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Vitamins and non-alcoholic fatty liver disease: A Molecular Insight*

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Abstract

The incidence of non-alcoholic fatty liver disease (NAFLD) is rising rapidly across the globe. NAFLD pathogenesis is largely driven by an imbalance in hepatic energy metabolism and at present, there is no approved drug for its treatment. The liver plays a crucial role in micronutrient metabolism and deregulation of this micronutrient metabolism may contribute to the pathogenesis of NAFLD. Vitamins regulate several enzymatic processes in the liver, and derangement in vitamin metabolism is believed to play a critical role in NAFLD progression. The anti-oxidant activities of vitamin C and E have been attributed to mitigate hepatocyte injury, and alterations in the serum levels of vitamin D, vitamin B12 and folate have shown a strong correlation with NAFLD severity. This review aims to highlight the role of these vitamins, which represent promising therapeutic targets for the management of NAFLD.

Keywords

Antioxidant; Autophagy; Non-alcoholic fatty liver disease (NAFLD); Non-alcoholic steatohepatitis (NASH); Vitamin A; Vitamin B; Vitamin C; Vitamin D; Vitamin E

1 Introduction

Non-alcoholic fatty liver disease (NAFLD) is the most common chronic hepatopathy worldwide. It is recognized as a hepatic manifestation of the metabolic syndrome, and characterized by lipid infiltration in hepatocytes. NAFLD comprises a range of diseases from simple steatosis to non-alcoholic steatohepatitis (NASH), fibrosis, cirrhosis, and may progress to hepatocellular carcinoma (HCC).[1,2] The worldwide prevalence of NAFLD is estimated to be 24%,[3] while it is reported to have much higher incidence in patients with metabolic syndrome and type 2 diabetes (T2D).[4] The mortality rate and the number of liver

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transplantations owing to NAFLD and NASH are increasing, making it the second leading cause of liver transplant in the United States.[5,6] A steady progress has been seen in the understanding of NAFLD epidemiology and pathogenesis; however, there is slow advancement in the development of therapeutics. Although several potential targets have been identified, currently, there is no FDA approved therapy for NAFLD/NASH.[7]

NAFLD is a multifactorial disease having various modifiers such as lifestyle, diet, and gut microbiota, which act together in a suitable genetic/epigenetic environment and alter the response to lipid excess. Two significant metabolic abnormalities commonly linked to NAFLD are insulin resistance (IR) and increased supply of fatty acids to the liver, which are largely attributed to obesity induced by high energy food consumption and sedentary lifestyle adopted by the modern society. The consumption of obesogenic diet, and deranged energy balance, result in lipid accumulation in the hepatocytes, leading to lipotoxicity, oxidative stress, endoplasmic reticulum (ER) stress, and liver inflammation, which are key drivers of NAFLD. The pathogenesis of NAFLD is substantially affected by individual lifestyle choices including diet and exercise. Lifestyle modifications (diet, physical activity and exercise), which primarily aim at controlling bodyweight and metabolic disorders, remain the mainstay approach of disease management.[8] However, a reduction in energy alone does not suffice and studies have highlighted that dietary composition also plays a critical role in the manifestation and development of NAFLD.[9]

The liver is involved in micronutrient metabolism, the impairment of which, may contribute to the pathogenesis of NAFLD.[10] In addition to hepatocytes, the liver contains monocytes, lymphocytes, Kupffer cells, natural killer (NK) cells, dendritic cells (DCs) and several other immigrant cells, which are closely associated with the immune system. Diet contains macronutrients which provide energy for body functions, and micronutrients that perform regulatory functions. Vitamins are essential nutrients of our diet which are well known to affect the immune system, including both innate and adaptive response.[11] The immune system is particularly associated with the entero-hepatic axis and involved in the development and progression of NAFLD. Recent studies have highlighted the relation between dietary vitamins and fat accumulation in the liver.[12] Some researchers have focused on the role of a specific vitamin on hepatic metabolism; however, a broader outlook of the role of vitamins in NAFLD remains unexplored.[13] In this review, we discuss the hepatic pathophysiology linking vitamins to NAFLD, aiming to summarise the role of some key vitamins in NAFLD progression and to highlight their potential in NAFLD management.

2 Vitamin E

Vitamin E, a fat-soluble and powerful chain breaking antioxidant in the human body, has the most significant evidence of therapeutic benefit in liver disease.[4] Vitamin E has the ability to reduce oxidative stress and decelerate the pathogenesis of NASH (Fig. 1).[14] The American Association for the Study of Liver Disease (AASLD) and the European Association for the Study of the Liver (EASL) recommend the use of vitamin E (800 IU/day) in non-diabetic adults with biopsy-proven NASH.[4,15] Despite the availability of no standard protocol for the treatment of NAFLD/NASH, vitamin E supplements are commonly prescribed to NAFLD patients.[16]

2.1 Molecular structure and function of Vitamin E

Vitamin E has eight natural forms including four tocopherols (α, β, γ, δ) and four tocotrienols (α, β, γ, δ), with a-tocopherol being the most abundant and efficacious in inhibiting lipid oxidation. Vitamin E reduces peroxidation and inhibits the expression of transforming growth factor-beta (TGF-β) which is involved in hepatic fibrosis and hepatocyte apoptosis through activation of hepatic stellate cells (HSCs).[17] It improves liver integrity by down-regulating the hepatic cluster of differentiation 36 (CD36), a membrane transporter protein responsible for the uptake of fatty acids into the liver.[18] A rat model based study for NASH showed that vitamin E enrichment caused a lowering in lipid peroxidation.[19] Elevated hepatic transaminase levels were normalized in chickens fed with a high-oxidant diet along with vitamin E supplementation.[20] PIVENS (previously reported randomized controlled trial, adult patients) and TONIC (Treatment of NAFLD in Children) trials (pediatric population), showed significant improvement in steatosis and inflammation in patients treated with vitamin E for 96 weeks compared to placebo.[21,22] However, one study reported no significant improvement in alanine transaminase (ALT) upon daily administration of 800 IU vitamin E for 96 weeks, although NAFLD activity score (NAS) and hepatocellular ballooning score were improved.[21] Similar results were seen in a pediatric population by Vos *et al.*,[23] where they reported that insufficient vitamin E consumption is related to a higher grade of hepatic steatosis. Nobili *et al.*24 showed improvement in transaminases and liver histology in children receiving vitamin E treatment. Similar results were reported by Nobili *et al.*,[25] who showed that vitamin E supplementation provided no improvement in NAFLD, in a cohort of 53 children and adolescents.

2.2 Anti-oxidant effect

Patients with NAFLD show increased oxidative stress. This oxidative stress is developed when reactive oxygen species (ROS) generation overcomes the cellular antioxidant mechanisms.[26,27] Antioxidant deficit may lead to increased lipid peroxidation and cell death caused due to mitochondrial compromise. Vitamin E has an inherent anti-oxidative activity; it can scavenge lipid peroxyl radicals by donating a hydrogen ion from its chromanol ring.[28,29] It acts as a scavenger of hydroxyl, peroxyl and superoxide radicals and provides protection against plasma lipid and low-density lipoprotein peroxidation. The ability of vitamin E to scavenge radicals is not limited to ROS, it has also been found to be active against reactive nitrogen species (RNS).[30] Higher vitamin E intake may, therefore, help to counteract the rise in oxidative stress in NAFLD patients.

The interaction of vitamin E with cellular components may help to foster the anti-oxidative environment.[28] Superoxide dismutase (SOD) is a crucial antioxidative enzyme, which can partition superoxide radicals into oxygen or hydrogen peroxide. Vitamin E supplementation is known to stimulate SOD levels.[27,31–34] Vitamin E also stimulates the action of other antioxidative enzymes including catalase and glutathione peroxidase.[27,31,33,34] Dietary vitamin E lowers c-myc and transforming growth factor-alpha (TGF-α) expression, causing reduced secretion of nitric oxide synthase (iNOS) and reduced form of nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, which significantly contribute to oxidative stress.[31,35]

2.3 Anti-inflammatory and anti-apoptotic effect

Vitamin E may mitigate hepatic fibrosis and prevent cirrhosis by modulating inflammatory response.[14,28] Vitamin E supplementation has been linked to increased adiponectin messenger RNA (mRNA) and protein levels.[36,37] Adiponectin suppresses hepatic fatty acid synthesis and reduces inflammation in patients with NASH.[36] Vitamin E suppresses the expression of pro-inflammatory cytokines such as TNF-α, IL-1, IL-2, IL-4, IL-6, and IL-8 and lowers inflammatory response in NAFLD.[28,31,38]

Vitamin E is also reported to play a role in cell death and apoptosis.[36,39] Studies have suggested that vitamin E increases the levels of anti-apoptotic protein BCL-2, and lowers the levels of pro-apoptotic proteins BAX and p53.[39] It decreases the activity of caspase-9 and cytochrome C, which are involved in the mitochondrial apoptosis pathway, and caspase-8 and caspase-3 involved in the Fas/FasL apoptotic pathway.[39] Some studies have also shown the drawbacks of vitamin E. A study linked the supplementation of high-dose vitamin E with increased mortality.[40] Further studies are needed to evaluate the safety and effectiveness of using vitamin E as a therapeutic in NAFLD.

3 Vitamin D

Vitamin D is an essential nutrient and a steroid hormone well known for its role in calcium homeostasis and mineral metabolism. Vitamin D is derived from 7-dehydrocholesterol present in the skin, which upon ultraviolet light B (UVB) irradiation converts to an inactive precursor (cholecalciferol) that further undergoes a two-step metabolism in the liver and the kidney, and gets converted into its biologically active form, 1, 25-dihydroxyvitamin D3 (calcitriol). Vitamin D mediates its action by interaction with the nuclear vitamin D receptor (VDR), which belongs to the nuclear receptor superfamily of ligand activated transcription factors.[41] The genomic actions of vitamin D involve the heterodimerization of the ligand activated VDR with the retinoid-X-receptor (RXR) causing transcriptional activation or repression of a number of target genes through binding to vitamin D response elements (VDREs) in the promoter region of target genes. The non-genomic actions of vitamin D are manifested through the activation of signaling molecules including phosphatidylinositol-3 kinase (PI3K), generation of secondary messengers (cyclic adenosine monophosphate (AMP), Ca^{2+}, etc.) and activation of protein kinases including protein kinase A, mitogen-activated protein (MAP) kinases, src, protein kinase C (PKC) and Ca^{2+}-calmodulin kinase II.[42] Remarkable scientific interest in the extra-skeletal actions of vitamin D in recent years has expanded its actions to cardiovascular disease, diabetes, immune modulation, cell proliferation and differentiation. Consistent with the multifaceted nature and diverse properties of vitamin D, circulating evidences provide a link between vitamin D and fatty liver disease. While vitamin D deficiency is widely prevalent in the world, concurrently, NAFLD is a rapidly emerging manifestation of the metabolic syndrome worldwide. Several epidemiological studies have reported the coexistence of hypovitaminosis D and NAFLD, and provide evidence that these conditions share multiple risk factors. It is notable that low serum vitamin D levels correlate with the severity of steatosis and necro-inflammatory damage.[43,44]

3.1 Role of vitamin D in insulin resistance

Vitamin D deficiency occurs in 55% of the patients with NAFLD.[45] Several experimental models have proposed vitamin D as a modulator of insulin sensitivity.[46] Epidemiological data reports an association between vitamin D levels and the presence of obesity, T2D and IR.[47] IR is a well-known precursor and accelerant of NAFLD, and is considered as a hallmark of the disease linked to the development of oxidative stress and lipotoxicity.[48] Vitamin D deficiency is reported to affect insulin secretion in both animal and human models. Vitamin D has a positive role in the modification of pancreatic β-cell function and may directly stimulate pancreatic insulin secretion owing to the presence of VDRs in the β-cells of pancreas, and by the expression of 1-a-hydroxylase enzyme.[49] Insulin secretion is a calciumdependent process, and changes in calcium flux may have an adverse effect on pancreatic β-cell secretion (Fig. 2). Vitamin D deficient-hypocalcemic rats show lower glucose-stimulated insulin secretion without correction of hypocalcemia.[50] Vitamin D deficiency may, therefore, contribute to IR and NAFLD.

3.2 Vitamin D as an immunomodulator

Various studies have shown the role of vitamin D in the development and function of the immune system. The detection of functional VDR in almost all immune cells including antigen-presenting cells (APCs), i.e. the macrophages and DCs, and activated T lymphocytes, provides an indirect evidence of the potential role of vitamin D as an immunomodulator. Vitamin D regulates both innate and adaptive immune system through VDR. The activated nuclear VDR is involved in the transcriptional regulation of the proliferation and differentiation of immune cells.[51] The immunomodulatory effects of vitamin D may be attributed to the ability of its biologically active form, calcitriol, to regulate the expression of various genes. The innate immune response involves activation of Toll-like receptors (TLRs) on polymorphonuclear cells, monocytes, macrophages, and epithelial cells. The TLRs are pattern recognition receptors, which play a key role in host cell recognition and response to pathogens. Among the 13 TLRs identified in mammals, TLR2, TLR4 and TLR9 are involved in the pathogenesis of NAFLD.[52] Vitamin D deficiency exacerbates the development and progression of NAFLD by the activation of TLR2 and TLR4 and stimulation of downstream inflammatory signaling molecules causing steatosis and inflammation.[52]

Adiponectin, the prototypic adipokine which is described as an anti-inflammatory agent, has been shown to decrease necro-inflammation and steatosis in NAFLD and improve IR.[53] In a large cohort of patients, a positive association was observed between 25 hydroxy vitamin D concentrations and adiponectin levels, independent of body mass index (BMI).[54] In another study,[55] mice fed with a high-fat Western diet (WD) along with vitamin D depletion (VDD) were compared to the WD alone group. The WD/VDD mice had increased hepatic mRNA levels of resistin, IL-4, IL-6 and TNF-a markers known to be implicated in oxidative stress and hepatic inflammation. The vitamin D deficient mice had increased levels of mRNA of TLR-2, TLR-4, and TLR-9 following WD. Similarly, in a study based on a rat NASH model, 25 hydroxy vitamin D and 1, 25 dihydroxy vitamin D levels were increased by phototherapy while lowering hepatocyte inflammation, fibrosis and apoptosis as compared to controls.[54]

In association with reduced hepatic expression of inflammatory genes TNF-a and TGF-P, phototherapy improved IR and increased serum adiponectin.

3.3 Vitamin D attenuates hepatic steatosis by inducing autophagy

Autophagy is a major cellular recycling process leading to the degradation of cytoplasmic contents, which are delivered to and degraded in the lysosomes, to supply energy and regenerate organelles. It helps to remove the misfolded cytosolic proteins, glycogen, lipids, nucleic acids, and clears damaged organelles including mitochondria, endoplasmic reticulum and peroxisomes. Following degradation, the breakdown products are released and recycled into macromolecular components; therefore, autophagy is believed to be a cell-survival mechanism to maintain cell viability under unfavourable conditions and balances energy sources under nutrient stress. The deregulation of autophagy may contribute to the pathogenesis of human diseases including liver associated diseases, neurodegenerative diseases and cancer.[56] Autophagy has been implicated as a disease associated factor in people with liver-related disorders, and is reported to contribute to the development of hepatic steatosis, fibrosis, cirrhosis, and HCC.[57] Hormone induced autophagy helps to maintain intracellular homeostasis in response to nutrient and energy deficit.[58] Hepatic autophagy serves as mean to regulate hepatic lipid content through delivery of lipid droplets to lysosomes in a process known as “Lipophagy”.[58] Lipophagy has been implicated in a number of anti-NAFLD action of drugs and hormones.[59,60] Murine models of NAFLD showed that pharmacological or genetic inhibition of autophagy increased hepatic fat content.[61] Furthermore, the down-regulation of hepatic autophagy is a consistent finding in human studies on NAFLD.[62]

1, 25-dihydroxy vitamin D has been shown to protect against high-fat diet (HFD) or free fatty acid (FFA) induced hepatic steatosis by inducing autophagy in FFA-treated HepG2 cells (Fig. 3).[63] Furthermore, HFD-fed mice treated with 1, 25-dihydroxy vitamin D showed increase in autophagic flux and increased expression of the markers of autophagy.[63] The protective effects of 1, 25-dihydroxy vitamin D were abrogated on the inhibition of autophagy by 3-methyladenine.[63] These findings suggest that 1, 25-dihydroxy vitamin D may modulate hepatic steatosis by inducing autophagy, however, the mechanism underlying this effect is not well understood. Some studies indicate a direct role of vitamin D in modulating liver inflammation and fibrogenesis, and improving hepatic response to insulin by its binding to specific VDR expressed on different cell types in the liver.[64] While the VDR is expressed at low levels in hepatocytes, their levels can be induced by lipotoxic insults.[65,66] Additionally, high expression of both nuclear and membrane VDR is seen in the non-parenchymal liver cells including HSCs, Kupffer cells, natural killer T (NKT) cells and sinusoidal endothelial cells.[67] HSCs are major effectors of hepatic fibrosis, and the expression of VDR in the HSCs has been reported to antagonise TGF-β signaling, which is the major pro-fibrogenic pathway in the liver.[68]

Although epidemiological studies correlating hypovitaminosis D to the presence of NAFLD reinforce the belief that restoration of optimal vitamin D levels may be a therapeutic approach to the management of NAFLD lack of consistent data from vitamin D supplementation trials warrants further studies.[47,69]

4 Vitamin B

The vitamin B group includes eight types of compounds including thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine (B6), biotin (B7), folic acid (B9), and cyanocobalamin (B12). Vitamin B3, also known as niacin, acts as a precursor of the coenzyme nicotinamide adenine dinucleotide (NAD) and nicotinamide adenine dinucleotide phosphate (NADPH), which have a crucial role in lipid metabolism.[70] It has been used for the treatment of dyslipidemia and cardiovascular diseases.[71] Vitamin B3 supplementation increased redox potential, lowered hepatic cholesterol content, and blocked the gain in liver weight in obesogenic diet-induced rat model of NAFLD. A protective effect was also seen on the pre-existing hepatic steatosis, displaying the therapeutic potential of vitamin B3 in NAFLD.[72] Niacin treated human hepatoblastoma cells showed a reduction in hepatic lipid accumulation by 40-60%, likely through the inhibition of diglyceride acyltransferase 2 and NADPH oxidase.[73] Plasma triglyceride concentration, hepatic fat content, and improved liver enzymes were lowered in dyslipidemic patients treated with niacin.[74] However, niacin treatment in a random controlled trial based on 27 obese individuals with NAFLD, failed to demonstrate a decrease in hepatic fat deposition although serum triglyceride and very low-density lipoprotein were reduced and insulin sensitivity was improved.[75] Some studies have demonstrated that long-term niacin supplementation may lead to IR.[76] As the pathogenesis of NAFLD involves IR and patients with NAFLD already have reduced insulin sensitivity, niacin may have some adverse side effects despite reducing the hepatic fat content.

Vitamin B12 exists in two forms in humans: methyl cobalamin and 5'-deoxyadenosylcobalamine and has been linked to hepatitis, cirrhosis and HCC. It acts as a cofactor for the mitochondrial enzyme, methyl malonyl CoA mutase, which regulates the rate of long-chain fatty acyl-CoA transfer into mitochondria and affects lipid metabolic pathways.[77] The liver acts as a storage site for vitamin B12. Some studies, in animal models, demonstrated the effect of vitamin B12 deficiency in lipid metabolism.[78] Low vitamin B12 intake in maternal diet led to high rates of adiposity and T2DM in offspring, along with a change in the expression of genes involved in hepatic lipid metabolism. These alterations were normalised upon reconstitution of vitamin B12.[78,79] Low serum vitamin B12 was associated with elevated serum ALT levels in NAFLD patients.[80] Increased body fat mass percentage, decreased fat-free mass, and impaired capacity to secrete insulin was seen in offspring of female weaning rats with restricted vitamin B12. Offspring born to mothers with B12 deficiency displayed dysregulation of fatty acid metabolism, amino acid metabolism, and glycolysis possibly due to alteration of peroxisome proliferator-activated receptor (PPAR) γ and PPARα hepatic expression.[81] In some other studies, offspring subjected to maternal vitamin B12 deficiency displayed enhanced plasma total cholesterol.[79] The protective role of vitamin B12 in NAFLD remains controversial as some studies also reported no protective effect of vitamin B12 in NAFLD.[82]

Folate or vitamin B9, a water-soluble vitamin, is involved in one-carbon transfer reactions which are essential for cell metabolism.[83,84] Dysregulated folate-dependent one-carbon metabolism has been implicated in NAFLD-related comorbidities including obesity, T2D, and metabolic syndrome.[85–88] Genetic mutations in folate pathway have been shown to dysregulate homocysteine metabolism.[89,90] Homocysteine, a sulphur-containing amino acid,

is formed as an intermediate in the biosynthesis of methionine and cysteine.[91] Hyperhomocysteinemia is known to affect intracellular lipid metabolism and increased homocysteine levels may promote hepatic fat accumulation.[92,93] A recent study reported that hyperhomocysteinemia promotes hepatic steatosis in mice via activation of the aryl hydrocarbon receptor/CD36 pathway.[94] Hepatic lipid accumulation was reported in various models of hyperhomocysteinemia.[95,96]

In mammals, dietary intake of folate is essential to meet physiological requirements as they lack the ability to synthesize folate.[97,98] Studies have reported an inverse association of serum folate levels with BMI in patients with obesity, NAFLD and T2D.[86,88] Low serum folate levels were found in obese and overweight patients as compared to individuals with normal weight.[87] It is suggested that folate deficiency may contribute to the development of steatosis.[99,100] Depletion of dietary folate was linked to high expression of lipid biosynthetic genes, leading to dysregulation of lipid metabolism in the liver.[101] Folate deficient mice showed impaired hepatic lipid transport by very low-density lipoprotein (VLDL).[85,99]

A recent study demonstrated that AMP activated protein kinase (AMPK) activation in HFD fed mice was restored upon folic acid supplementation and improved hyperinsulinemia, lipid and glucose metabolism.[102] Hepatic IR disturbs lipid metabolism leading to disrupted glucose and lipid production in the liver, a feature commonly observed in NAFLD.[103] This dysregulated lipid and carbohydrate metabolism is often associated with disturbed AMPK, a key regulator of energy metabolism.[104] The inactivation of AMPK is linked to hepatic lipid accumulation, hyperinsulinemia and hyperglycemia in animal models with HFD induced NAFLD.[102,105] Further studies are warranted to elaborate upon the role of folate in metabolic disease and explore its potential as a therapeutic for NAFLD.

5 Vitamin A

Vitamin A or retinoic acid is an essential fat-soluble vitamin obtained from carotenoids such as β-carotene (found in carrots and green leafy vegetables such as spinach) or retinyl esters from rich animal sources like eggs, fish and the liver. They are absorbed and transported as retinyl esters in chylomicrons, to the liver where they are hydrolyzed to form retinol. Retinol is mainly stored in the HSCs, which are responsible for fibrosis, and plays a central role in vitamin A metabolism.[106] Retinol mainly exerts its action via activation of the retinoic acid receptor (RAR) or RXR. Hepatocytes are known to actively metabolize vitamin A and alter glucose and lipid metabolism in response to the vitamin A metabolites. [107,108] Vitamin A is crucial for several physiological processes such as vision, cell proliferation and differentiation, immune regulation, embryogenesis, glucose and lipid metabolism.[106]

Retinoic acid via RARs increases hepatic expression of genes promoting fatty acid oxidation (PPARα, fibroblast growth factor 21 (FGF21), carnitine palmitoyltransferase I (CPT1), and uncoupling protein 2 (UCP2)).[106] In line with these findings retinoic acid treatment causes reduction in liver triacylglycerol content and circulating VLDL fraction, and moderately increase ketogenesis.[109]

Hepatic lipid accumulation results primarily due to influx of dietary lipids, non-esterified fatty acids (NEFAs) from adipose tissue and hepatic *de novo* lipogenesis (DNL). Vitamin A is directly or indirectly involved in the regulation of these processes. Retinoic acids, as well as synthetic ligands of RXRα (*e.g.,* bexarotene), enhance hepatic DNL and plasma TG levels by activating liver X receptor (LXR)/RXR and PPARγ/RXR, which, in turn, enhance the expression of sterol regulatory element-binding protein (SREBP)-1c and carbohydrateresponsive element binding protein (ChREBP).[110] Both SREBP-1c and ChREBP increase hepatic lipogenic genes such as acetyl-CoA synthase and lipogenic enzymes including acetyl-CoA carboxylase 1 (ACC1), fatty acid synthase, stearyl-CoA desaturase and glycerol-3-phosphate acyltransferase, mitochondrial (GPAT) in the liver. The inhibition of SREBP-1c or ChREBP leads to impaired lipid synthesis and decreases hepatic steatosis.[111,112]

These apparent opposing effects of retinoic acid signalling may be due to differential action of RARs (lipolytic) and RXRs (lipogenic) transcriptional activities. Furthermore, model systems, ligand and doses of retinoic acid used in different studies may also lead to these contrasting effects.

Along with their anti-steatotic effects in hepatocytes, a highly selective RARβ2 agonist AC261066, was shown to reduce the activation of HSCs, marked by decreased HSC expression of alpha-smooth muscle actin (a-SMA), in mice with HFD-induced NAFLD.[113]

Several genomic loci are known to increase the predisposition to NAFLD, the most prominent being a genetic variant of patatin-like phospholipase domain-containing 3 (PNPLA3-I148M), a distinguished heritable factor linked to NAFLD. It is known to predispose for disease progression and NAFLD-associated HCC.[114] PNPLA3 is a multifunctional enzyme which acts as a triglyceride hydrolase, retinyl esterase and acetyl-CoA-independent transacylase.[115] Its genetic variant, PNPLA3-I148M has lowered hydrolase activity and promotes triglyceride accumulation in the liver. Overexpression of PNPLA3-I148M is reported to cause hepatic steatosis in mice and alters circulating retinol levels in humans.[116]

In human studies involving NAFLD/NASH patients, serum retinoic acid concentrations were lowered and the extent of hepatic steatosis was inversely correlated with retinoid X receptor mRNA expression.[117] NAS and hepatic ballooning were also associated with alteration in serum retinoic acid concentration.[117,118]

6 Vitamin C

The impact of oxidative stress and inflammation is well demonstrated in the development of NAFLD, metabolic syndrome, cardiovascular disease, and diabetes mellitus.[119] The production of ROS leads to peroxidation, resulting in inflammation and the activation of HSCs, thereby causing fibrosis. Oxidative stress accelerates IR and inflammation in hepatic cells, which are critical mechanisms leading to dislipidemia.[120] Vitamin C (ascorbic acid) is a powerful antioxidant in human health, capable of scavenging free radicals.[121] In isolated rat liver mitochondria, vitamin C decreases mitochondrial ROS generation and enhances

manganese SOD and glutathione peroxidase (GPx) activity.[122] Vitamin C treatment may, therefore, relieve hepatic oxidative stress. It has also been inversely linked to the inflammatory markers, C-reactive protein (CRP) and myeloperoxidase.[123,124] Ascorbic acid is also suggested to regulate adiponectin, which lowers lipid accumulation in liver, systemic IR and inflammation, and protects against NAFLD.[125,126] Additionally, ascorbic acid supplementation inhibits hepatic steatosis and stress via increase in the mRNA levels of PPARa-dependent fatty acid β-oxidation genes in livers activation of the FGF21/FGFR2/adiponectin pathway.[127,128]

Vitamin C is believed to play a role in circulating and hepatic lipid homeostasis.[129] Vitamin C supplementation in rats with glucose intolerance induced by dexamethasone led to improved insulin sensitivity.[130] A decrease in serum vitamin C levels was related to increase in hepatic ballooning in pediatric patients with NAFLD.[23] A cross-sectional study by Han *et al.*[131] in Korean males showed a positive association between low vitamin C intake and NAFLD. Similarly, an inverse association between dietary vitamin C intake and NAFLD in middleaged and older adults, especially for the male population and non-obesity population.[132] In contrast to this, another cross-sectional study showed similar level of vitamin C concentrations in NAFLD patients and healthy controls.[100] Another study by Madan *et al.*[133]reported no difference in plasma vitamin C levels in NAFLD patients and healthy control population.

Vitamin C deficiency is reported to accelerate dyslipidemia and hepatic consequences, while increased intake of vitamin C reduced the severity of dyslipidemia and lipid accumulation in the hepatocytes of guinea pigs.[134] Another study showed that vitamin C supplementation improved oxidative stress, hepatocellular ballooning and inflammation in a rat model.[135] Harrison *et al.*[136] reported that a combination treatment of vitamin C and E led to improved hepatic fibrosis in NASH patients. A study by Foster *et al.*[137] suggested that vitamin C and E, along with atorvastatin (20 mg), effectively reduced hepatic steatosis by 71% in individuals with NAFLD. Some other trials suggested that a combination supplementation of vitamin C and vitamin E did not produce better effect than lifestyle intervention.[24,25] These studies did not, however, assess the independent effect of vitamin C supplementation. There is a deficit of literature on the role of vitamin C in NAFLD and the association between vitamin C and NAFLD remains controversial.

7 Conclusions

NAFLD is a multifaceted and complex liver disease, having strong association with oxidative stress, IR, lipid profile, metabolic deregulation, obesity, immune regulation and gut microbiota, among others. The deficiency of several micronutrients, particularly several vitamins, is commonly associated with NAFLD and has been correlated with disease severity. Several pieces of experimental data have shown that deficiency of different vitamins may cause metabolic deregulation. Some studies have demonstrated the anti-inflammatory and insulin-sensitizing properties exerted by these vitamins in the hepatic cells. Based on these observations, several vitamins such as vitamin E, D, B9, B12, A and C represent potential therapeutic options for liver damage in NAFLD and NASH. More clinical trials are warranted to directly evaluate the efficacy of supplementation of these vitamins on

disease progression in NAFLD, as some of them may also have adverse outcomes. It is also crucial to study the interactions between these vitamins and how their intake affects lipid metabolism. Well-defined studies are required to establish the roles of these vitamins as therapeutic agents in NAFLD/NASH.

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References

1. Raza S, Rajak S, Anjum B, Sinha RA. Molecular links between non-alcoholic fatty liver disease and hepatocellular carcinoma. Hepatoma Res. 2019; 5:42. doi: 10.20517/2394-5079.2019.014 [PubMed: 31867441]
2. Younossi Z, Stepanova M, Ong JP, et al. Nonalcoholic steatohepatitis is the fastest growing cause of hepatocellular carcinoma in liver transplant candidates. Clin Gastroenterol Hepatol. 2019; 17:748–755. DOI: 10.1016/j.cgh.2018.05.057 [PubMed: 29908364]
3. Younossi Z, Anstee QM, Marietti M, et al. Global burden of NAFLD and NASH: trends, predictions, risk factors and prevention. Nat Rev Gastroenterol Hepatol. 2018; 15:11–20. DOI: 10.1038/nrgastro.2017.109 [PubMed: 28930295]
4. Chalasani N, Younossi Z, Lavine JE, et al. The diagnosis and management of nonalcoholic fatty liver disease: practice Guideline by the American Association for the Study of Liver Diseases, American College of Gastroenterology, and the American Gastroenterological Association. Hepatology. 2012; 55:2005–2023. DOI: 10.1002/hep.25762 [PubMed: 22488764]
5. Charlton MR, Burns JM, Pedersen RA, Watt KD, Heimbach JK, Dierkhising RA. Frequency and outcomes of liver transplantation for nonalcoholic steatohepatitis in the United States. Gastroenterology. 2011; 141:1249–1253. DOI: 10.1053/j.gastro.2011.06.061 [PubMed: 21726509]
6. Wong RJ, Aguilar M, Cheung R, et al. Nonalcoholic steatohepatitis is the second leading etiology of liver disease among adults awaiting liver transplantation in the United States. Gastroenterology. 2015; 148:547–555. DOI: 10.1053/j.gastro.2014.11.039 [PubMed: 25461851]
7. Raza S, Rajak S, Upadhyay A, Tewari A, Anthony Sinha R. Current treatment paradigms and emerging therapies for NAFLD/NASH. Front Biosci (Landmark Ed). 2021; 26:206–237. [PubMed: 33049668]
8. Mahady SE, George J. Exercise and diet in the management of nonalcoholic fatty liver disease. Metabolism. 2016; 65:1172–1182. DOI: 10.1016/j.metabol.2015.10.032 [PubMed: 26805014]
9. Perdomo CM, Frühbeck G, Escalada J. Impact of nutritional changes on nonalcoholic fatty liver disease. Nutrients. 2019; 11:677. doi: 10.3390/nu11030677
10. Pickett-Blakely O, Young K, Carr RM. Micronutrients in nonalcoholic fatty liver disease pathogenesis. Cell Mol Gastroenterol Hepatol. 2018; 6:451–462. DOI: 10.1016/j.jcmgh.2018.07.004 [PubMed: 30294653]
11. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol. 2008; 8:685–698. DOI: 10.1038/nri2378 [PubMed: 19172691]
12. Li J, Cordero P, Nguyen V, Oben JA. The role of vitamins in the pathogenesis of nonalcoholic fatty liver disease. Integr Med Insights. 2016; 11:19–25. DOI: 10.4137/IMI.S31451 [PubMed: 27147819]
13. Cicero AFG, Colletti A, Bellentani S. Nutraceutical approach to non-alcoholic fatty liver disease (NAFLD): the available clinical evidence. Nutrients. 2018; 10:1153. doi: 10.3390/nu10091153
14. Oseini AM, Sanyal AJ. Therapies in non-alcoholic steatohepatitis (NASH). Liver Int. 2017; 37:97–103. DOI: 10.1111/liv.13302 [PubMed: 28052626]

15. Blond E, Disse E, Cuerq C, et al. EASL-EASD-EASO clinical practice guidelines for the management of non-alcoholic fatty liver disease in severely obese people: do they lead to over-referral? Diabetologia. 2017; 60:1218–1222. DOI: 10.1007/s00125-017-4264-9 [PubMed: 28352941]
16. Amanullah I, Khan YH, Anwar I, Gulzar A, Mallhi TH, Raja AA. Effect of vitamin E in non-alcoholic fatty liver disease: a systematic review and meta-analysis of randomised controlled trials. Postgrad Med J. 2019; 95:601–611. DOI: 10.1136/postgradmedj-2018-136364 [PubMed: 31434683]
17. Hasegawa T, Yoneda M, Nakamura K, Makino I, Terano A. Plasma transforming growth factor-beta1 level and efficacy of alpha-tocopherol in patients with non-alcoholic steatohepatitis: a pilot study. Aliment Pharmacol Ther. 2001; 15:1667–1672. DOI: 10.1046/j.1365-2036.2001.01083.x [PubMed: 11564008]
18. Podszun MC, Grebenstein N, Spruss A, et al. Dietary alpha-tocopherol and atorvastatin reduce high-fat-induced lipid accumulation and down-regulate CD36 protein in the liver of guinea pigs. J Nutr Biochem. 2014; 25:573–579. DOI: 10.1016/j.jnutbio.2014.01.008 [PubMed: 24725433]
19. Miyazaki H, Takitani K, Koh M, Yoden A, Tamai H. The alpha-tocopherol status and expression of alpha-tocopherol-related proteins in methionine-choline deficient rats treated with vitamin E. J Clin Biochem Nutr. 2014; 54:190–197. DOI: 10.3164/jcbn.13-74 [PubMed: 24895482]
20. Lu T, Harper AF, Zhao J, Corl BA, LeRoith T, Dalloul RA. Effects of a dietary antioxidant blend and vitamin E on fatty acid profile, liver function, and inflammatory response in broiler chickens fed a diet high in oxidants. Poult Sci. 2014; 93:1658–1666. DOI: 10.3382/ps.2013-03827 [PubMed: 24864279]
21. Lavine JE, Schwimmer JB, Van Natta ML, et al. Effect of vitamin E or metformin for treatment of nonalcoholic fatty liver disease in children and adolescents: the TONIC randomized controlled trial. JAMA. 2011; 305:1659–1668. DOI: 10.1001/jama.2011.520 [PubMed: 21521847]
22. Sanyal AJ, Chalasani N, Kowdley KV, et al. Pioglitazone, vitamin E, or placebo for nonalcoholic steatohepatitis. N Engl J Med. 2010; 362:1675–1685. DOI: 10.1056/NEJMoa0907929 [PubMed: 20427778]
23. Vos MB, Colvin R, Belt P, et al. Correlation of vitamin E, uric acid, and diet composition with histologic features of pediatric NAFLD. J Pediatr Gastroenterol Nutr. 2012; 54:90–96. DOI: 10.1097/MPG.0b013e318229da1a [PubMed: 22197855]
24. Nobili V, Manco M, Devito R, Ciampalini P, Piemonte F, Marcellini M. Effect of vitamin E on aminotransferase levels and insulin resistance in children with non-alcoholic fatty liver disease. Aliment Pharmacol Ther. 2006; 24:1553–1561. DOI: 10.1111/j.1365-2036.2006.03161.x [PubMed: 17206944]
25. Nobili V, Manco M, Devito R, et al. Lifestyle intervention and antioxidant therapy in children with nonalcoholic fatty liver disease: a randomized, controlled trial. Hepatology. 2008; 48:119–128. DOI: 10.1002/hep.22336 [PubMed: 18537181]
26. Li L, Yang X. The essential element manganese, oxidative stress, and metabolic diseases: links and interactions. Oxid Med Cell Longev. 2018; 2018 7580707 doi: 10.1155/2018/7580707 [PubMed: 29849912]
27. Debbabi M, Nury T, Zarrouk A, et al. Protective effects of alpha-tocopherol, gammatocopherol and oleic acid, three compounds of olive oils, and no effect of trolox, on 7-ketocholesterol-induced mitochondrial and peroxisomal dysfunction in microglial BV-2 cells. Int J Mol Sci. 2016; 17:1973. doi: 10.3390/ijms17121973
28. Rimbach G, Moehring J, Huebbe P, Lodge JK. Gene-regulatory activity of alphatocopherol. Molecules. 2010; 15:1746–1761. DOI: 10.3390/molecules15031746 [PubMed: 20336011]
29. Jiang Q. Natural forms of vitamin E: metabolism, antioxidant, and anti-inflammatory activities and their role in disease prevention and therapy. Free Radic Biol Med. 2014; 72:76–90. DOI: 10.1016/j.freeradbiomed.2014.03.035 [PubMed: 24704972]
30. Niki E. Role of vitamin E as a lipid-soluble peroxyl radical scavenger: in vitro and in vivo evidence. Free Radic Biol Med. 2014; 66:3–12. DOI: 10.1016/j.freeradbiomed.2013.03.022 [PubMed: 23557727]

31. Ahsan H, Ahad A, Iqbal J, Siddiqui WA. Pharmacological potential of tocotrienols: a review. Nutr Metab (Lond). 2014; 11:52. doi: 10.1186/1743-7075-11-52 [PubMed: 25435896]
32. Singh N, Chander Narula S, Kumar Sharma R, Tewari S, Kumar Sehgal P. Vitamin E supplementation, superoxide dismutase status, and outcome of scaling and root planing in patients with chronic periodontitis: a randomized clinical trial. J Periodontol. 2014; 85:242–249. DOI: 10.1902/jop.2013.120727 [PubMed: 23688096]
33. Tabei SM, Fakher S, Djalali M, et al. Effect of vitamins A, E, C and omega-3 fatty acids supplementation on the level of catalase and superoxide dismutase activities in streptozotocin-induced diabetic rats. Bratisl Lek Listy. 2015; 116:115–118. DOI: 10.4149/bll_2015_022 [PubMed: 25665478]
34. Nor Azman NHE, Goon JA, Abdul Ghani SM, Hamid Z, Wan Ngah WZ. Comparing palm oil, tocotrienol-rich fraction and alpha-tocopherol supplementation on the antioxidant levels of older adults. Antioxidants (Basel). 2018; 7:74. doi: 10.3390/antiox7060074
35. Calvisi DF, Ladu S, Hironaka K, Factor VM, Thorgeirsson SS. Vitamin E down-modulates iNOS and NADPH oxidase in c-Myc/TGF-alpha transgenic mouse model of liver cancer. J Hepatol. 2004; 41:815–822. DOI: 10.1016/j.jhep.2004.07.030 [PubMed: 15519655]
36. Nan YM, Wu WJ, Fu N, et al. Antioxidants vitamin E and 1-aminobenzotriazole prevent experimental non-alcoholic steatohepatitis in mice. Scand J Gastroenterol. 2009; 44:1121–1131. DOI: 10.1080/00365520903114912 [PubMed: 19606393]
37. Mohseni F, Moghbelinejad S, Najafipour R. Major components of metabolic parameters and nutritional intakes in different genotypes of adiponectin +276 G>T gene polymorphism in non-diabetes and non-alcoholic iranian fatty liver patients. Avicenna J Med Biotechnol. 2017; 9:155–161. [PubMed: 28706613]
38. Ortiz GG, Pacheco-Moisés FP, Gómez-Rodríguez VM, González-Renovato ED, Torres-Sánchez ED, Ramirez-Anguiano AC. Fish oil, melatonin and vitamin E attenuates midbrain cyclooxygenase-2 activity and oxidative stress after the administration of 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine. Metab Brain Dis. 2013; 28:705–709. DOI: 10.1007/s11011-013-9416-0 [PubMed: 23703110]
39. Jin X, Song L, Liu X, et al. Protective efficacy of vitamins C and E on p,p'-DDT-induced cytotoxicity via the ROS-mediated mitochondrial pathway and NF-kappaB/FasL pathway. PLoS One. 2014; 9 e113257 doi: 10.1371/journal.pone.0113257 [PubMed: 25464339]
40. Bjelakovic G, Nikolova D, Gluud C. Antioxidant supplements and mortality. Curr Opin Clin Nutr Metab Care. 2014; 17:40–44. DOI: 10.1097/MC0.0000000000000009 [PubMed: 24241129]
41. Fleet JC. Rapid, membrane-initiated actions of 1,25 dihydroxyvitamin D: what are they and what do they mean? J Nutr. 2004; 134:3215–3218. DOI: 10.1093/jn/134.12.3215 [PubMed: 15570014]
42. Hii CS, Ferrante A. The non-genomic actions of vitamin D. Nutrients. 2016; 8:135. doi: 10.3390/nu8030135 [PubMed: 26950144]
43. Yodoshi T, Orkin S, Arce-Clachar AC, et al. Vitamin D deficiency: prevalence and association with liver disease severity in pediatric nonalcoholic fatty liver disease. Eur J Clin Nutr. 2020; 74:427–435. DOI: 10.1038/s41430-019-0493-y [PubMed: 31444465]
44. Zhu S, Wang Y, Luo F, et al. The level of vitamin D in children and adolescents with nonalcoholic fatty liver disease: a Meta-analysis. Biomed Res Int. 2019; 2019 7643542 doi: 10.1155/2019/7643542 [PubMed: 31380438]
45. Nelson JE, Roth CL, Wilson LA, et al. Vitamin D deficiency is associated with increased risk of non-alcoholic steatohepatitis in adults with non-alcoholic fatty liver disease: possible role for MAPK and NF-κB? Am J Gastroenterol. 2016; 111:852–863. DOI: 10.1038/ajg.2016.51 [PubMed: 27002799]
46. Elseweidy MM, Amin RS, Atteia HH, Ali MA. Vitamin D3 intake as regulator of insulin degrading enzyme and insulin receptor phosphorylation in diabetic rats. Biomed Pharmacother. 2017; 85:155–159. DOI: 10.1016/j.biopha.2016.11.116 [PubMed: 27930980]
47. Lee I, Park E, Cho J. Association of nonalcoholic fatty liver disease with serum vitamin D levels in combination of physical fitness in korean older adults. J Steroid Biochem Mol Biol. 2020; 198 105569 doi: 10.1016/j.jsbmb.2019.105569 [PubMed: 31891747]

48. Khan RS, Bril F, Cusi K, Newsome PN. Modulation of insulin resistance in nonalcoholic fatty liver disease. Hepatology. 2019; 70:711–724. DOI: 10.1002/hep.30429 [PubMed: 30556145]
49. Kjalarsdottir L, Tersey SA, Vishwanath M, et al. 1,25-Dihydroxyvitamin D3 enhances glucose-stimulated insulin secretion in mouse and human islets: a role for transcriptional regulation of voltage-gated calcium channels by the vitamin D receptor. J Steroid Biochem Mol Biol. 2019; 185:17–26. DOI: 10.1016/j.jsbmb.2018.07.004 [PubMed: 30071248]
50. Beaulieu C, Kestekian R, Havrankova J, Gascon-Barré M. Calcium is essential in normalizing intolerance to glucose that accompanies vitamin D depletion in vivo. Diabetes. 1993; 42:35–43. DOI: 10.2337/diab.42.1.35 [PubMed: 8380563]
51. Sassi F, Tamone C, D'Amelio P. Vitamin D: nutrient, hormone, and immunomodulator. Nutrients. 2018; 10:1656. doi: 10.3390/nu10111656
52. Miura K, Ohnishi H. Role of gut microbiota and Toll-like receptors in nonalcoholic fatty liver disease. World J Gastroenterol. 2014; 20:7381–7391. DOI: 10.3748/wjg.v20.i23.7381 [PubMed: 24966608]
53. Liu Y, Palanivel R, Rai E, et al. Adiponectin stimulates autophagy and reduces oxidative stress to enhance insulin sensitivity during high-fat diet feeding in mice. Diabetes. 2015; 64:36–48. DOI: 10.2337/db14-0267 [PubMed: 25071026]
54. Vaidya A, Williams JS, Forman JP. The independent association between 25-hydroxyvitamin D and adiponectin and its relation with BMI in two large cohorts: the NHS and the HPFS. Obesity (Silver Spring). 2012; 20:186–191. DOI: 10.1038/oby.2011.210 [PubMed: 21760630]
55. Roth CL, Elfers CT, Figlewicz DP, et al. Vitamin D deficiency in obese rats exacerbates nonalcoholic fatty liver disease and increases hepatic resistin and Toll-like receptor activation. Hepatology. 2012; 55:1103–1111. DOI: 10.1002/hep.24737 [PubMed: 21994008]
56. Levine B, Packer M, Codogno P. Development of autophagy inducers in clinical medicine. J Clin Invest. 2015; 125:14–24. DOI: 10.1172/JCI73938 [PubMed: 25654546]
57. Ueno T, Komatsu M. Autophagy in the liver: functions in health and disease. Nat Rev Gastroenterol Hepatol. 2017; 14:170–184. DOI: 10.1038/nrgastro.2016.185 [PubMed: 28053338]
58. Sinha RA, Singh BK, Yen PM. Reciprocal crosstalk between autophagic and endocrine signaling in metabolic homeostasis. Endocr Rev. 2017; 38:69–102. DOI: 10.1210/er.2016-1103 [PubMed: 27901588]
59. Sinha RA, Singh BK, Yen PM. Nonalcoholic fatty liver disease and hypercholesterolemia: roles of thyroid hormones, metabolites, and agonists. Thyroid. 2019; 29:1173–1191. DOI: 10.1089/thy.2018.0664 [PubMed: 31389309]
60. Sinha RA, Rajak S, Singh BK, Yen PM. Hepatic lipid catabolism via PPARa-lysosomal crosstalk. Int J Mol Sci. 2020; 21:2391. doi: 10.3390/ijms21072391
61. Singh R, Kaushik S, Wang Y, et al. Autophagy regulates lipid metabolism. Nature. 2009; 458:1131–1135. DOI: 10.1038/nature07976 [PubMed: 19339967]
62. Wu WKK, Zhang L, Chan MTV. Autophagy, NAFLD and NAFLD-related HCC. Adv Exp Med Biol. 2018; 1061:127–138. DOI: 10.1007/978-981-10-8684-7_10 [PubMed: 29956211]
63. Li R, Guo E, Yang J, et al. 1,25$(OH)_2$ D_3 attenuates hepatic steatosis by inducing autophagy in mice. Obesity (Silver Spring). 2017; 25:561–571. DOI: 10.1002/oby.21757 [PubMed: 28145056]
64. Dong B, Zhou Y, Wang W, et al. Vitamin D receptor activation in liver macrophages ameliorates hepatic inflammation, steatosis, and insulin resistance in mice. Hepatology. 2020; 71:1559–1574. DOI: 10.1002/hep.30937 [PubMed: 31506976]
65. Han S, Chiang JY. Mechanism of vitamin D receptor inhibition of cholesterol 7alpha-hydroxylase gene transcription in human hepatocytes. Drug Metab Dispos. 2009; 37:469–478. DOI: 10.1124/dmd.108.025155 [PubMed: 19106115]
66. Bozic M, Guzmán C, Benet M, et al. Hepatocyte vitamin D receptor regulates lipid metabolism and mediates experimental diet-induced steatosis. J Hepatol. 2016; 65:748–757. DOI: 10.1016/j.jhep.2016.05.031 [PubMed: 27245430]
67. Gascon-Barré M, Demers C, Mirshahi A, Néron S, Zalzal S, Nanci A. The normal liver harbors the vitamin D nuclear receptor in nonparenchymal and biliary epithelial cells. Hepatology. 2003; 37:1034–1042. DOI: 10.1053/jhep.2003.50176 [PubMed: 12717384]

68. Ding N, Yu RT, Subramaniam N, et al. A vitamin D receptor/SMAD genomic circuit gates hepatic fibrotic response. Cell. 2013; 153:601–613. DOI: 10.1016/j.cell.2013.03.028 [PubMed: 23622244]
69. Wei Y, Wang S, Meng Y, et al. Effects of vitamin D supplementation in patients with nonalcoholic fatty liver disease: a systematic review and meta-analysis. Int J Endocrinol Metab. 2020; 18 e97205 doi: 10.5812/ijem.97205 [PubMed: 33257903]
70. Leaf A, Lansdowne Z. Vitamins--conventional uses and new insights. World Rev Nutr Diet. 2014; 110:152–166. DOI: 10.1159/000358464 [PubMed: 24751627]
71. Ganji SH, Kamanna VS, Kashyap ML. Niacin and cholesterol: role in cardiovascular disease (review). J Nutr Biochem. 2003; 14:298–305. DOI: 10.1016/s0955-2863(02)00284-x [PubMed: 12873710]
72. Ganji SH, Kukes GD, Lambrecht N, Kashyap ML, Kamanna VS. Therapeutic role of niacin in the prevention and regression of hepatic steatosis in rat model of nonalcoholic fatty liver disease. Am J Physiol Gastrointest Liver Physiol. 2014; 306 G320-327 doi: 10.1152/ajpgi.00181.2013 [PubMed: 24356885]
73. Ganji SH, Kashyap ML, Kamanna VS. Niacin inhibits fat accumulation, oxidative stress, and inflammatory cytokine IL-8 in cultured hepatocytes: impact on non-alcoholic fatty liver disease. Metabolism. 2015; 64:982–990. DOI: 10.1016/j.metabol.2015.05.002 [PubMed: 26024755]
74. Hu M, Chu WC, Yamashita S, et al. Liver fat reduction with niacin is influenced by DGAT-2 polymorphisms in hypertriglyceridemic patients. J Lipid Res. 2012; 53:802–809. DOI: 10.1194/jlr.P023614 [PubMed: 22315393]
75. Fabbrini E, Mohammed BS, Korenblat KM, et al. Effect of fenofibrate and niacin on intrahepatic triglyceride content, very low-density lipoprotein kinetics, and insulin action in obese subjects with nonalcoholic fatty liver disease. J Clin Endocrinol Metab. 2010; 95:2727–2735. DOI: 10.1210/jc.2009-2622 [PubMed: 20371660]
76. Heemskerk MM, van den Berg SA, Pronk AC, et al. Long-term niacin treatment induces insulin resistance and adrenergic responsiveness in adipocytes by adaptive downregulation of phosphodiesterase 3B. Am J Physiol Endocrinol Metab. 2014; 306:E808–E813. DOI: 10.1152/ajpendo.00641.2013 [PubMed: 24473440]
77. O'Leary F, Samman S. Vitamin B12 in health and disease. Nutrients. 2010; 2:299–316. DOI: 10.3390/nu2030299 [PubMed: 22254022]
78. Deshmukh U, Katre P, Yajnik CS. Influence of maternal vitamin B12 and folate on growth and insulin resistance in the offspring. Nestle Nutr Inst Workshop Ser. 2013; 74:145–154. DOI: 10.1159/000348463 [PubMed: 23887113]
79. Khaire A, Rathod R, Kale A, Joshi S. Vitamin B12 and omega-3 fatty acids together regulate lipid metabolism in Wistar rats. Prostaglandins Leukot Essent Fatty Acids. 2015; 99:7–17. DOI: 10.1016/j.plefa.2015.04.006 [PubMed: 26003565]
80. Koplay M, Gulcan E, Ozkan F. Association between serum vitamin B12 levels and the degree of steatosis in patients with nonalcoholic fatty liver disease. J Investig Med. 2011; 59:1137–1140. DOI: 10.2310/JIM.0b013e31822a29f5
81. Ahmad S, Kumar KA, Basak T, et al. PPAR signaling pathway is a key modulator of liver proteome in pups born to vitamin B(12) deficient rats. J Proteomics. 2013; 91:297–308. DOI: 10.1016/j.jprot.2013.07.027 [PubMed: 23928364]
82. Polyzos SA, Kountouras J, Patsiaoura K, et al. Serum vitamin B12 and folate levels in patients with non-alcoholic fatty liver disease. Int J Food Sci Nutr. 2012; 63:659–666. DOI: 10.3109/09637486.2011.649249 [PubMed: 22229957]
83. Stover PJ. Physiology of folate and vitamin B12 in health and disease. Nutr Rev. 2004; 62:S3–12. DOI: 10.1111/j.1753-4887.2004.tb00070.x [PubMed: 15298442]
84. Tibbetts AS, Appling DR. Compartmentalization of mammalian folate-mediated one-carbon metabolism. Annu Rev Nutr. 2010; 30:57–81. DOI: 10.1146/annurev.nutr.012809.104810 [PubMed: 20645850]
85. da Silva RP, Kelly KB, Al Rajabi A, Jacobs RL. Novel insights on interactions between folate and lipid metabolism. Biofactors. 2014; 40:277–283. DOI: 10.1002/biof.1154 [PubMed: 24353111]

86. Hirsch S, Poniachick J, Avendaño M, et al. Serum folate and homocysteine levels in obese females with non-alcoholic fatty liver. Nutrition. 2005; 21:137–141. DOI: 10.1016/j.nut.2004.03.022 [PubMed: 15723740]

87. Mahabir S, Ettinger S, Johnson L, et al. Measures of adiposity and body fat distribution in relation to serum folate levels in postmenopausal women in a feeding study. Eur J Clin Nutr. 2008; 62:644–650. DOI: 10.1038/sj.ejcn.1602771 [PubMed: 17457338]

88. Nilsson E, Matte A, Perfilyev A, et al. Epigenetic alterations in human liver from subjects with type 2 diabetes in parallel with reduced folate levels. J Clin Endocrinol Metab. 2015; 100:E1491–1501. DOI: 10.1210/jc.2015-3204 [PubMed: 26418287]

89. Friso S, Girelli D, Trabetti E, et al. A1298C methylenetetrahydrofolate reductase mutation and coronary artery disease: relationships with C677T polymorphism and homocysteine/folate metabolism. Clin Exp Med. 2002; 2:7–12. DOI: 10.1007/s102380200001 [PubMed: 12049191]

90. Schreuder TC, Verwer BJ, van Nieuwkerk CM, Mulder CJ. Nonalcoholic fatty liver disease: an overview of current insights in pathogenesis, diagnosis and treatment. World J Gastroenterol. 2008; 14:2474–2486. DOI: 10.3748/wjg.14.2474 [PubMed: 18442193]

91. Faeh D, Chiolero A, Paccaud F. Homocysteine as a risk factor for cardiovascular disease: should we (still) worry about? Swiss Med Wkly. 2006; 136:745–756. DOI: 10.2006/47/smw-11283 [PubMed: 17225194]

92. Werstuck GH, Lentz SR, Dayal S, et al. Homocysteine-induced endoplasmic reticulum stress causes dysregulation of the cholesterol and triglyceride biosynthetic pathways. J Clin Invest. 2001; 107:1263–1273. DOI: 10.1172/JCI11596 [PubMed: 11375416]

93. Obeid R, Herrmann W. Homocysteine and lipids: S-adenosyl methionine as a key intermediate. FEBS Lett. 2009; 583:1215–1225. DOI: 10.1016/j.febslet.2009.03.038 [PubMed: 19324042]

94. Yao L, Wang C, Zhang X, et al. Hyperhomocysteinemia activates the aryl hydrocarbon receptor/CD36 pathway to promote hepatic steatosis in mice. Hepatology. 2016; 64:92–105. DOI: 10.1002/hep.28518 [PubMed: 26928949]

95. Namekata K, Enokido Y, Ishii I, Nagai Y, Harada T, Kimura H. Abnormal lipid metabolism in cystathionine beta-synthase-deficient mice, an animal model for hyperhomocysteinemia. J Biol Chem. 2004; 279:52961–52969. DOI: 10.1074/jbc.M406820200 [PubMed: 15466479]

96. Hamelet J, Demuth K, Paul JL, Delabar JM, Janel N. Hyperhomocysteinemia due to cystathionine beta synthase deficiency induces dysregulation of genes involved in hepatic lipid homeostasis in mice. J Hepatol. 2007; 46:151–159. DOI: 10.1016/j.jhep.2006.07.028 [PubMed: 17030070]

97. Lucock M. Folic acid: nutritional biochemistry, molecular biology, and role in disease processes. Mol Genet Metab. 2000; 71:121–138. DOI: 10.1006/mgme.2000.3027 [PubMed: 11001804]

98. Zhao Y, Su B, Jacobs RL, et al. Lack of phosphatidylethanolamine N-methyltransferase alters plasma VLDL phospholipids and attenuates atherosclerosis in mice. Arterioscler Thromb Vasc Biol. 2009; 29:1349–1355. DOI: 10.1161/ATVBAHA.109.188672 [PubMed: 19520976]

99. Christensen KE, Wu Q, Wang X, Deng L, Caudill MA, Rozen R. Steatosis in mice is associated with gender, folate intake, and expression of genes of one-carbon metabolism. J Nutr. 2010; 140:1736–1741. DOI: 10.3945/jn.110.124917 [PubMed: 20724492]

100. Da Silva HE, Arendt BM, Noureldin SA, Therapondos G, Guindi M, Allard JP. A cross-sectional study assessing dietary intake and physical activity in Canadian patients with nonalcoholic fatty liver disease vs healthy controls. J Acad Nutr Diet. 2014; 114:1181–1194. DOI: 10.1016/j.jand.2014.01.009 [PubMed: 24631112]

101. Champier J, Claustrat F, Nazaret N, Fèvre Montange M, Claustrat B. Folate depletion changes gene expression of fatty acid metabolism, DNA synthesis, and circadian cycle in male mice. Nutr Res. 2012; 32:124–132. DOI: 10.1016/j.nutres.2011.12.012 [PubMed: 22348461]

102. Sid V, Wu N, Sarna LK, Siow YL, House JD, O K. Folic acid supplementation during high-fat diet feeding restores AMPK activation via an AMP-LKB1-dependent mechanism. Am J Physiol Regul Integr Comp Physiol. 2015; 309:R1215–R1225. DOI: 10.1152/ajpregu.00260.2015 [PubMed: 26400185]

103. Birkenfeld AL, Shulman GI. Nonalcoholic fatty liver disease, hepatic insulin resistance, and type 2 diabetes. Hepatology. 2014; 59:713–723. DOI: 10.1002/hep.26672 [PubMed: 23929732]

104. Hardie DG, Ross FA, Hawley SA. AMPK: a nutrient and energy sensor that maintains energy homeostasis. Nat Rev Mol Cell Biol. 2012; 13:251–262. DOI: 10.1038/nrm3311 [PubMed: 22436748]
105. Pu P, Gao DM, Mohamed S, et al. Naringin ameliorates metabolic syndrome by activating AMP-activated protein kinase in mice fed a high-fat diet. Arch Biochem Biophys. 2012; 518:61–70. DOI: 10.1016/j.abb.2011.11.026 [PubMed: 22198281]
106. Saeed A, Dullaart RPF, Schreuder TCMA, Blokzijl H, Faber KN. Disturbed vitamin A metabolism in non-alcoholic fatty liver disease (NAFLD). Nutrients. 2017; 10:29. doi: 10.3390/nu10010029
107. Senoo H, Yoshikawa K, Morii M, Miura M, Imai K, Mezaki Y. Hepatic stellate cell (vitamin A-storing cell) and its relative-past, present and future. Cell Biol Int. 2010; 34:1247–1272. DOI: 10.1042/CBI20100321 [PubMed: 21067523]
108. Saeed A, Bartuzi P, Heegsma J, et al. Impaired hepatic vitamin A metabolism in NAFLD mice leading to vitamin A accumulation in hepatocytes. Cell Mol Gastroenterol Hepatol. 2021; 11:309–325. DOI: 10.1016/j.jcmgh.2020.07.006 [PubMed: 32698042]
109. Amengual J, Ribot J, Bonet ML, Palou A. Retinoic acid treatment enhances lipid oxidation and inhibits lipid biosynthesis capacities in the liver of mice. Cell Physiol Biochem. 2010; 25:657–666. DOI: 10.1159/000315085 [PubMed: 20511711]
110. Lalloyer F, Pedersen TA, Gross B, et al. Rexinoid bexarotene modulates triglyceride but not cholesterol metabolism via gene-specific permissivity of the RXR/LXR heterodimer in the liver. Arterioscler Thromb Vasc Biol. 2009; 29:1488–1495. DOI: 10.1161/ATVBAHA.109.189506 [PubMed: 19592467]
111. Papazyan R, Sun Z, Kim YH, et al. Physiological suppression of lipotoxic liver damage by complementary actions of HDAC3 and SCAP/SREBP. Cell Metab. 2016; 24:863–874. DOI: 10.1016/j.cmet.2016.10.012 [PubMed: 27866836]
112. Iizuka K, Horikawa Y. ChREBP: a glucose-activated transcription factor involved in the development of metabolic syndrome. Endocr J. 2008; 55:617–624. DOI: 10.1507/endocrj.k07e-110 [PubMed: 18490833]
113. Trasino SE, Tang XH, Jessurun J, Gudas LJ. A retinoic acid receptor β2 agonist reduces hepatic stellate cell activation in nonalcoholic fatty liver disease. J Mol Med (Berl). 2016; 94:1143–1151. DOI: 10.1007/s00109-016-1434-z [PubMed: 27271256]
114. Sookoian S, Pirola CJ. Meta-analysis of the influence of I148M variant of patatin-like phospholipase domain containing 3 gene (PNPLA3) on the susceptibility and histological severity of nonalcoholic fatty liver disease. Hepatology. 2011; 53:1883–1894. DOI: 10.1002/hep.24283 [PubMed: 21381068]
115. Severson TJ, Besur S, Bonkovsky HL. Genetic factors that affect nonalcoholic fatty liver disease: a systematic clinical review. World J Gastroenterol. 2016; 22:6742–6756. DOI: 10.3748/wjg.v22.i29.6742 [PubMed: 27547017]
116. Li JZ, Huang Y, Karaman R, et al. Chronic overexpression of PNPLA3I148M in mouse liver causes hepatic steatosis. J Clin Invest. 2012; 122:4130–4144. DOI: 10.1172/JCI65179 [PubMed: 23023705]
117. Liu Y, Chen H, Wang J, Zhou W, Sun R, Xia M. Association of serum retinoic acid with hepatic steatosis and liver injury in nonalcoholic fatty liver disease. Am J Clin Nutr. 2015; 102:130–137. DOI: 10.3945/ajcn.114.105155 [PubMed: 25948673]
118. Pettinelli P, Arendt BM, Teterina A, et al. Altered hepatic genes related to retinol metabolism and plasma retinol in patients with non-alcoholic fatty liver disease. PLoS One. 2018; 13 e0205747 doi: 10.1371/journal.pone.0205747 [PubMed: 30379862]
119. Friedman SL, Neuschwander-Tetri BA, Rinella M, Sanyal AJ. Mechanisms of NAFLD development and therapeutic strategies. Nat Med. 2018; 24:908–922. DOI: 10.1038/s41591-018-0104-9 [PubMed: 29967350]
120. Gambino R, Musso G, Cassader M. Redox balance in the pathogenesis of nonalcoholic fatty liver disease: mechanisms and therapeutic opportunities. Antioxid Redox Signal. 2011; 15:1325–1365. DOI: 10.1089/ars.2009.3058 [PubMed: 20969475]

121. Moser MA, Chun OK. Vitamin C and heart health: a review based on findings from epidemiologic studies. Int J Mol Sci. 2016; 17:1328. doi: 10.3390/ijms17081328

122. Valdecantos MP, Pérez-Matute P, Quintero P, Martínez JA. Vitamin C, resveratrol and lipoic acid actions on isolated rat liver mitochondria: all antioxidants but different. Redox Rep. 2010; 15:207–216. DOI: 10.1179/135100010X12826446921464 [PubMed: 21062536]

123. Aasheim ET, Hofsø D, Hjelmesaeth J, Birkeland KI, Bøhmer T. Vitamin status in morbidly obese patients: a cross-sectional study. Am J Clin Nutr. 2008; 87:362–369. DOI: 10.1093/ajcn/87.2.362 [PubMed: 18258626]

124. Mah E, Matos MD, Kawiecki D, et al. Vitamin C status is related to proinflammatory responses and impaired vascular endothelial function in healthy, college-aged lean and obese men. J Am Diet Assoc. 2011; 111:737–743. DOI: 10.1016/j.jada.2011.02.003 [PubMed: 21515122]

125. Kim JY, van de Wall E, Laplante M, et al. Obesity-associated improvements in metabolic profile through expansion of adipose tissue. J Clin Invest. 2007; 117:2621–2637. DOI: 10.1172/JCI31021 [PubMed: 17717599]

126. Rose FJ, Webster J, Barry JB, Phillips LK, Richards AA, Whitehead JP. Synergistic effects of ascorbic acid and thiazolidinedione on secretion of high molecular weight adiponectin from human adipocytes. Diabetes Obes Metab. 2010; 12:1084–1089. DOI: 10.1111/j.1463-1326.2010.01297.x [PubMed: 20977580]

127. Lee H, Ahn J, Shin SS, Yoon M. Ascorbic acid inhibits visceral obesity and nonalcoholic fatty liver disease by activating peroxisome proliferator-activated receptor a in high-fat-diet-fed C57BL/6J mice. Int J Obes (Lond). 2019; 43:1620–1630. DOI: 10.1038/s41366-018-0212-0 [PubMed: 30283077]

128. Gu X, Luo X, Wang Y, et al. Ascorbic acid attenuates cell stress by activating the fibroblast growth factor 21/fibroblast growth factor receptor 2/adiponectin pathway in HepG2 cells. Mol Med Rep. 2019; 20:2450–2458. DOI: 10.3892/mmr.2019.10457 [PubMed: 31322211]

129. Ipsen DH, Tveden-Nyborg P, Lykkesfeldt J. Does vitamin C deficiency promote fatty liver disease development? Nutrients. 2014; 6:5473–5499. DOI: 10.3390/nu6125473 [PubMed: 25533004]

130. Williams DB, Wan Z, Frier BC, Bell RC, Field CJ, Wright DC. Dietary supplementation with vitamin E and C attenuates dexamethasone-induced glucose intolerance in rats. Am J Physiol Regul Integr Comp Physiol. 2012; 302:R49–R58. DOI: 10.1152/ajpregu.00304.2011 [PubMed: 22031784]

131. Han JM, Jo AN, Lee SM, et al. Associations between intakes of individual nutrients or whole food groups and non-alcoholic fatty liver disease among Korean adults. J Gastroenterol Hepatol. 2014; 29:1265–1272. DOI: 10.1111/jgh.12520 [PubMed: 24955455]

132. Wei J, Lei GH, Fu L, Zeng C, Yang T, Peng SF. Association between dietary vitamin C intake and non-alcoholic fatty liver disease: a cross-sectional study among middle-aged and older adults. PLoS One. 2016; 11 e0147985 doi: 10.1371/journal.pone.0147985 [PubMed: 26824361]

133. Madan K, Bhardwaj P, Thareja S, Gupta SD, Saraya A. Oxidant stress and antioxidant status among patients with nonalcoholic fatty liver disease (NAFLD). J Clin Gastroenterol. 2006; 40:930–935. DOI: 10.1097/01.mcg.0000212608.59090.08 [PubMed: 17063114]

134. Nambisan B, Kurup PA. Ascorbic acid and glycosaminoglycan and lipid metabolism in guinea pigs fed normal and atherogenic diets. Atherosclerosis. 1975; 22:447–461. DOI: 10.1016/0021-9150(75)90024-6 [PubMed: 128367]

135. Rezazadeh A, Yazdanparast R, Molaei M. Amelioration of diet-induced nonalcoholic steatohepatitis in rats by Mn-salen complexes via reduction of oxidative stress. J Biomed Sci. 2012; 19:26. doi: 10.1186/1423-0127-19-26 [PubMed: 22375551]

136. Harrison SA, Torgerson S, Hayashi P, Ward J, Schenker S. Vitamin E and vitamin C treatment improves fibrosis in patients with nonalcoholic steatohepatitis. Am J Gastroenterol. 2003; 98:2485–2490. DOI: 10.1111/j.1572-0241.2003.08699.x [PubMed: 14638353]

137. Foster T, Budoff MJ, Saab S, Ahmadi N, Gordon C, Guerci AD. Atorvastatin and antioxidants for the treatment of nonalcoholic fatty liver disease: the St Francis Heart Study randomized clinical trial. Am J Gastroenterol. 2011; 106:71–77. DOI: 10.1038/ajg.2010.299 [PubMed: 20842109]

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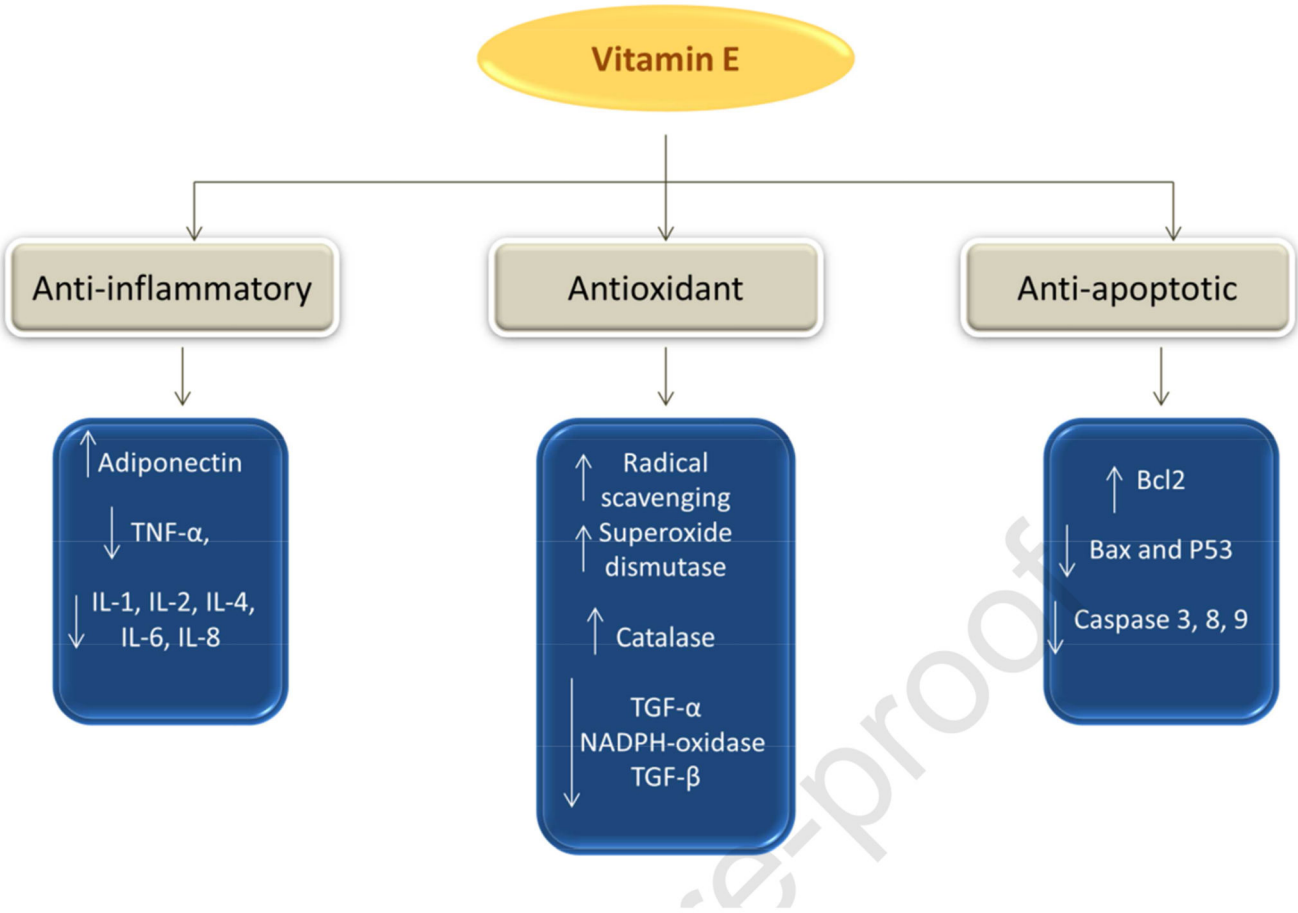

Fig. 1. The role of vitamin E in regulating hepatic oxidative stress, inflammation and apoptosis.

Vitamin E lowers inflammatory response by increasing the expression of adiponectin and suppresses the expression of several cytokines including tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1, IL-2, IL-4, IL-6, and IL-8. It also acts as a scavenger of hydroxyl, peroxyl and superoxide radicals and stimulates superoxide dismutase (SOD) levels. Vitamin E exerts anti-apoptotic effects by enhancing the levels of anti-apoptotic protein BCL-2, and lowers the pro-apoptotic proteins BCL-2 associated-X (BAX) protein and p53.

Abbreviations: NADPH, nicotinamide adenine dinucleotide phosphate; TGF, transforming growth factor.

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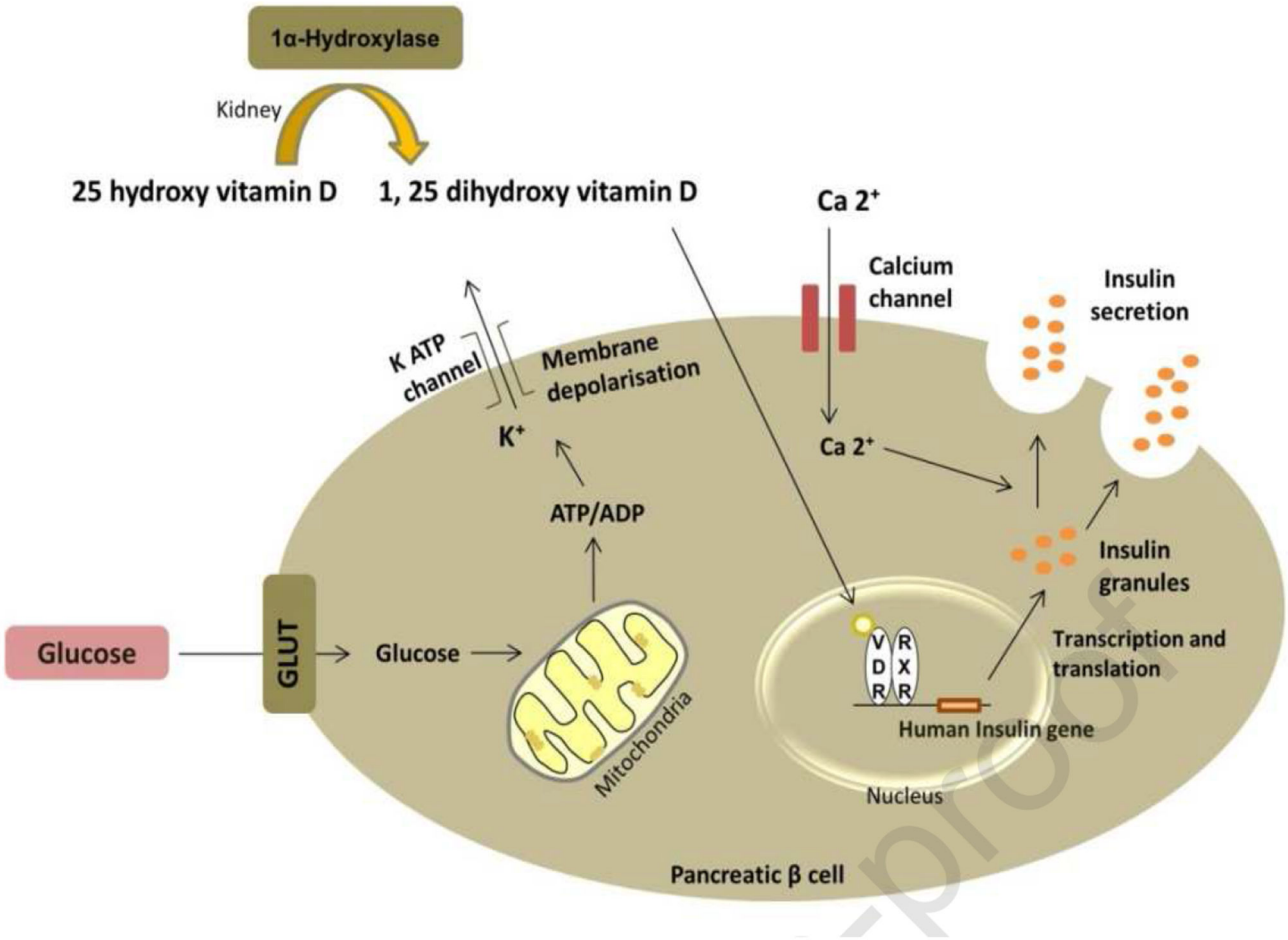

Fig. 2. Vitamin D stimulates insulin secretion in pancreatic β-cells.

Vitamin D is involved in direct stimulation of insulin secretion through binding to the vitamin D receptor (VDR) expressed by the pancreatic β-cells and activating the transcription of human insulin. An additional effect of vitamin D is the regulation of calcium flux through pancreatic β-cells. Insulin secretion is a calcium dependent process, therefore, vitamin D affects insulin secretion by modulating changes in calcium concentration. Abbreviations: ADP, adenosine diphosphate; ATP, adenosine triphosphate; GLUT, glucose transporter; RXR, retinoid-X-receptor.

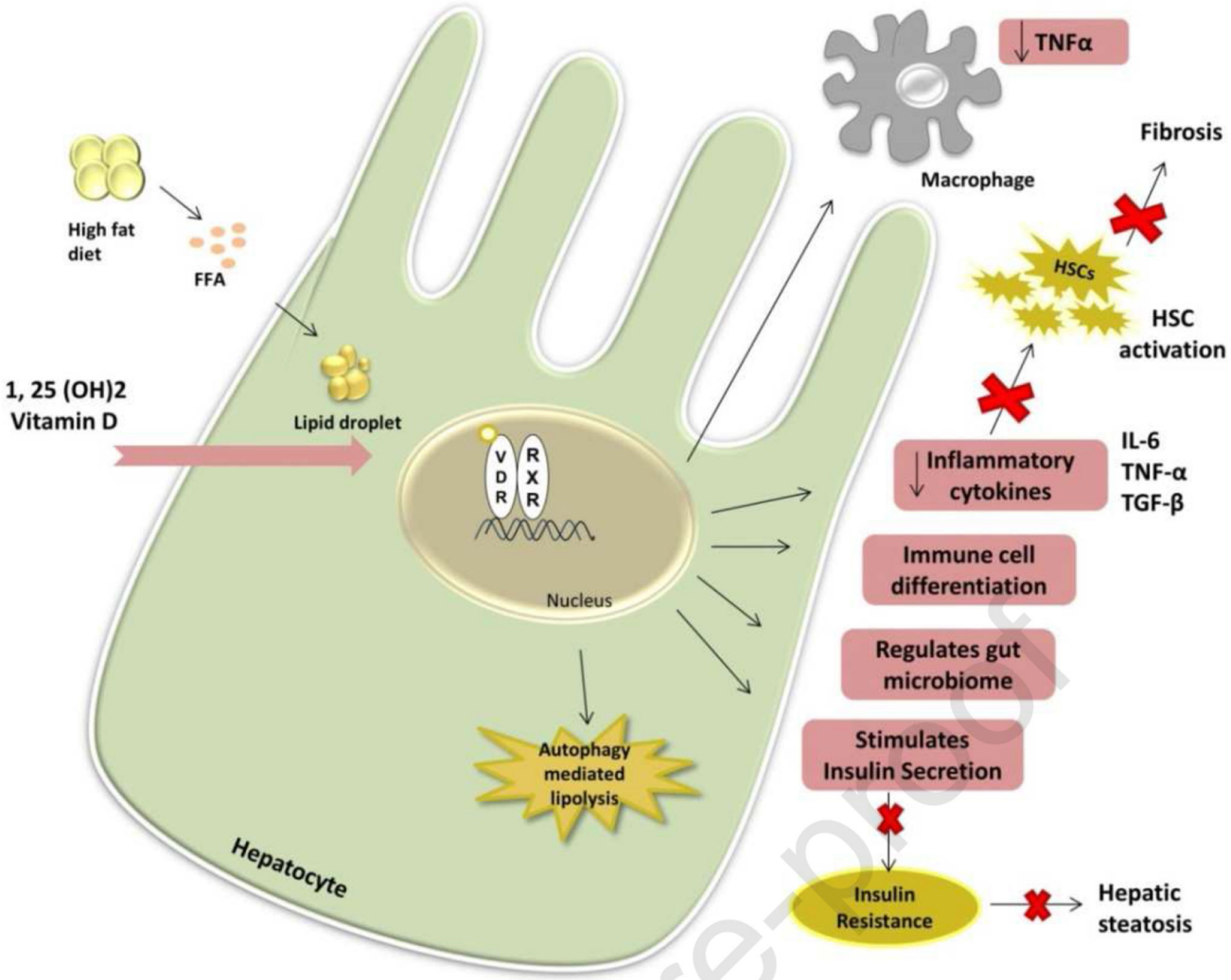

Fig. 3. Modulation of hepatic pathophysiology by vitamin D.

Vitamin D acts as a modulator of insulin sensitivity and is involved in the transcriptional regulation of the proliferation and differentiation of immune cells. Vitamin D also attenuates hepatic steatosis by inducing autophagy and exerts anti-inflammatory and anti-fibrotic effects through vitamin D signaling. Abbreviations: FFA, free fatty acid; HSCs, hepatic stellate cells; TGF-β, transforming growth factor-beta; TNF-α, tumor necrosis factor-alpha; VDR, vitamin D receptor; RXR, retinoid-X-receptor.