann–Pick C1-Like 1 (NPC1L1) and scavenger receptor class B member 1 (SR-B1), and metabolized to retinol inside enterocytes. Next, retinol is re-esterified to retinyl esters, mainly by lecithin:retinol acyl transferase (LRAT) and diacylglycerol *O*-acyltransferase (DGAT1), sequestered into chylomicrons (CM) and secreted to the circulation [34,35]. CM remnants that still contain most of the retinyl esters are taken up by hepatocytes, mostly through the LDL receptor (LDLR) [36]. The retinyl esters are then hydrolyzed to retinol through the action of REHs [37], followed by transfer of retinol to RBP4 and transthyretin (TTR), which stimulates its secretion into the circulation [38–40]. From here, retinol is directed to either of two main destinations: (1) peripheral tissues in demand of retinol (–metabolites). Here, the RBP4-TTR-retinol complex binds to “stimulated by retinoic acid gene 6 homolog” (STRA6), which facilitates uptake of retinol [41] and makes it available for conversion to bioactive retinoic acids; or (2) hepatic stellate cells (HSC) that convert it back again to retinyl esters (by LRAT and DGAT1 [42,43]) and store it in large cytoplasmic lipid droplets. It is estimated that 60–95% of the whole body’s reservoir of vitamin A resides in the liver of a healthy individual, but considerable amounts may also reside in adipose tissue, the pancreas, the intestines, and the eyes. Still, the liver is considered to be the central player in providing retinol to peripheral tissues in times of insufficient dietary intake. This is a tightly controlled process maintaining well-balanced levels of approximately 2 $\mu\text{mol/L}$ retinol in the blood. However, few details of how this is achieved are known, e.g., it is unknown how retinol gets in and out of HSC and which (molecular) signals control this. Mobilization of retinol from lipid droplets in HSC is catalyzed by REHs, and several enzymes are implicated in this process, including adipose triglyceride lipase (ATGL/PNPLA2) [44], patatin-like phospholipase domain-containing 3 (PNPLA3) [44–46], and hormone-sensitive lipase (HSL) [47,48]. Interestingly, genetic studies have identified the PNPLA3-I148M variant as a prominent genetic factor associated with NAFLD, and even more prominently with disease progression within NAFLD to NASH and NASH-associated cirrhosis [49–51]. PNPLA3 affects vitamin A homeostasis, as will be discussed in more detail in the following sections. Liver diseases, in particular chronic liver diseases that lead to liver fibrosis, have major impact on hepatic vitamin A metabolism and storage. Quiescent vitamin A-storing HSCs (qHSCs) become activated as a result of liver injury, and transdifferentiate to migratory and highly-proliferative myofibroblasts (aHSCs) that produce excessive amounts of extracellular matrix proteins (ECM), mainly collagens and fibronectins, leading to fibrosis. HSCs lose their vitamin A stores during this transdifferentiation process. Consequently, chronic liver diseases, including NAFLD, may lead to vitamin A inadequacy.

Given the various forms and storage sites of vitamin A in the body, it is unclear whether the reported vitamin A deficiency (VAD) in NAFLD is truly a reflection of complete depletion of vitamin A from the body, or whether it is rather a reflection of impaired vitamin A metabolism. Clinical examination of vitamin A status is typically performed by determining serum retinol levels, where levels below 0.7 $\mu\text{mol/L}$ are considered deficient. Retinol is also present in the liver, but most vitamin A is esterified, predominantly as retinyl palmitate. Both forms reside in hepatocytes (the initial site of absorption from the circulation) and HSCs (the final destination and controller of serum retinol levels). In addition, a significant amount of vitamin A is present in adipose tissue and the pancreas, both as retinol and retinyl esters. Thus, for thorough evaluation of the vitamin A status, both retinol and retinyl esters need to be quantified in the blood, the liver, and preferably also the adipose tissue. Hepatic retinol levels are sometimes analyzed in liver biopsies or explant livers [25,52], but quantification of retinyl ester is rarely performed [52]. Therefore, when scanning the literature for the vitamin A status in liver disease, it is important to take into account what exactly is measured and keep in mind that the limited data on hepatic retinyl ester levels prevents us from establishing the true VAD prevalence in humans.

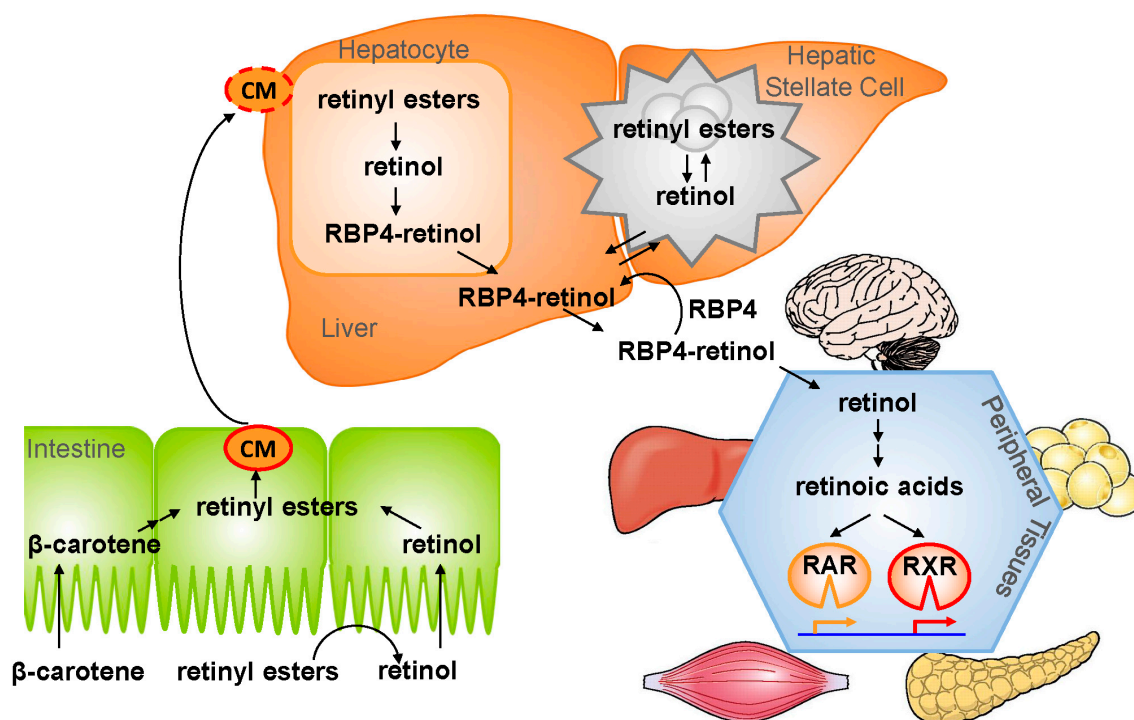


Figure 1. Schematic representation of intestinal vitamin A absorption, transport to, and storage in the liver and redistribution to peripheral tissues (see main text for details). Carotenes (from plants) and retinyl esters (from animals) are the main dietary sources of vitamin A (lower left corner). They are absorbed in the proximal small intestine and transported as retinyl esters in chylomicrons (CM) to the liver. Chylomicron remnants are taken up by hepatocytes and retinyl esters are hydrolyzed to form retinol. Hepatocytes produce retinol binding protein 4 (RBP4) and retinol binding to RBP4 stimulates the secretion of retinol-carrying holo-RBP4 to the circulation. Retinol is then either transported to hepatic stellate cells for storage as retinyl esters or transported to peripheral tissues where it is converted to retinoic acids that activate the transcription factors retinoic acid receptor (RAR) or retinoid X receptor (RXR). In times of inadequate vitamin A intake, retinol is released from the HSC stores to maintain stable levels of circulating retinol ($\sim 2 \mu\text{M}$ in human).

3. Vitamin A and RBP4 in the Clinical Course of NAFLD and Metabolic Syndrome

NAFLD is characterized by the accumulation of fat in the liver, in particular non-esterified fatty acids (NEFA), triglycerides, and non-esterified cholesterol. NAFLD is regarded as a consequence of excessive dietary intake of fat and/or sugars (glucose and fructose) typical of the “Western” lifestyle, in combination with limited physical activity. Benign steatosis may progress to an inflammatory state in the liver, leading to chronic liver injury, e.g., non-alcoholic steatohepatitis (NASH). In turn, this causes a chronic healing response leading to liver fibrosis, which may progress to cirrhosis, which predisposes for liver cancer. NAFLD is commonly appreciated to be the hepatic manifestation of metabolic syndrome (MetS). Numerous studies have reported on vitamin A status in MetS, while reports specifically focusing on NAFLD are limited. Almost all studies documenting vitamin A status in MetS report reductions in serum retinol, retinoic acid, and/or β -carotene that are inversely correlated with MetS features, including obesity, insulin resistance, glucose intolerance, and hypertriglyceridemia [53–62]. In line with these observations, inadequate serum retinol levels ($<1.05 \mu\text{mol/L}$) were found in 11–36% of morbidly obese adults with ultrasonography-proven NAFLD, and a significant association between low retinol levels and insulin resistance (IR) was found [25,53]. A similar trend was observed in obese children with NAFLD [23]. Moreover, serum retinol levels were inversely associated with body mass and serum transaminases in patients with NAFLD, suggesting a link between retinol inadequacy and development of disease [24]. In one study, both serum and

hepatic retinol levels were analyzed in NAFLD patients and the latter was more frequently found to be inadequate (36% vs. 68% for serum and hepatic retinol inadequacy, respectively) in these patients [25]. Hepatic retinol levels showed a strong inverse correlation with the histological classification of the disease (sub-classified in mild and severe steatosis, NASH and hepatocyte necrosis), which was not observed for serum retinol levels. These observations were confirmed by Trasino et al. [63], who reported an inverse correlation between the level of steatosis and hepatic retinol and retinyl palmitate concentrations. However, the cause of hepatic steatosis was unknown in this study, as liver tissue was obtained from deceased individuals after motor vehicle accidents or head trauma [63]. More recently, serum retinoic acid levels were also shown to be inversely associated with hepatic steatosis and liver injury in NAFLD. While reference values for retinol are approximately 2 $\mu\text{mol/L}$ in human blood, atRA concentrations are approximately 200-fold lower (~ 10 pmol/L). Still, also for circulating atRA, levels were markedly reduced in NAFLD (-47%) and even more pronounced in NASH (-58%) patients compared to control subjects [64]. Moreover, atRA concentration and RXR α levels were inversely correlated to liver triglyceride content, grade of hepatic steatosis, and severity of liver disease [64]. In comparing the expression of 51 genes involved in RA signaling in control, simple steatotic, and NASH livers, Ashla et al. [65] observed a hyper-dynamic state of RA metabolism and degradation in the liver of NAFLD patients, which further increased when it included NASH. Hepatic expression of genes involved in vitamin A storage (LRAT and DGAT1) as well as RA production retinaldehyde dehydrogenase 1 and 3 (RALDH1 and 3) and degradation (Cyp26A) were all significantly increased in NAFLD patients. This expression profile may indeed lead to low hepatic retinol and retinoic acids levels, but not necessarily to VAD, as it suggests that production of retinyl esters is also enhanced. Low retinol levels appear predictive for the development of hepatocellular carcinoma (HCC) in cirrhotic patients [66,67], though this has not yet been studied specifically for NAFLD-associated HCC. Impaired RAR- and RXR-mediated signaling is assumed to promote HCC. Hepatocyte-specific overexpression of a dominant negative form of RAR induces hepatic tumor development, which is suppressed by a diet containing retinoic acid [68].

In contrast to reduced retinol, serum levels of RBP4 are typically elevated in MetS patients and obese animals. A landmark paper by Yang et al. [69] revealed a direct role of serum RBP4 in the development of insulin resistance in obesity and type 2 diabetes [69]. RBP4 expression was selectively enhanced in adipose tissue in animal models of type 2 diabetes, but not in the liver. Transgenic overexpression of human RBP4 in mice or injection with recombinant RBP4 in normal mice led to insulin resistance. These findings suggest that adipose-derived RBP4 increases serum levels of RBP4 and plays a pathological role in type 2 diabetes (T2D). Many papers have confirmed the elevated serum RBP4 levels in obese patients with or without T2D (for example see [69–73]). However, a significant number of similar studies did not replicate the enhanced levels of RBP4 in the serum of these patients (for example see [74–78]). Thus, the specific correlation between serum RBP4 levels and components of the MetS spectrum remains an active debate today. Since serum retinol levels are typically reduced in MetS, this feature may be an important factor to consider together with RBP4. Low serum retinol in combination with stable or enhanced RBP4 levels implies the presence of more retinol-free (apo-) RBP4 in circulation. The few studies that quantified both retinol and RBP4 in serum indeed confirm that a low retinol-to-RBP4 ratio is a better predictor for obesity, T2D, and other components of metabolic syndrome in children and adults than RBP4 alone [79–81].

In addition to the debate on the relevance of serum RBP4 levels as indicator for MetS components, the origin of the increased levels of RBP4 is also an ongoing puzzle. Enhanced RBP4 production by adipose tissue was the original hypothesis, because of the selective increase of RBP4 mRNA levels in this tissue in T2D mice but not in the liver [69]. More recent data indicate that elevated serum RBP4 levels are specifically associated with obesity- and T2D-associated reduced kidney function, suggesting that impaired renal clearance of RBP4 is an important contributing factor [82–86]. Recently, it was found that hepatocyte-specific deletion of *Rbp4* in mice completely abolishes RBP4 from the circulation, both in lean and obese animals, providing strong evidence that the liver, more specifically

the hepatocytes, is the primary—if not sole—source of serum RBP4 [87]. In line with this finding is that adipocyte-specific overexpression of human RBP4 did not increase circulating RBP4, but did cause hepatic steatosis in mice [88]. These findings suggest that adipocyte-produced RBP4 acts locally to activate signaling cascades that cause fat accumulation in the liver, but it is not a circulating adipokine itself. Secretion of RBP4 by hepatocytes is strongly stimulated by retinol [38–40]; this may be impaired in NAFLD patients when both hepatic and serum retinol levels are reduced. RBP4 indeed accumulates in the livers of NAFLD patients, as determined by immunohistochemistry [89]. Hepatic RBP4 retention in low-retinol NAFLD livers suggests that impaired renal clearance might even be a more prominent factor in enhancing serum RBP4 levels.

Bariatric surgery is nowadays a common approach to treat morbid obesity, where an adjustable gastric band (AGB), Roux-en-Y gastric bypass (RYGB), biliopancreatic diversion with a duodenal switch (BPD-DS), and vertical sleeve gastrectomy (VSG) are the four most common procedures. Remarkably, serum retinol levels do not return to normal after bariatric surgery and in most studies even further decline in the 6–12 months post-surgery, also under impressive weight loss and improvement of MetS components [90–94]. Ocular problems related to low vitamin A status, such as night blindness, are commonly reported in patients who underwent bariatric surgery. BPD-DS appears to induce a stronger decline in serum retinol compared to RYGB [91,95] and vitamin A deficiency was still observed in 23–69% of patients 4–10 years post-PBD-DS [96–98]. Impaired serum retinol levels were also observed in neonates from mothers who underwent RYGB 11–69 months before the onset of pregnancy, which may cause irreversible eye problems in the child [99]. In contrast to retinol, circulating levels of vitamin D and E were higher in neonates of mothers who had undergone bariatric surgery as compared to neonates from healthy mothers [100]. This argues against a general deficiency in fat-soluble vitamins in these children. Inadequate serum retinol levels before and/or after bariatric surgery are often linked to inadequate dietary intake, as well as the anatomical changes resulting from bariatric surgery. Large parts of the jejunum do not receive dietary input post-surgery, and this is exactly the site where most vitamin A is normally absorbed. However, intramuscular [101] or dietary vitamin A supplementation (alone or in multivitamins) does not effectively elevate serum retinol levels and/or prevent the decline in serum retinol post-surgery [91,92,94,102]. A few case reports have shown that only very high doses of vitamin A relieve the signs of severe VAD, like night blindness [103]. Little is currently known about the effect of diet-induced weight loss on serum retinol levels. Serum RBP4 declines after this treatment, but this is not consistently associated with an improvement in insulin sensitivity [104–107].

4. PNPLA3 Variant I148M Regulates Vitamin A in NAFLD

Several genomic loci have been identified to increase the susceptibility for NAFLD. The most prominent NAFLD-associated genetic risk factor is a specific variant of PNPLA3, PNPLA3-I148M, which also predisposes for disease progression and NAFLD-associated hepatocellular carcinoma [108–111]. PNPLA3 is a multifunctional enzyme acting as a triglyceride hydrolase, an acetyl-CoA-independent transacylase, and a retinyl esterase [112]. Originally, it was found to contain hydrolase activity towards triglycerides, in particular those containing mono- and poly-unsaturated fatty acids. PNPLA3-I148M shows reduced hydrolase activity and promotes hepatic triglyceride accumulation, all in line with the primary phenotype of NAFLD: fat accumulation in hepatocytes. Likewise, chronic overexpression of PNPLA3-I148M (but not PNPLA3-I148) in mice leads to hepatic steatosis [113]. Notably, while the variant is associated with increased liver fat content, PNPLA3-I148M appears not to be associated with other features of metabolic syndrome, like insulin resistance [114,115]. Serum triglycerides (TG) levels are either the same or lower in PNPLA3-I148M carriers compared to non-carriers, consistent with a lack of association with insulin resistance [115].

A recent paper, however, showed that PNPLA3 mRNA and protein levels are significantly higher in HSC compared to hepatocytes. PNPLA3 was found to contain retinyl esterase activity and promotes the release of retinol from lipid droplets [45]. Carriers of the PNPLA3-I148M allele with either NAFLD or obesity alone have reduced fasting circulating retinol and RBP4 levels. No association

was found between this genotype and β -carotene, indicating a specific association with retinol [46]. On the other hand, hepatic retinyl palmitate levels are increased in individuals homozygous for PNPLA3-I148M [116], supporting a role for PNPLA3 in hepatic retinoid metabolism [116]. PNPLA3 expression in HSC is regulated by retinol and insulin and is inversely related to lipid droplet content. Retinol suppresses PNPLA3 expression in HSC, while it is induced upon retinol depletion. Moreover, PNPLA3 expression is induced upon HSC activation and the PNPLA3-I148M variant further promotes fibrogenic features of HSC, including enhanced proliferation, migration and expression of collagen type 1 alpha 1 (COL1A1), pro-inflammatory cytokines, and chemokines alongside lower cellular retinol levels. Remarkably, PNPLA3-I148M-carrying HSC contain more lipid droplets, which is a typical characteristic of HSC quiescence [117]. These features are in line with a higher risk for progressive liver disease in PNPLA3-I148M carriers, but seemingly in contrast to the increased hepatic retinyl palmitate levels in those patients. Thus, these NAFLD patients did not have VAD, although the low circulating retinol levels are interpreted as such. It remains to be determined whether this is a more general phenomenon in NAFLD. Since (1) dietary retinyl esters are first delivered to—and hydrolyzed—in hepatocytes before they move as retinol to HSC to become esterified again, and since (2) PNPLA3 is expressed both in hepatocytes and HSC, it remains unclear which hepatic cell type retinyl esters accumulate in NAFLD and specifically in PNPLA3-I148M patients.

5. Vitamin A and Hepatic Lipid Metabolism

Hepatic lipid content is a result of the following steps: (1) de novo lipogenesis (DNL) in the liver; (2) an influx of dietary lipids (delivered as non-esterified free fatty acids (NEFAs) or as TG in chylomicrons); (3) an influx of NEFAs produced by adipose tissue (primarily from white adipose tissue (WAT)); (4) the esterification of lipids (mainly to TG) and packaging into lipid droplets; (5) an influx of TG carried in CM remnants and low density lipoproteins (LDL); (6) an efflux of TG carried in very low density lipoprotein (VLDL)-particles; (7) TG hydrolysis producing NEFAs; and (8) catabolism of NEFAs through mitochondrial and peroxisomal β -oxidation (Figure 2). NAFLD is characterized by hepatic TG accumulation, enhanced VLDL production, and secretion leading to hypertriglyceridemia. Vitamin A metabolites, especially retinoic acids, are involved in regulatory networks that affect all these processes either directly or indirectly, as described below and schematically depicted in Figure 2.

Hepatic DNL (#1 in Figure 2) is under primary the transcriptional control of the sterol response element binding protein-1c (SREBP-1c) and carbohydrate response element binding protein (ChREBP), which induce expression of key glycolytic enzymes (glucokinase (GCK), pyruvate kinase isozymes R/L (PKLR), ATP citrate lyase (ACL), acetyl-CoA synthetase (ACS) and lipogenic enzymes (acetyl-CoA carboxylase 1 (ACC1), fatty acid synthase (FASN), ELOVL fatty acid elongase 6 (ELOVL6), stearoyl-CoA desaturase-1 (SCD), glycerol-3-phosphate acyltransferase, mitochondrial (GPAT)) in the liver. The absence or inhibition of SREBP-1c or ChREBP impairs lipid synthesis and reduces hepatic steatosis [118–120]. Insulin, glucose, and fructose stimulate SREBP-1c and ChREBP expression to promote hepatic DNL. Retinoic acids, as well as synthetic ligands of RXR α (e.g., bexarotene), enhance hepatic DNL and plasma TG levels by activating Liver X receptor (LXR)/RXR and peroxisome proliferator-activated receptor γ (PPAR γ)/RXR, which, in turn, enhance expression of SREBP-1c and ChREBP [121]. Although LXR and PPAR γ are typically activated by oxysterols and NEFAs, respectively, RXR α is a permissive dimerization partner, meaning that RXR ligands enhance DNL through those heterodimers independently of the co-presence of ligands for LXR or PPAR γ . LXR/RXR also directly induces FAS expression, thereby promoting DNL and enhancing plasma triglyceride levels in mice [122]. In contrast, atRA suppresses DNL by activating RAR α , which, via induction of Hes family BHLH transcription factor 6 (HES6) and subsequent inhibition of hepatocyte nuclear factor 4 α (HNF4 α), reduces PPAR γ expression and downstream SREBP-1c activity. In a counteracting mechanism, 9cRA-activated RXR α induces expression of a small heterodimer partner (SHP), which inhibits HES6 expression, promoting DNL via the PPAR γ -SREBP-1c axis [123]. However, SHP also inhibits LXR/RXR transcriptional activity, thereby simultaneously inhibiting SREBP-1c-mediated

DNL [124]. This highlights the delicate position of SHP in the development of hepatic steatosis, inhibiting RXR/LXR-ChREBP/SREBP-1c-mediated DNL, while at the same time promoting DNL via the HES6-HNF4 α -PPAR γ pathway. The absence of SHP protects mice from diet-induced hepatic steatosis, suggesting a most prominent role for the HES6-HNF4 α -PPAR γ axis, which is activated by atRA and RAR α [123].

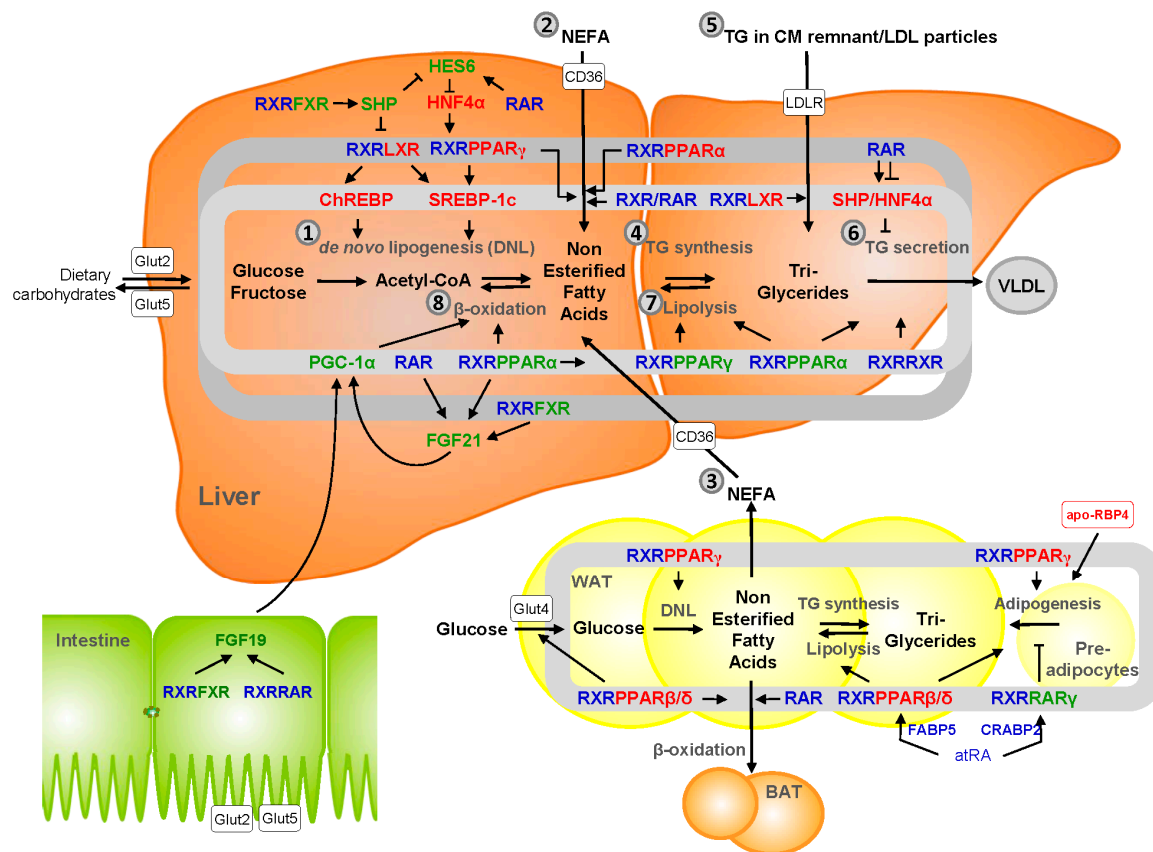


Figure 2. Regulation of hepatic lipid metabolism by vitamin A metabolites. Triglyceride synthesis and breakdown is subdivided into eight steps: (1) de novo lipogenesis (DNL) in the liver, (2) influx of dietary lipids (delivered as non-esterified free fatty acids (NEFAs) or as triglycerides (TG) in chylomicrons), (3) influx of NEFAs produced by adipose tissue (primarily from white adipose tissue (WAT)), (4) esterification of lipids (mainly to TG) and packaging into lipid droplets, (5) influx of TG carried in CM remnants and low density lipoproteins (LDL), (6) efflux of TG carried in very low density lipoprotein (VLDL)-particles, (7) TG hydrolysis producing NEFAs, and (8) catabolism of NEFAs through mitochondrial and peroxisomal β -oxidation. Direct transcriptional regulation of lipogenic/lipolytic genes is shown in the inner (light gray) ring. Indirect transcriptional regulation is shown inside or outside the outer (dark gray) ring. Vitamin A-related factors are indicated in blue. Factors that promote lipogenesis are shown in red; factors promoting lipolysis in green. Relevant regulation and factors in adipose tissue and the intestine are also included (see main text for details about the specific genes that are regulated in each step). Additional abbreviations: FXR—Farnesoid X Receptor, SHP—Small Heterodimer Partner 1, HES6—Hes family BHLH transcription factor 6, HNF4 α —Hepatocyte Nuclear Factor 4 alpha, LXR—Liver X Receptor, PPAR γ —Peroxisome Proliferator-Activated Receptor gamma, chREBP—carbohydrate Response Element Binding Protein, SREBP-1c—Sterol Response Element Binding Protein-1c, PGC-1 α —PPAR γ -Coactivator 1-alpha, FGF—Fibroblast Growth Factor, BAT—Brown Adipose Tissue.

Influx of NEFA, either from dietary sources or adipose tissue (#2, 3 in Figure 2) is facilitated by fatty acid translocase (FAT/CD36). Hepatocyte-specific deletion of CD36 protects against HFD-induced

lipid accumulation in the mouse liver, underscoring its role in NAFLD pathogenesis. Expression of CD36 is controlled by SREBP-1c, RXR/PPAR γ , and RXR/PPAR α , transcription factors that are regulated directly or indirectly by RA (see above). Moreover, RAR/RXR may also directly enhance expression of CD36, though this regulatory pathway has only been studied in human THP-1 monocytes so far [125,126].

Hepatic TG synthesis (#4 in Figure 2) is catalyzed by GPAT, mannosyl (alpha-1,6-)-glycoprotein beta-1,2-*N*-acetylglucosaminyltransferase (MGAT2), and diacylglycerol *O*-acyltransferase 2 (DGAT2), all of which are under the transcriptional control of ChREBP. In addition, GPAT is controlled by SREBP-1c. Though no specific data are available on the RA-mediated expression of those genes, it is likely that they are co-regulated with key genes in DNL as a result of RXR/LXR and RAR-mediated effects on ChREBP and SREBP-1c.

Hepatic uptake of TG-containing CM remnants or LDL particles (#5 in Figure 2) is controlled by the LDL receptor (LDLR). Expression of human LDLR is controlled by LXR/RXR [127], but co-regulation by retinoic acids has not yet been studied in detail. However, given the potent effects of RXR ligands on LXR/RXR-mediated regulation of SREBP-1c and ChREBP (described above), it is likely that retinoic acids may also promote the LDLR-mediated uptake of TG in the liver.

Hepatic VLDL particle formation and secretion (#6 in Figure 2) are facilitated by apo-CIII [128]. Apo-CIII null mice fail to stimulate VLDL production upon HFD feeding, while Apo-CIII overexpressing mice show enhanced diet-induced triglyceride accumulation in the liver [129]. A genetic variant of Apo-CIII leads to enhanced circulating Apo-CIII in humans and is associated with NAFLD [130]. Hepatic Apo-CIII expression is suppressed by RAR α via a pathway involving SHP and HNF4 α , thereby reducing hepatic and plasma triglyceride levels [131]. Earlier studies have shown that RXR ligands sort the opposite effect and enhance hepatic apo-CIII expression, either via RXR homodimers or RXR/PPAR α , and thereby promote hypertriglyceridemia, a well-known adverse effect of pharmacological ligands of RXR and a risk factor for cardiovascular disease (CVD) [132]. This emphasizes the opposite roles of RAR ligands (e.g., atRA) and RXR-ligands (e.g., 9cRA) on VLDL particle production and secretion by the liver. In addition, Apo-CIII expression is controlled by ChREBP, adding an additional layer of indirect RA responsiveness, as described above [133].

Key enzymes involved in TG lipolysis (#7 in Figure 2) in hepatocytes are adipose triglyceride lipase (ATGL/PNPLA2), hormone-sensitive lipase (HSL), and PNPLA3. Those are exactly the same enzymes responsible for retinyl ester hydrolysis that release retinol from cellular stores, though that activity is believed to occur predominantly in HSC (see above). The absence of either ATGL or HSL aggravates diet-induced hepatic TG accumulation and steatosis in mice [134–136]. Hepatic overexpression of ATGL and/or HSL reduced TG levels by 40–60% in ob/ob mice and enhanced fatty acid oxidation and ameliorated hepatic steatosis, while fasting plasma TG and NEFA were not affected [137]. The expression of both ATGL and HSL is controlled by PPAR α , and the PPAR α -agonist-mediated decrease in hepatic lipids in HFD-fed mice was mirrored by a strong increase in the expression of these genes [138]. PPAR α ligands also induce hepatic ATGL expression in rats and reduce hepatic TG levels [139]. It is interesting to note that hepatic lipolysis produces ligands for PPAR α to further enhance catabolism via mitochondrial and/or peroxisomal β -oxidation. Moreover, HSL expression is under the (positive) control of PPAR γ [140]. LXR α -agonists, on the other hand, were found to suppress HSL expression but, so far, this has only been analyzed in adipocytes [141]. There is no information available on the effect of RA on PPAR α - and/or PPAR γ -mediated regulation of ATGL and HSL, but these vitamin A metabolites are likely have modulatory functions on their expression given the collaborative actions of those factors with RXR α . Interestingly, PNPLA3 expression is under the direct control of SREBP-1c and ChREBP [142,143], which was linked to its role in the conversion of TG to NEFA. Given recent data that PNPLA3 also contains retinyl esterase activity and is highly expressed in HSC, this may imply a direct role of these transcription factors in vitamin A metabolism.

Finally, hepatic fatty acid β -oxidation (#8 in Figure 2) is largely controlled by PPAR α /RXR. There is a wealth of information about PPAR α agonists and how they protect against and/or

relieve fat accumulation in the liver (for recent reviews, see [144,145]). There is, however, limited information on whether vitamin A-metabolites have a modulatory effect on RXR/PPAR α -mediated fatty acid catabolism. atRA treatment does enhance hepatic PPAR α and RXR α levels in mice, as well as key target genes uncoupling-protein-2 (UCP2), carnitine-palmitoyltransferase 1A (CPT1), and carnitine/acylcarnitine carrier, while suppressing SREBP-1c and FAS levels [146]. Both 9cRA and atRA were shown to induce CPT1 *in vitro*, most likely via RXR/PPAR α [147]. PPAR α also induces expression of Fibroblast Growth Factor 21 (FGF21), a hepatocyte-derived hormone suppressing obesity-induced fatty liver. FGF21 controls glucose and lipid metabolism and induces PPAR γ -coactivator 1-alpha (PGC-1 α) signaling, resulting in enhanced fatty acid oxidation and suppression of lipid synthesis (reviewed in [148]). atRA induces expression of FGF21 through RAR α and RAR β . Adenoviral overexpression of RAR β enhances hepatic production and secretion of FGF21 and promotes hepatic fatty acid β -oxidation [149]. FGF21 expression is also controlled by RXR/Farnesoid X receptor (FXR), where RXR acts as a permissive partner. Thus, FGF21 expression is enhanced by 9cRA via FXR/RXR [150]. Hepatic lipid metabolism is also modulated by another FGF, e.g., FGF19 (the ortholog of FGF15 in rodents). Murine FGF15 is produced in the intestine, while human FGF19 is produced in the intestine as well as in the liver [151–153]. FGF19 suppresses lipogenesis by blocking SREBP-1c signaling and simultaneously inducing fatty acid β -oxidation by blocking ACC2 (reviewed in [154]). Mouse FGF15 expression is under the control of RXR/FXR, where ligands of RXR induce its expression independently from bile acid-induced FXR activation. A similar effect of retinoic acids was found for human FGF19 expression; however, mechanistically, a more prominent role was observed for RXR/RAR-mediated regulation of FGF19 [155].

Taken together, it is evident that vitamin A metabolites are key (co-)regulators of hepatic lipid metabolism. RAR-mediated signaling (via atRA or synthetic ligands) most consistently induces suppression of hepatic NEFA and TG accumulation. RXR-mediated signaling (via 9cRA, synthetic ligands, or other NR, like PPARs, LXR, and FXR) may cause opposing effects at different levels in the metabolic pathway, leading to hepatic lipid accumulation. However, the liver is not the only tissue involved in obesity-induced hepatic steatosis that is heavily regulated by vitamin A metabolites. The most important—and most intensively studied—being adipose tissue, which is discussed next.

6. Vitamin A and Fat Metabolism in Adipose Tissue

Besides controlling lipid metabolism in the liver, vitamin A metabolites also play key roles in the differentiation, maturation, and function of adipose tissue. In obesity-associated NAFLD, there is an increase in NEFA flowing from adipose tissue to the liver, in part as a result of insulin resistance. Adipogenesis is a tightly regulated cellular differentiation process, in which preadipocytes are transformed into lipid-storing adipocytes with enhanced expression of lipogenic genes. Insulin promotes glucose transport to adipocytes and PPAR γ -dependent DNL leads to lipid accumulation.

atRA has a dual role in adipocyte differentiation and functionality: (1) it suppresses adipogenesis and (2) promotes lipolysis in differentiated adipocytes. Two RA-binding proteins, cellular retinoic acid binding protein 2 (CRABP2) and Fatty Acid Binding Protein 5 (FABP5), play a key role in directing atRA to either RXR/RAR γ or RXR/PPAR β/δ , activation of which differentiates between the two pathways. atRA inhibits adipogenesis through the CRABP2-RXR/RAR γ pathway, which induces expression of inhibitors of adipocyte differentiation, including SOX9, which blocks CCAAT/enhancer binding protein beta (C/EBP β) and CCAAT/enhancer binding protein gamma (C/EBP γ)-mediated differentiation, and Kruppel-like factor 2 (KLF2), which blocks CCAAT/enhancer binding protein alpha (C/EBP α)-, SCREBP-1c-, and PPAR γ -mediated adipogenesis. KLF2 also induces RAR γ and CRABP2, providing a positive feedback loop to suppress adipogenesis [156,157]. Adipocyte differentiation (for instance, induced by insulin) is initiated by lowering CRABP2 levels and redirection of atRA-mediated signaling to FABP5-RXR/PPAR β/δ , which induces lipolysis (via HSL upregulation), mitochondrial activity (via uncoupling proteins/UCP1), and fatty acid β -oxidation, as well as enhancing the insulin-responsive glucose transporter type 4 (GLUT4). *In vivo*, atRA raises body

temperature, decreases body weight, and reduces plasma triglycerides and insulin levels in obese mice, and might do so more potently than selective PPAR β/δ ligands [156,157]. Obviously, this is not a stand-alone effect on adipose tissue, but heavily intertwined with the effects of hepatic lipid metabolism described above. Interestingly, impaired supply of retinols to (pre)adipocytes may also stimulate adipogenesis, as an excess of (retinol-free) apoRBP4 (as observed in obese individuals with a low retinol:RBP4 ratio) promotes retinol efflux via STRA6, thereby reducing RAR activity and leading to enhanced adipogenesis [158]. As stated earlier, adipocytes are the main extrahepatic cells that express RBP4, but this does not contribute to circulating RBP4. Adipocyte-specific overexpression of (human) RBP4 aggravated diet-induced obesity, glucose intolerance, and hepatic TG levels. RBP4-induced inflammation in adipose tissue stimulated lipolysis in adipocytes, leading to enhanced circulating NEFA, leading to elevated triglycerides in the liver [88].

In addition to atRA signaling, synthetic ligands for RXR promote adipogenesis in 3T3-L1 cells, a commonly used model to study adipocyte differentiation, by activation of RXR/PPAR γ -mediated adipogenesis [159]. On the other hand, retinaldehyde, the precursor for retinoic acid, inhibits 9cRA-mediated activation of RXR/PPAR γ thereby suppressing adipogenesis and lipid accumulation in adipose tissue. Moreover, retinaldehyde activates RAR, thereby recruiting PGC-1 α and inducing UCP1 expression leading to enhanced mitochondrial respiration and adaptive thermogenesis, which promotes “browning” of white adipose tissue [160]. While endogenous levels of retinoic acids are generally undetectable in tissues, retinaldehyde levels in mouse adipose tissue are ~1 nmol/g [161]. Intraperitoneal administration of retinaldehyde significantly suppressed adipogenesis and diet-induced obesity in mice, while such an effect was not observed after oral delivery of retinaldehyde [161,162]. Genetic ablation of *Aldh1a1* (encoding RALDH1) and administration of RALDH inhibitors increase tissue levels of retinaldehyde and protect against diet-induced obesity and diabetes [160,161].

Finally, glucose may be an important modulator of the effect of RA on adipocytes as recent data show that RA suppresses lipid accumulation under normal glucose levels, while this effect shifts to lipid accumulation at high glucose conditions, a metabolic switch controlled by SREBP-1c [163].

7. Insulin and Vitamin A Cross-Talk in NAFLD

Vitamin A is required for normal development and endocrine functions of the pancreas, including the insulin-producing β -cells and the glucagon-producing α -cells in the islets of Langerhans. The pancreas stores retinoids in pancreatic stellate cells that are essential for normal islet function. Similar to the liver, retinoid storage in the pancreas is impaired during development of pancreatic diseases. VAD reduces β -cell mass and increases α -cell mass. Consequently, VAD in mice leads to aberrant pancreatic endocrine function due to lower insulin secretion and promotes hyperglycemia [164]. atRA-activated RAR α induces pancreatic glucose transporter type 2 (Glut2) and Gck expression and is required in the adult pancreas for maintaining β -cell mass and function [165,166]. Similarly, RAR β 2 agonists improved insulin sensitivity, lowered serum glucose and insulin levels, and reduced triglycerides and steatosis in the liver, pancreas, and kidneys of obese and diabetic mice [167].

In the liver, insulin promotes the activation of HSC via the phosphorylation of forkhead box gene, group O1 (FoxO1). Active (non-phosphorylated) FoxO1 suppresses HSC activation. Insulin signals via the PI3/AKT pathway to phosphorylate FoxO1, thereby allowing activation of HSC, characterized by enhanced proliferation and expression of fibrotic markers and aggravation of bile duct ligation-induced fibrosis in FoxO1+/- heterozygous mice compared to FoxO1+/+ wild types [168–170]. A recent paper suggests, though, that the effect of insulin may be reversed in the presence of vitamin A. Co-treatment with insulin potentiated the vitamin A-mediated suppression of HSC activation markers through stimulating Janus kinase 2/Signal transducer and activator of transcription 5A (JAK2/STAT5) signaling and SREBP1 expression [171]. Thus, VAD and hyperinsulinemia may synergize to activate HSC and promote fibrosis in NAFLD.

8. Vitamin A Therapy in NAFLD

Despite extensive historical and recent evidence that (1) vitamin A metabolism is disturbed in obesity and NAFLD and (2) vitamin A metabolites, especially atRA and synthetic RAR ligands, have beneficial effects on hepatic lipid metabolism and obesity-induced NAFLD in animal models, no clinical trials are ongoing to evaluate their therapeutic potential in patients. Instead, multiple trials are being performed to test the therapeutic value of synthetic ligands that modulate the activity of other nuclear receptors that control hepatic glucose and lipid metabolism, such as PPAR α , PPAR β/δ , PPAR γ , and FXR, all dimerization partners of RXR α . Also, variants of RAR-controlled FGF19 and FGF21 are in phase II clinical trials for the treatment of NAFLD [172]. As outlined above, vitamin A metabolism is heavily disturbed in NAFLD and will affect the activation status of RXRs and RARs. As an additional result, it will also modulate the activity of PPARs and FXR via the heterodimer partner RXR. Thus, the synthetic ligands for these receptors that are currently in clinical trials for the treatment of NAFLD and/or NASH may only bear partial effects because of impaired activation of the heterodimer partner RXR. Re-establishing proper levels of vitamin A metabolites, either systemically or directed to the liver, may have therapeutic value on its own, or potentiate the therapeutic effect of ligands of PPARs and/or FXR. Moreover, vitamin A metabolites also regulate bile acid synthesis directly via RXR- and RAR-mediated regulation of SHP and FGF15/19, as well as indirectly via RXR/FXR [155,173–176], which may feedback into FXR-mediated regulation of lipid and glucose metabolism.

In addition, retinaldehyde was identified about 10 years ago as promising compound to treat diet-induced obesity and diabetes in animal models. *Raldh1*^{−/−} mice, which accumulate retinaldehyde in tissues, showed reduced hepatic lipid accumulation compared to wild-type (WT) mice when fed a high-fat diet (HFD) [161]. However, no application of retinaldehyde or RALDH inhibitors in NAFLD patients has been reported so far or is in the early phase of clinical testing.

Fenretinide (4-hydroxy(phenyl)retinamide; 4-HPR) is a synthetic retinoid that has been extensively studied for its potential therapeutic action against cancers, especially breast cancer, non-small cell lung cancer, neuroblastoma, and prostate cancer. Both RXR- and RAR-dependent and independent mechanisms have been proposed to underlie the therapeutic action of fenretinide, including inhibition of cell proliferation and the induction of apoptosis in cancer cells [177–179]. Fenretinide is well tolerated, with limited side effects in daily treatment regimens for five years or more [180,181]. Fenretinide also improves symptoms of diet-induced obesity, insulin resistance, and NAFLD. In addition, fenretinide improved insulin sensitivity and decreased serum leptin levels in a clinical trial in overweight women [182]. Fenretinide reduces circulating RBP4 levels, but the key importance of this effect in the therapeutic action of fenretinide is controversial, as it also prevents and/or reverses obesity, insulin resistance, and hepatic steatosis in *Rbp4* knockout mice on HFD [183]. Indeed, additional RAR-dependent and -independent mechanisms have also been identified that may contribute to the therapeutic effect of fenretinide in obesity-related pathologies, including enhanced mitochondrial and peroxisomal β -oxidation [184–188], ER-stress-mediated degradation of SCD1 [189], inhibition of ceramide synthesis, enhanced reactive oxygen species (ROS) production [184,190], enhanced retinoid signaling [191], and inhibition of hepatic FGF21 expression [192]. The many clinical trials aimed at evaluating fenretinide therapy in cancer have, however, shown that it dose-dependently reduces plasma retinol levels up to 90% compared to baseline pre-therapy, leading to vitamin A deficiency and impaired dark-adaptation as a regularly observed adverse effect [193–212]. The drop in circulating retinol cannot be prevented by vitamin A supplementation [196]. The retinol-lowering effects of fenretinide may be particularly relevant for patients with metabolic syndrome and diabetes as plasma retinol levels are already low in those patients. A phase 2 clinical trial to evaluate the insulin-sensitizing effect of fenretinide in subjects with insulin resistance and NAFLD was initiated in 2007, but no results have been reported yet [213].

In summary, both natural and synthetic retinoids show important potential for the treatment of NAFLD and associated syndromes, like diabetes. However, these compounds act also on many other biological processes. Thus, tissue-specific targeting and/or characterization of derivatives that

selectively modulate specific pathways may be required to arrive at a safe and effective treatment for NAFLD.

9. Conclusions

It is evident that hepatic glucose and lipid metabolism are regulated by vitamin A metabolites at many different levels. Moreover, disease progression within the NAFLD spectrum to NASH, cirrhosis, and cancer is associated with declining circulating and hepatic retinol levels. This is not necessarily true for hepatic retinyl esters as individuals homozygous for the PNPLA3-I148M risk allele are predisposed to NAFLD and disease progression, while their hepatic retinyl palmitate levels are increased compared to NAFLD-I148 (protective allele) carriers. It is unknown whether this shift from retinol to retinyl esters is more common in NAFLD patients. Thus, we still lack important knowledge on hepatic vitamin A metabolism and the true meaning of VAD in NAFLD. To specify a few open questions: (1) are retinyl ester stores depleted in NAFLD or is retinol release from such stores impaired? (2) How can PNPLA3-I148M predispose for fibrosis while it leads to increased hepatic retinyl ester levels? (3) What is the contribution of hepatocytes and stellate cells to impaired retinol metabolism in NAFLD? (4) What is the absolute contribution of adipose-derived lipids and de novo lipogenesis in NAFLD and how is this controlled by vitamin A metabolites? (5) Why do circulating retinol levels stay low or even further decline after bariatric surgery, even under impressive weight loss and/or vitamin A supplementation therapy? (6) Is the therapeutic efficacy of nuclear receptor ligands that are currently under investigation for NAFLD limited by impaired vitamin A metabolism in the liver? (7) Does VAD actually contribute to the development of fatty liver?

With respect to the latter: Severe VAD in lean rats decreases serum triacylglycerol, cholesterol, and HDL cholesterol levels as well as hepatic phospholipids compared to VA-sufficient animals [214]. Expression of acetyl-CoA carboxylase decreased, suggesting impaired fatty acid synthesis, while mitochondrial fatty acid β -oxidation was enhanced. However, (free) cholesterol levels were enhanced in the hearts of VAD rats [215], as well as concentrations of triglycerides, total cholesterol, free and esterified cholesterol, and phospholipids in the aorta [216]. In contrast, VAD in mice appears to have the opposite effect. Hepatic TG levels are enhanced in VAD mice compared to control animals, which is associated with strongly reduced expression of PPAR α and genes involved in mitochondrial and peroxisomal β -oxidation [217]. Thus, it also remains unclear whether VAD contributes to hepatic steatosis, and human data are so far lacking on this topic.

Thus, there is still a lot to learn about vitamin A metabolism in the liver in healthy and pathological conditions, which hopefully will reveal novel therapeutic targets for the treatment of NAFLD, in particular to prevent pathological conditions caused by NASH, cirrhosis, and hepatocellular carcinoma.

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