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Review Article

Molecular Crosstalk Between Vitamin D and Non-alcoholic Fatty Liver Disease

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Abstract

Non-alcoholic fatty liver disease (NAFLD) is one of the leading causes of chronic liver disease. The worldwide increasing prevalence of NAFLD has become a cause of concern for clinicians. Furthermore, the molecular mechanism of NAFLD pathogenesis remains poorly understood. Moreover, therapeutic interventions are presently limited. Balanced diet, physical exercise and lifestyle modifications have been recommended. Several studies have revealed that vitamin D deficiency is correlated with NAFLD, and its supplementation may play a vital role in this regard. Sufficient information was obtained from full articles written in the English language, and accessible in PubMed, Google Scholar, Web of Science, and Scopus. The increasing prevalence of vitamin D deficiency remains as a global health risk factor, and this is linked to NAFLD pathogenesis. *In vitro* and *in vivo* studies, and clinical trials have revealed the beneficial role of vitamin D supplementation to control NAFLD. Vitamin D potentially regulates the molecular pathways associated with NAFLD risk factors, such as obesity, insulin resistance, and diabetes. It acts on adipocytes to control free fatty acid (FFA) trafficking, lipogenesis, and inflammation. Similarly, vitamin D acts on hepatocytes to reduce *de novo* lipogenesis and cellular FFA trafficking. Furthermore, it acts on pancreatic β-cells to improve insulin secretion, cell survival, and cellular functions. Vitamin D supplementation improves glucose uptake and insulin sensitivity. In addition, it decreases inflammation and liver injury, and acts on mitochondria to control reactive oxygen species (ROS)-mediated cellular toxicity. Vitamin D deficiency is a major risk factor for NAFLD pathogenesis. Thus, there is an urgent need to conduct molecular level analysis for further discernment.

Introduction

Non-alcoholic fatty liver disease (NAFLD) is one of the emerging causes of chronic liver disease. Furthermore, this has become a cause of concern for clinicians due to the increasing burden of this disease. The overall global prevalence rate of NAFLD is 32.4%, with a prevalence rate of 39.7% for males and 25.6% for females.[1] The worldwide prevalence of this disease is presently increasing. The common clinicopathological conditions of NAFLD are abnormal accumulation of lipids in the cytoplasm of hepatocytes, and the persistence of abnormal levels of liver enzymes.[2] The histopathological determinants are crucial for characterizing the disease progression.[3] The advanced subtype of NAFLD is characterized as non-alcoholic steatohepatitis (NASH), which can further lead to cirrhosis of the liver. The increasing risk of NAFLD and NASH is associated with the development of hepatocellular carcinoma (HCC). However, NAFLD-associated HCC may be developed with or without cirrhosis.[4] Recently, NAFLD has become more precisely termed as, metabolic dysfunction-associated fatty liver disease (MAFLD). The proposed criteria for MAFLD comprise of the evidence of hepatic steatosis, combined with the presence of overweight/obesity, or metabolic abnormalities or type-2 diabetes mellitus. In this context, MAFLD shows high risk of disease progression, when compared to NAFLD.[5,6] The treatment options for NAFLD remain limited.[7] Dietary restrictions, physical exercise,

Keywords: Non-alcoholic fatty liver; Vitamin D; Free fatty acids; White adipose tissue; Insulin sensitivity; Adipocyte; Hepatocyte; Liver damage.

Abbreviations: Akt/mTOR, threonine protein kinase B/mammalian target of rapamycin; AMPK, AMP-activated protein kinase; BMI, body mass index; FAS, fatty acid synthase; FFA, free fatty acid; HCC, hepatocellular carcinoma; HNF4α, hepatocyte nuclear factor-4 alpha; HPLC, High-Performance Liquid Chromatography; IL, Interleukin; INS1E, Insulinoma cell line; KO, knockout; IL1β, interleukin 1 beta; IR, insulin receptor; IRS, insulin receptor substrate; MAFLD, metabolic dysfunction-associated fatty liver disease; MCP-1, Monocyte chemoattractant protein-1; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; NF-κB, nuclear factor-kappa B; NOX, NADPH oxidase; PI3K, phosphatidylinositol 3-kinase; PPARγ, Peroxisome proliferator-activated receptor gamma; PTH, Parathyroid hormone; RAS, renin-angiotensin system; ROS, reactive oxygen species; SOD1, super oxide dismutase type 1; SREBP1, sterol regulatory element binding protein 1; T2DM, Type-2 Diabetes Mellitus; TG, triglyceride; TLR, toll-like receptors; TNFα, tumor necrosis factor alpha; WAT, white adipose tissue; VDR, vitamin D receptor; 25(OH)D, 25-hydroxy vitamin D.

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lifestyle modifications, and treatment of the metabolic syndrome are recommended to improve the hepatic fibrosis.[8–10] Multiple trials on combination therapies and drugs are presently in the preclinical and clinical stages.[11]

The underlying mechanisms of NAFLD is poorly understood. Extensive research is being undertaken to elucidate the close association of NAFLD with metabolic syndrome, insulin resistance, and obesity. Previous studies have revealed that the genetic variation in the rs738409 G allele of the *PNPLA3* (Patatin-like phospholipase domain-containing protein 3) gene that encodes for adiponutrin is associated with NAFLD susceptibility and disease pathogenesis, through increasing liver fat content.[12] *PNPLA3*, which is present in hepatocytes and stellate cells, play major roles in hydrolyzing triglyceride (TG) and polyunsaturated fatty acid transportation to phosphocholine. NAFLD predisposes to T2DM through the elevation of insulin secretion and β-cell failure.[10] In this context, the hepatic diacylglycerol content in the cytoplasm is a good predictor of insulin resistance through the activation of protein kinase C epsilon. Furthermore, metabolic syndrome-associated parameters glucose and triglyceride are overproduced by fatty liver in NAFLD.[13] In addition, NAFLD with metabolic syndrome has been reported in a study population, irrespective of insulin resistance and central obesity.[10,14]

In connection with these metabolic abnormalities, it is important to note that the long-term effect of malnutrition plays a significant role in NAFLD pathogenesis, which induces liver steatosis and insulin resistance.[15] In addition, micronutrients, such as vitamin deficiency, can also be correlated with NAFLD pathogenesis.[16] Recently, vitamin D has received tremendous attention, not only as a part of the proposed supplementation therapy, but also as a key player to regulate molecular interactions and cellular functions in NAFLD.[17–19] The present review focused on vitamin D deficiency and the molecular consequences in the pathogenesis of NAFLD. Additionally, the present study confers the plausible effect of vitamin D on molecular interactions and cellular functions, in order to ameliorate NAFLD pathogenesis and liver dysfunctions.

Vitamin D deficiency and prevalence of NAFLD

Vitamin D is a unique micronutrient, which can be synthesized by the epidermis upon sunlight (290–315 nm) exposure.[20] Vitamin D can be identified into two dominant forms: vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol). The intestines can more efficiently absorb vitamin D_3, when compared to vitamin D_2.[21] In wild mushrooms, ergosterol is converted to vitamin D_2 in the presence of sunlight. On the other hand, the skin can synthesize vitamin D_3 upon natural or artificial ultraviolet B light irradiation.[22] Food supplements, such as milk, egg yolk, fish and meat (offal, such as liver), are good sources of vitamin D_3, while the plant source of vitamin D_2 is mushroom.[23] The vitamin D_3 obtained from different sources is incorporated into chylomicrons, and subsequently delivered in the lymphatic and venous circulation.[24] Vitamin D, in the form of D_2 or D_3, requires the successive hydroxylation process to produce its active form in the body. Vitamin D produces its biologically active intermediate, 25-hydroxyvitamin D or 25(OH)D, in the liver through 25-hydroxylase, and 1,25-dihydroxyvitamin D (calcitriol), in the kidney through 1α-hydroxylase. 25(OH)D is an active hormone, and this has endocrine functions, such as calcium absorption, maintenance of bone integrity, the regulation of cell growth, etc.[25,26] Serum 25(OH)D is a good indicator for measuring the vitamin D level. A serum or plasma 25(OH)D level of <75 nmol/L (<30 ng/ml) is considered as vitamin D deficiency.[27,28] In this context, various studies have reported the serum/plasma vitamin D concentration of <20 ng/ml as vitamin D deficiency.[29,30] However, the supplementation dose of vitamin D is presently a subject of debate.[31]

Vitamin D deficiency is intensely and inversely associated with the worldwide prevalence of NAFLD. A population-based observational study conducted from 1990 to 2017 revealed a steep increase in worldwide NAFLD cases (882.1 million).[32] The prevalence rate of NAFLD is greater in East Asia (12.6%), Southeast Asia (14.5%), the Middle East, and North Africa (19.3%). Other systematic review and meta-analysis studies have also published these results.[33,34] On the other hand, the global prevalence of vitamin D deficiency has been reported to be high in Asia, Africa and Europe.[35,36] It has been reported that vitamin D is remarkably deficient in South Asian adults, with a prevalence rate of 68%.[37] In addition, the younger generation was identified to be more prevalent to have vitamin D deficiency, when compared to the elderly population.[38,39] Latitude, seasons, skin pigmentation, the use of sun protection, lifestyle and nutritional variation, and lack of sufficient exposure of skin to sunlight can be the potential reasons for vitamin D deficiency. It is important to note that adolescents and young adults have high risks of developing NAFLD due to obesity, T2DM, smoking, lifestyle, and ethnic variations.[40,41] The studies related to the low serum or plasma vitamin D status in NAFLD patients are presented in Table 1.[32,42–66]

Conceptualization of the mechanisms of NAFLD pathogenesis

The mechanisms underlying NAFLD pathogenesis are quite complicated and multifactorial. Previously, NAFLD pathogenesis was described by the "two hits" hypothesis.[67,68] The first hit explains the accumulation of triglyceride in hepatocytes (i.e. hepatic steatosis) due to insulin resistance, metabolic abnormalities, obesity, and sedentary lifestyle. The second hit describes the development of hepatic fibrosis and liver injury from steatosis. Several triggering factors and cellular conditions have been reported to be involved in the development of fibrosis and liver injury, which include lipid peroxidation, inflammation, drugs, mitochondrial dysfunction, and adipokines (Fig. 1). Recently, NAFLD pathogenesis was explained by the multiple-hit hypothesis.[69] According to this hypothesis, the progression of NAFLD-associated liver toxicity and inflammation is accomplished through multiple mechanisms, which include insulin resistance, nutritional factors, gut microbiota, genetic and epigenetic alterations, adipocyte-specific secretion of steroid hormones, cytokine prostaglandins, fatty acids, and cholesterol.[70] In this context, insulin resistance promotes hepatic lipogenesis, and impairs adipose tissue lipolysis. This generates the pull of free fatty acid (FFA) flux towards the liver, and causes adipose tissue dysfunction with altered adepokine and cytokine secretion.[71] It is noteworthy that 90–95% of patients with NAFLD are associated with simple steatosis, while 5–10% of NAFLD patients arise from NASH, which further lead to cirrhosis and HCC.[69]

Role of vitamin D to control NAFLD risk factors

Metabolic disorders

Role of vitamin D in obesity

According to the Centers for Disease Control and Prevention, a body mass index (BMI) of 25 to <30 is defined as overweight, while a BMI of ≥30 indicates obesity.[72] Excess triglyceride storage

Table 1. Low vitamin D level in NAFLD patients

Author(s)	Year	Country	Sample size (N) for NAFLD*		Age (mean ± SD or, average or, range) (years)		NAFLD evaluation criteria	Methods of vitamin D estimation in plasma/serum	Level of 25(OH)D (mean ± SD or, average) (ng /mL)		
			Male	Female	Male	Female			Male	Female	Total
Bennouar *et al.*[42]	2021	Algeria	112	205	51.2 ± 12.6		Fatty Liver Index >60 points	Sequential competitive immunofuoro-assay method by VIDAS®	13.6 ± 7 µg/l	9.4 ± 6.8	10.9 ± 7.2 µg/l
Wang *et al.*[43]	2022	China	330		40.35 ± 8.14		Guidelines for the prevention and treatment of non-alcoholic fatty liver disease: a 2018 update (https://pubmed.ncbi.nlm.nih.gov/29804393/)	ELISA	Both		≥20 ng/mL
Xing *et al.*[44]	2022	China	-	234	56.98 ± 13.45		Ultrasonography (hepatorenal echo contrast, liver brightness, deep attenuation, and vascular blurring)	Electrochemiluminescence Immunoassays	Female		15.89 mmol/l
Hamzehzadeh Alamdari *et al.*[45]	2022	Iran	66		49.98 ± 10.55		Ultrasonography findings	-	Both		8.74 ± 2.47 ng/dl
Gad *et al.*[32]	2020	Egypt	40		47 ± 9		Ultrasonography findings (bright hepatic texture)	ELISA	Both		16.13 ± 10.23 (ng/mL
Wang *et al.*[46]	2021	China	Lean: 163; Obese: 690		Lean: 54.84; Obese: 54.23		Ultrasonography findings as per the standards of the Chinese Liver Disease Association	-	Male		Lean: 60.95 nmol/L; Obese: 59.03 nmol/L
Cordeiro *et al.*[47]	2017	Brazil	7	43	45.7 ± 6.6	41.3 ± 8.6	Liver Biopsy	HPLC	17.9 ± 9.8 ng/mL	22.9 ± 7.2 ng/mL	-
Sayed *et al.*[48]	2021	Egypt	50		<60		Ultrasonography findings based on liver echogenicity	ELISA	Both		26.34 ± 11.28 ng/ml

(continued)

Table 1. *(continued)*

Author(s)	Year	Country	Sample size (N) for NAFLD*		Age (mean ± SD or, average or, range) (years)		NAFLD evaluation criteria	Methods of vitamin D estimation in plasma/serum	Level of 25(OH)D (mean ± SD or, average) (ng /mL)		
			Male	Female	Male	Female			Male	Female	Total
Kasapoglu *et al.*[49]	2013	Turkey	Stage 1: 133; Stage 2: 106; Stage 3: 99		Stage 1: 51.2 ± 10.5; Stage 2: 53.1 ± 9.7; Stage 3: 56.5 ± 8.9		Ultrasonography findings based on liver steatosis scores	-	Both		Stage 1: 20.0 ± 9.2; Stage 2: 13.3 ± 6.7; Stage 3: 8.8 ± 7.4
Ehrampoush *et al.*[50]	2019	Iran	745		49 ± 8		Fatty liver index >60	ELISA	Both		15.84 ± 5.50 nmol/L
Ahmed *et al.*[51]	2016	Egypt	47		11.13 ± 2.7		Ultrasonography findings	ELISA	Both		52.1 ± 41.3 nmol/L
Dasarathy *et al.*[52]	2017	USA	NAFLD with NASH: 26; NAFLD with HS: 16		NAFLD with NASH: 51.6 ± 13.0; NAFLD with HS: 51.6 6 11.4		Liver biopsy findings as per the NASH CRN scoring system	Direct Competitive Chemiluminescent Assay	Both		NAFLD with NASH: 19.3 ± 5.4 ng/mL; NAFLD with HS: 21.5 ± 4.5 ng/mL
Rageh *et al.*[53]	2021	Egypt	85		36.1 ± 9.2		Ultrasonography findings	Quantitative Chemiluminescent Microparticle Immunoassay	Both		16.3 ± 7.7
Cai *et al.*[54]	2020	China	Mild: 191; Moderate: 128; Severe: 66		43.57 ± 5.75		As per NASH Clinical Research Network Pathology Society	-	Both		Mild: 17.23 ± 2.61 nmol/l; Moderate: 15.47 ± 2.38 nmol/l; Severe: 13.83 ± 2.26 nmol/l
Kuçukazman[55]	2014	Turkey	154		46.3 ± 10.7		Ultrasonography findings	Competitive radioimmunoassay	Both		12.3 ± 8.9 ng/dl
Kim *et al.*[56]	2017	USA	Mild: 1,491; Moderate: 1,707; Severe: 817		Mild: 24.7 ± 0.42; Moderate: 23.7 ± 0.37; Severe: 23.6 ± 0.60		Ultrasonography findings	chemiluminescent immunoassay	Mild: 25.7 ± 0.45 mg/dl; Moderate: 25.0 ± 0.50 mg/dl; Severe: 25.6 ± 0.74 mg/dl	Mild: 23.9 ± 0.50 mg/dl; Moderate: 22.3 ± 0.49 mg/dl; Severe: 20.9 ± 0.68 mg/dl	Mild: 24.7 ± 0.42 mg/dl; Moderate: 23.7 ± 0.37 mg/dl; Severe: 23.6 ± 0.60 mg/dl
Shawky *et al.*[57]	2018	Egypt	50		49.88 ± 9.126		Ultrasonography findings	ELISA	Both		18.76 ± 14.37 ng/dl

(continued)

Table 1. *(continued)*

Author(s)	Year	Country	Sample size (N) for NAFLD*		Age (mean ± SD or, average or, range) (years)		NAFLD evaluation criteria	Methods of vitamin D estimation in plasma/serum	Level of 25(OH)D (mean ± SD or, average) (ng /mL)		
			Male	Female	Male	Female			Male	Female	Total
Chakraborty *et al.*[58]	2019	India	94		18 to 40		Ultrasonography findings	Chemiluminescent assay	Both		17.21 ± 6.34 ng/ml
Hao *et al.*[59]	2018	China	242		79.98 ± 8.33		Ultrasonography findings	high-performance liquid chromatography/ tandem mass spectrometry	Both		11.55 ± 7.66 ng/ml
Mohamed *et al.*[60]	2017	Saudi Arabia	56		34.6 ± 10.6		Ultrasonography findings	Immunoassay (Abbott Architect i1000 Chemiflex device)	Male		17.45 ± 6.14
Chung *et al.*[61]	2016	Korea	1,660		53.6 ± 9.5		Ultrasonography findings	Chemiluminescnece immunoassay	Both		21.75 ± 7.54 ng/ml
Alamdari *et al.*[62]	2022	Iran	33		51.30 ± 10.78		Ultrasonography findings	-	Both		8.19 ± 2.60 ng/dl
Gungor *et al.*[63]	2020	Turkey	33		1 to 17		Ultrasonography findings		Both		Non-obese NAFLD: 20.83 ± 10.44; Obese NAFLD: 16.69 ± 8.22
Sah *et al.*[64]	2021	Nepal	70		44.3 ± 12.1		Ultrasonography findings	-	Both		Mild: 22.61 ± 28.07; Moderate: 24.89 ± 26.45; Severe: 17.4 ± 6.4
Wang *et al.*[65]	2018	China	9,182		Quartile 1: 54.3 ± 13.2; Quartile 2: 54.2 ± 13.2; Quartile 3: 54.6 ± 12.9; Quartile 4: 54.8 ± 12.8		Ultrasonography findings	Chemiluminescence assay	Both		Genetic risk score- Quartile 1 (low) to Quartile 4 (high):; Quartile 1: 41.8 ± 12.9 nmol/L; Quartile 2: 40.4 ± 12.3 nmol/L; Quartile 3: 39.6 ± 12.5 nmol/L; Quartile 4: 38.7 ± 11.9 nmol/L
Lorvand Amiri *et al.*[66]	2016	Iran	40		39.8 ± 11		Ultrasonography findings	ELISA	Both		9.9 ± 3.9 ng/mL

*The non-NAFLD and healthy controls of the respective studies were excluded. HPLC, High-Performance Liquid Chromatography; NAFLD, non-alcoholic fatty liver disease; SD, standard deviation.

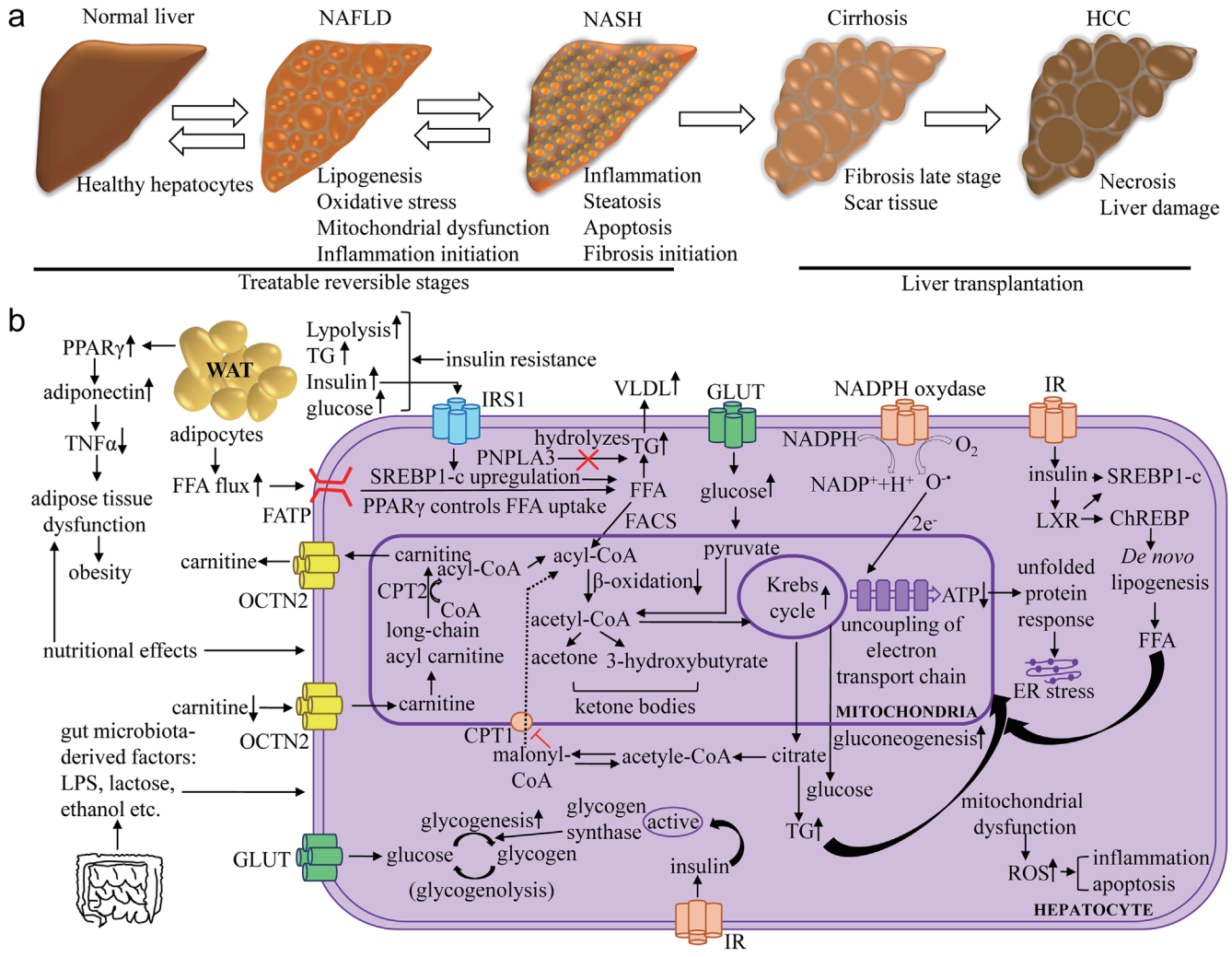

Fig. 1. Different stages of pathophysiological conditions, starting from NAFLD to HCC, can be characterized based on the biological and molecular aspect (Panel A). The molecular understanding of multifactorial NAFLD pathogenesis (panel B). The progression of NAFLD pathogenesis is multifactorial, in which several molecular pathways are involved. The high FFA flux generated by WATs resulted in the functional modulation of hepatocytes by reducing the β-oxidation, and increasing the Krebs cycle and gluconeogenesis. It causes low ATP production, mitochondrial dysfunction, and ER stress. In this context, the high TG and VLDL signature the pathophysiological state of the disease. Insulin stress mediates the increase in glycogenesis and *de novo* lipogenesis inside the hepatocyte. The genetic variation of PNPLA3 effects the hepatic TG hydrolyzation. The less biosynthesis of carnitine resulted in the low transportation of fatty acids to the mitochondria for β-oxidation. The high insulin level promoted the SREBP1-c upregulation, and increased the fatty acids in hepatocytes. As the uncoupling of the electron transport chain took place, the superoxide produced by NADPH oxidase induced liver injury. In addition, gut commensal-released products, such as LPS, lactose and ethanol, contributed to the NAFLD pathogenesis. The symbols "↑", "↓", and "⊥" refer to "high", "low", and "inhibition", respectively. ATP, Adenosine triphosphate; ChREBP, carbohydrate response element binding protein; CPT2, carnitine palmitoyltransferase 2; e⁻, electron; ER, endoplasmic reticulum; FATP, fatty acid-transport protein 1; FFA, free fatty acids; GLUT, glucose transporter; HCC, hepatocellular carcinoma; IR, insulin receptor; IRS, insulin receptor substrate; IRS1, Insulin receptor substrate 1; LPS, lipopolysaccharide; LXR, liver X receptor; NADP, nicotinamide adenine dinucleotide phosphate; NAFLD, non-alcoholic fatty liver disease; NASH, non-alcoholic steatohepatitis; PNPLA3, patatin-like phospholipase domain-containing protein 3; OCTN2, organic cation transporter; PPARγ, peroxisome proliferator- activated receptor gamma; ROS, reactive oxygen species; SREBP1c, sterol regulatory element binding protein 1; TG, triglyceride; TNFα, tumor necrosis factor alpha; WAT, white adipose tissue; VLDL, very low-density lipoprotein.

in white adipose tissues develops into obesity, which subsequently causes fat accumulation in the liver, and FFA release through adipokine secretions.[73,74] Moreover, excessive fat accumulation results in adipocyte hypertrophy, inflammation, insulin resistance, and fibrosis (Fig. 2). These are the key mechanisms for the development of NAFLD.[75] On the other hand, brown adipose tissue or the "browning" of white adipose tissue through adequate fat oxidation is crucial for energy dispersion.[76] Genes that encode peroxisome proliferator-activated receptor gamma (PPARγ), enhancer-binding proteins, sterol regulatory element binding protein 1 (SREBP1), acetyl CoA carboxylase, fatty acid synthase (FAS), and fatty acid binding protein are involved in the regulation of adipogenesis.[74] The activation of the renin-angiotensin system (RAS) is potentially involved in obesity.[77] Thus, it is pivotal to mention that the activation of AMP-activated protein kinase (AMPK) attenuates the pathways and transcription factors related to adipogenesis.[74]

Vitamin D is capable of reducing obesity by regulating the expression of lipogenic genes. It was reported that diabetic mice

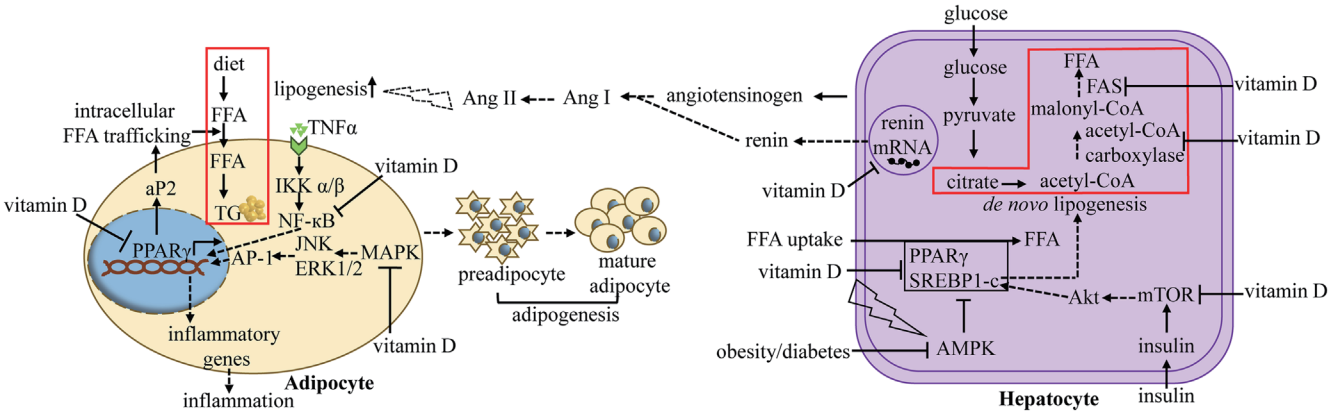

Fig. 2. Vitamin D-induced modulation of molecular pathways linked to obesity. One of the key functions of vitamin D is to restrict aP2-mediated FFA trafficking by inhibiting PPARγ in adipocytes. Vitamin D consequently blocks NFκB and MAPK to reduce PPARγ. The effect of vitamin D on RAS contributes to the reduction in lipogenesis through the inhibition of the renin expression. Furthermore, vitamin D plays a pivotal role in restricting adipocyte differentiation. On the other hand, vitamin D inhibits PPARγ and SREBP1c, which may lead to the control of the *de novo* lipogenesis in hepatocytes. The expression of SREBP1c is decreased by the vitamin D-mediated inhibition of the Akt/mTOR signaling pathway. The effect of vitamin D may directly control the *de novo* lipogenesis by inhibiting two major enzymes (acetyl-CoA carboxylase and FAS), ultimately leading to FFA synthesis. The "↑" and "⊥" refer to "high" and "inhibition", respectively. Akt, serine/threonine-protein kinase; AMPK, AMP-activated protein kinase; Ang I, Angiotensin I; Ang II, Angiotensin II; aP1, activator protein 1; aP2, activator protein 2; ERK1/2, extracellular signal-regulated protein kinase 1/2; FAS, fatty acid synthase; FFA, free fatty acid; IKK α/β, inhibitory-κB Kinase alpha/beta; JNK, c-Jun N-terminal kinases; MAPK, Mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NFκB, nuclear factor kappa B; PPARγ, Peroxisome proliferator-activated receptor gamma; RAS, renin-angiotensin system; TG, triglyceride.

supplemented with 300 ng/kg of vitamin D presented with a significantly decreased expression of FAS, SREBP1c and PPARγ. In addition, vitamin D supplementation activates AMPK, and blocks the threonine protein kinase B/mammalian target of rapamycin (Akt/mTOR) signaling pathway, resulting hepatic lipid reduction.[78] These study observations are crucial for establishing the beneficial effect of vitamin D supplementation in NAFLD under diabetic conditions. In addition, vitamin D can successfully inhibit nuclear factor-kappa B (NFκB) and mitogen-activated protein kinases, which in turn reduce adipose tissue inflammation.[79–81] It was reported that overweight patients (BMI: 28.3 ± 3.4 kg/m^2) with vitamin D deficiency (18.5 ± 6.4 ng/ml) and hypertension had enhanced RAS activity.[82] RAS contributes to the development of obesity and NAFLD progression, while a RAS inhibitor may be used to stop the development of NAFLD.[83] Vitamin D supplementation (15,000 IU/day for 30 days) can decrease RAS activity.[84] In addition, vitamin D has been shown to be associated with the decrease in plasma angiotensin II and renin mRNA expression levels, which may be correlated with the decrease in lipogenesis and TG accumulation in adipocytes.[85] However, the molecular understanding of the vitamin D-mediated depletion of RAS activity remains poorly understood.

Role of vitamin D in insulin resistance

Insulin resistance is one of the key mechanisms of NAFLD pathogenesis. In NAFLD, both hepatic and adipose tissues present with insulin resistance and decreased insulin sensitivity.[86–88] The liver exhibits inadequate fatty acid oxidation and glucose uptake during NAFLD, and these processes are controlled by adiponectin. Insulin resistance results in the flux of FFA to the liver. In addition, hyperinsulinemia subsequently effects the downstream anabolic process. Vitamin D deficiency is associated with insulin resistance.[89] A recent *in vivo* study reveals that the liver-specific deletion of vitamin D receptor (VDR) and hepatocyte nuclear factor-4 alpha (HNF4α) genes promote insulin resistance, and present histological observations that are similar to human NASH. This study has concluded that vitamin D can downregulate insulin resistance in NAFLD by interacting with HNF4α, and activating VDR.[21] Vitamin D plays a pivotal role in insulin sensibilization through an anti-inflammatory mechanism, and effects insulin secretion.[90] It was evidenced from various randomized clinical trials that vitamin D supplementation from a minimum 10 weeks to a maximum of 12 months can improve insulin resistance by reducing the homeostatic model assessment for insulin resistance.[19] Besides, vitamin D can improve the fasting blood glucose and serum insulin concentration.[91]

The treatment of human promonocytic cells with vitamin D leads to the transcriptional regulation of the insulin receptor (IR) gene, which results in the stimulation of phosphatidylinositol 3-kinase (PI3K) activity (Fig. 3). This activation leads to the improvement in insulin-stimulated glucose oxidation and cellular transport.[92,93] The binding of PI3K with the pleckstrin homology domain leads to the phosphorylation of phosphoinositide-dependent protein kinase and protein kinase B. This activation induces the regulation of serine/threonine-specific kinase cascades, followed by insulin receptor substrate (IRS) phosphorylation, enhancing insulin sensitivity.[93,94] It was evidenced from an *in vivo* study that the adipocyte specific deletion of p110β (catalytic site of PI3K) can result in adipose tissue insulin resistance, obesity, and liver steatosis.[95] In this context, oncogenic PI3K (PIK3CA^{H1047R}) would promote *de novo* lipogenesis.[96] However, these mechanisms have not yet been established in the context of NAFLD. In addition, vitamin D supplementation (5,000 IU/day for six months) can improve the pancreatic β-cell function in T2DM patients, inducing insulin secretion, and maintaining insulin sensitivity.[97] A high level of VDRs is present in pancreatic β-cells. Thus, an adequate supply of vitamin D can maintain the calcium influx to β-cells, and promote Ca^{2+}-induced insulin secretion.[98] Vitamin D induces PPARγ gene expression.[99] Ligand-activated transcription factor PPARγ plays an indispensable role in increasing insulin sensitivity through regulating insulin signaling. PPARγ competes with VDR for heterodimer formation with the retinoic X receptor. The binding of PPARγ and VDR induces the transcriptional activation of genes responsible for insulin sensitivity in mature adipocytes.[100]

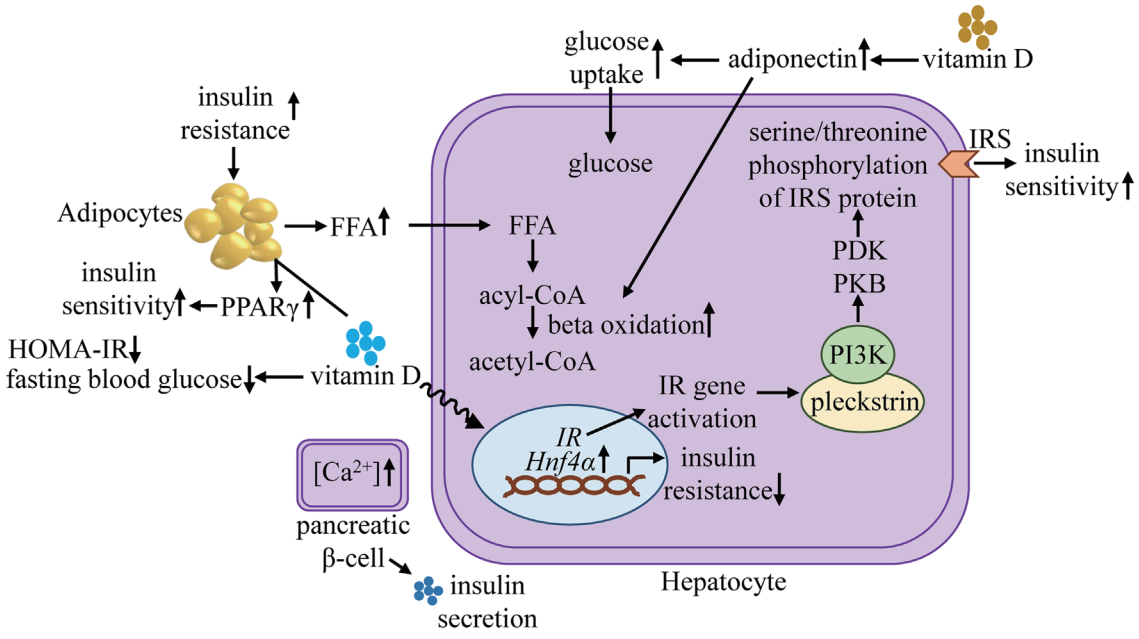

Fig. 3. Molecular targets of vitamin D to regulate insulin resistance mechanism. The major role of vitamin D is to enhance insulin sensitivity by regulating the molecular pathways controlled by adipocytes, pancreatic β-cells, and hepatocytes in the liver. In adipocytes, vitamin D increases the PPARγ expression, which in turn, facilitates insulin sensitivity. In addition, vitamin D acts on pancreatic β-cells to improve insulin secretion. In hepatocytes, vitamin D enhances IR gene activation, followed by the phosphorylation of the IRS protein, which ultimately leads to the induction of insulin sensitivity. In addition, vitamin D induces Hnf4α, and controls insulin resistance. Furthermore, vitamin D increases the adiponectin level to promote the insulin-dependent glucose uptake, and improve glucose homeostasis. Symbols "↑" and "↓" refer to "high" and "low", respectively. Ca^{2+}, calcium ion; FFA, free fatty acid; Hnf4α, hepatocyte nuclear factor 4α; HOMA-IR, homeostatic model assessment for insulin resistance; IR, insulin receptor; IRS, insulin receptor substrate; PDK, phosphoinositide-dependent protein kinase; PI3K, phosphoinositide 3-kinases; PKB, phosphorylate and activate protein kinase B; PPARγ, Peroxisome proliferator-activated receptor gamma.

The activation of PPARγ leads to the maintenance of glucose/lipid uptake and storage, M2 polarization, fatty acid oxidation, and insulin secretion, which in turn, ultimately results in the improvement of insulin sensitivity.[101]

Role of vitamin D in diabetes

Obesity and insulin resistance often lead to the progression of T2DM. The underlying mechanism of T2DM involves the reduction in β-cells mass, and deterioration of β-cell functions.[102] The improper function of β-cells would result in defective or inadequate insulin secretion, and poor glucose homeostasis. As mentioned earlier, vitamin D stimulates pancreatic β-cells to maintain insulin secretion. The effect of vitamin D has already been published, in which INS1E cells were used as an alternative for pancreatic β-cells.[103] It was suggested that $1,25(OH)_2D$ is more effective, when compared to the 25(OH)D type, in inducing insulin secretion.[103] Vitamin D increases autophagy, and reduces the chance of apoptosis of pancreatic β-cells (Fig. 4). It has been demonstrated that treating mouse insulinoma β-cells with $1,25(OH)_2D$ increases the expression of autophagy-related genes *LC3* and *Beclin 1*, while the anti-apoptotic gene *Bcl-2* expression increases after the vitamin D treatment of streptozotocin-treated MIN6 cells.[104] Unlike T2DM, type-1 diabetes mellitus develops due to the autoimmunity-mediated damage of pancreatic β-cells. Vitamin D supplementation restored the functions of pancreatic β-cells in a type-1 diabetic mellitus mice model. It was demonstrated that vitamin D supplementation downregulates the cathepsin G expression, and inhibits CD4+ T cell activation, which in turn, improves β-cell function.[105] Another important mediator of T2DM is RAS, which minimizes insulin secretion by reducing

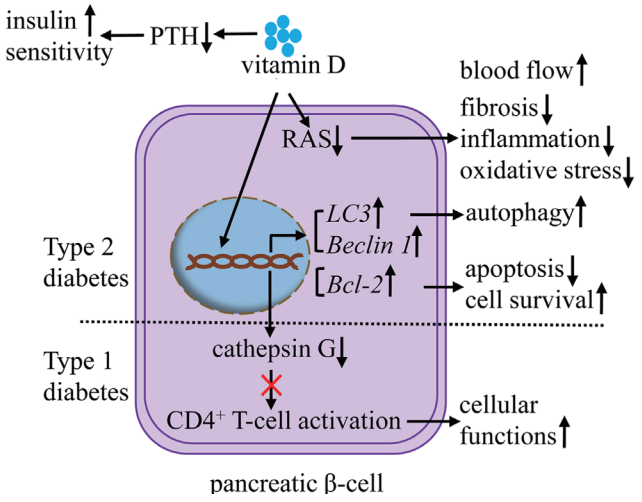

Fig. 4. The role of vitamin D to regulate molecular pathways linked to diabetes. The major targets of vitamin D are elucidated to improve the pancreatic β-cell function. In T2DM, vitamin D reduces PTH, and recovers insulin sensitivity. Vitamin D also reduces RAS activity, which minimizes fibrosis, inflammation and oxidative stress, but increases blood flow. In addition, vitamin D induces autophagy, and reduces apoptosis, ultimately resulting in the survival of pancreatic β-cells. In type-1 diabetes mellitus, vitamin D reduces the cathepsin G expression, and inhibits $CD4^+$ T-cell activation, which in turn, improves β-cell functions. Symbols "↑" and "↓" refer to "high" and "low", respectively. Bcl2, B-cell lymphoma-2; LC3, microtubule-associated protein 1 light chain 3; PTH, parathyroid hormone; RAS, renin-angiotensin system.

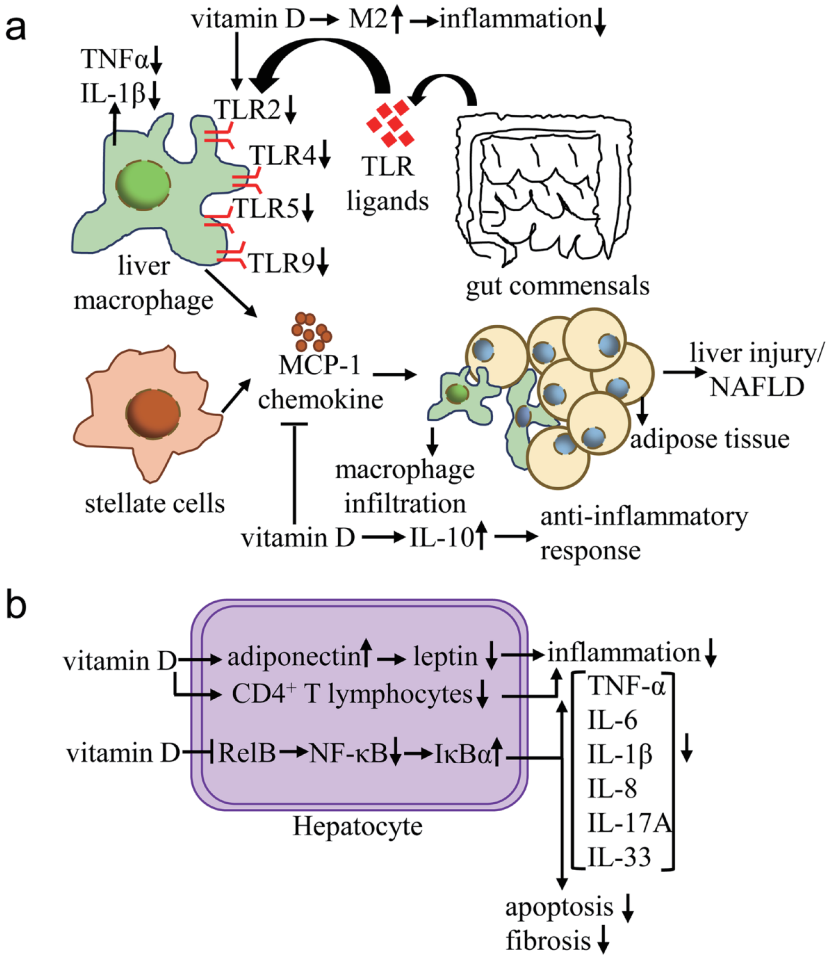

Fig. 5. A complex molecular understanding of the vitamin D-mediated control of liver inflammation. Several cell types, such as adipocytes, hepatocytes, stellate cells, and liver macrophages/Kupffer cells, take part in the process of liver inflammation. Vitamin D downregulates the expression of TLR genes, and decreases the gut microbiota-derived activation of TLR, which further reduces the secretion of proinflammatory cytokines, such as TNFα and IL1β. One of the key mechanisms of vitamin D is to inhibit the secretion of MCP1 chemokines released by both liver macrophages and stellate cells, which in turn, restricts the macrophage infiltration inside adipose tissues, and minimizes liver injury. In addition, vitamin D improves anti-inflammatory response by elevating the IL10 level. In hepatocytes, vitamin D acts to minimize the lectin expression and $CD4^+$ T-cells, which ultimately reduces the chance of liver inflammation. Furthermore, vitamin D inhibits RelB (NFκB subunit), and enhances the IκBα expression to minimize proinflammatory response, fibrosis and apoptosis. Symbols "↑", "↓", and "⊥" refer to "high", "low", and "inhibition", respectively. IκBα, inhibitory κB (IκB) proteins; IL1β, interleukin 1 beta; MCP-1, Monocyte chemoattractant protein 1; NAFLD, non-alcoholic fatty liver disease; RelB, transcription factor RelB (NFκB subunit); TLR, toll-like receptor; TNFα, tumor necrosis factor alpha.

pancreatic blood flow, and promoting islets fibrosis, inflammation, and oxidative stress.[106] It was reported that VDR-knockout (KO) mice presented with an increased expression of RAS components (renin and angiotensinogen), while the vitamin D treatment significantly suppressed the expression of RAS components in isolated KO mice pancreatic islets.[107] Parathyroid hormone (PTH) plays a crucial role in NAFLD. An *in vivo* study revealed that PTH increases the expression of *Ppargc1α* and *Cpt1α* genes linked to lipid β-oxidation, while PTH downregulates the genes (*Pparg*, *Acaca*, and *Fasn*) for *de novo* lipogenesis and lipid uptake (*Cd36*). The expression of these genes leads to the activation of the cAMP/PKA/CREB pathway, and facilitates NAFLD steatosis.[108] NAFLD in pregnancy is a risk factor for maternal and child health.[109] In this context, PTH reduces insulin sensitivity and β-cell functions in pregnancy.[110] Various clinical trials have been documented, ensuring the effect of vitamin D supplementation on the reduction in serum PTH levels in obese populations.[111]

Role of vitamin D in hepatic inflammation

Inflammation plays an important role in the development of advanced stage NAFLD, and progression of NASH. Inflammation occurs through the liver, white adipose tissues (WATs), and the intestines (Fig. 5a). WATs functionally work to secrete bioactive substances, such as adipokines and cytokines, which participate in inflammatory pathways.[112] An *in vivo* study revealed that the surgical removal of epididymal WATs from high-fat diet-fed mice diminished the development of NASH.[113] Furthermore, the antibody treatment against proinflammatory mediators can improve the steatosis.[114] Inflammation in the progressive stage of NAFLD may be explained through the "multiple parallel hit model".[115] According to this hypothesis, lipotoxicity, the gut microbiota, lack of short-chain fatty acids, toll-like receptors (TLR), nutrients (trans fatty acids and fructose), adipokines, cytokines, Fas death receptor, and PPARγ are involved in hepatic inflammation.[115] In addition, the FFA pool would result in increased tumor necrosis factor alpha

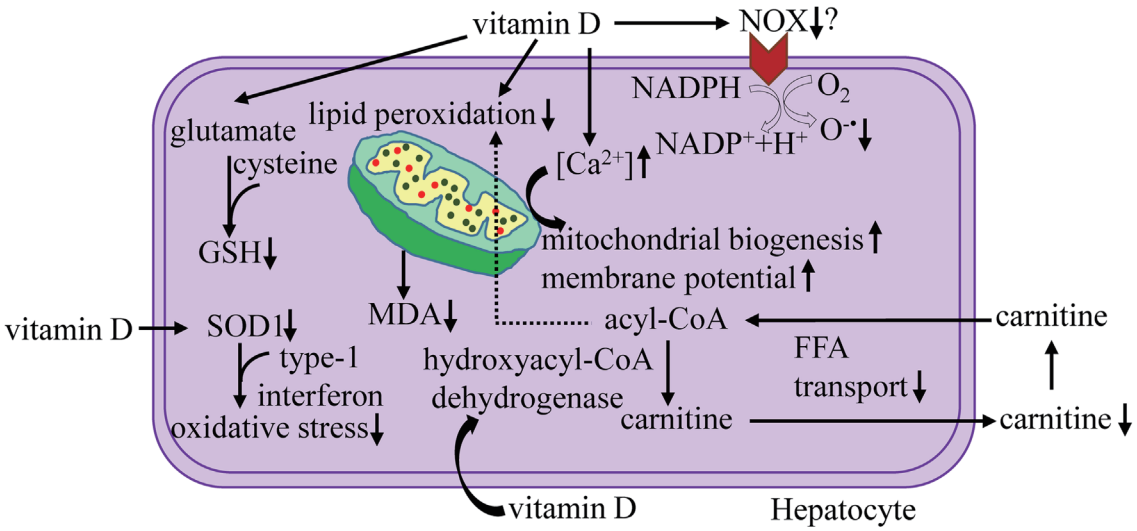

Fig. 6. Molecular targets of vitamin D to control oxidative stress linked to liver injury and NAFLD. Vitamin D induces the reduction in lipid peroxidation, GSH, MDA, and SOD1 levels, improving the ROS-mediated cellular toxicity. In addition, vitamin D increases the cellular (Ca^{2+}) content, in order to improve mitochondrial biogenesis and membrane potential. Vitamin D interacts with hydroxyacyl-CoA dehydrogenase, and suppresses the biosynthesis of carnitine, ultimately leading to the restriction of cellular FFA trafficking. Symbols "↑" and "↓" refer to "high" and "low", respectively. FFA, free fatty acid; GSH, glutathione; MDA, malondialdehyde; NAFLD, nonalcoholic fatty liver disease; NOX, NADPH oxidase; SOD1, superoxide dismutase 1.

(TNFα)- and reactive oxygen species (ROS)-mediated hepatocyte apoptosis.[116] Excessive triglyceride accumulation and less VDR in adipocytes may regulate the gene expression of adipokines. Moreover, vitamin D deficiency is associated with low levels of adiponectin and elevated levels of leptin.[117,118] In this context, the upregulation of hepatocyte adiponectin or serum adiponectin, and the downregulation of leptin may be promising therapeutic approaches to control hepatic inflammation in advanced stage NAFLD.[119] It was reported that vitamin D supplementation (100,000 IU bolus and 4,000 IU/day for 16 weeks) can elevate adiponectin levels in an obese adult population.[120] Another study revealed that vitamin D-fortified yogurt can significantly increase the serum adiponectin concentration in patients with T2DM.[121] It is also reported that aerobic exercise can help to promote the vitamin D-mediated elevation of adiponectin level in T2DM.[122] Moreover, a single intramuscular injection of vitamin D (300,000 IU) can improve the adiponectin level in gestational diabetes mellitus.[123] Multiple studies have revealed that vitamin D is inversely correlated with the level of proinflammatory cytokines, such as TNFα, interleukin (IL) 1 beta (IL1β), IL6, IL8, IL17A and IL33 (Fig. 5b).[124] In this context, vitamin D supplementation can improve inflammation by lowering the level of proinflammatory cytokines, especially IL6 and TNFα.[125] Vitamin D and VDR are strong regulators of T cell-mediated immunity. It has been reported that vitamin D inhibits the proliferation of $CD4^+$ T helper cells, thereby diminishing the secretion of proinflammatory cytokines.[126] In addition, vitamin D diminishes NFκB by inhibiting the RelB protein, and elevating the production of IκBα. RelB, which is an NFκB subunit, has been reported to promote liver fibrosis by inducing inflammation.[127] It has been reported that the degradation of phosphorylated IκB kinase (α and β subunits) would result in the entry of NFκB from the cytoplasm to the nucleus. This would subsequently upregulate genes that encode different cytokines and chemokines, and activate the NFκB pathway, leading to apoptosis-mediated liver damage.[128] Hepatic macrophages are a potential source of liver inflammation through the gut-liver axis. The TLR2, TLR4, TLR5 and TLR9 expressed on hepatic macrophages interact with TLR ligands released by commensal gut microbiota, and promote the secretion of proinflammatory cytokines, such as TNFα and IL1β.[129] However, TLR-mediated hepatic inflammation may be reduced by vitamin D through the downregulation of the TLR gene expression.[130] The M1/M2 polarization of Kupffer cell exhibits more M1 than M2 in NAFLD, which in turn, promotes the increase in secretion of proinflammatory cytokines, and generates profound liver inflammation, injury and fibrosis.[131] An *in vivo* study suggested that vitamin D deficiency is correlated with increased M1 macrophages, while the supplementation of vitamin D may reduce proinflammatory cytokines, and elevate M2 macrophages.[132] It is pivotal to note that the infiltration of monocyte-derived macrophages plays a crucial role in inflammation and NAFLD progression (Fig. 5a). The monocyte chemoattractant protein 1 (MCP1) chemokine secreted by Kupffer cells or stellate cells promote the infiltration of these macrophages to adipose tissues.[133] However, the inhibition of MCP1 may diminish the NAFLD progression and liver injury.[134] Vitamin D has been shown to be effective in downregulating the MCP1 expression, which may be beneficial for controlling adipocyte differentiation, insulin resistance, T2DM, and NAFLD pathogenesis.[135] The deficiency of anti-inflammatory cytokines, such as IL10, is potentially linked with the pathogenesis of NAFLD. An *in vivo* study revealed that a lack of IL10 would result in liver inflammation and insulin resistance. Additionally, it has been reported that vitamin D increases the expression of IL10 in dendritic cells and T cells, and impairs inflammation.[136]

Role of vitamin D in oxidative stress

An excessive FFA supply beyond the capacity of hepatocytes may lead to mitochondrial dysfunction (Fig. 6). FFA successively undergoes the process of β-oxidation and Krebs cycle.[137] Briefly, the FFA passes through fatty acid-transport protein 1, and enters the cytosol. In the cytosol, the FFA is converted into acyl-CoA through fatty acyl-CoA synthase. The elevated acyl-CoA would result in the production of increased ketone bodies (acetone and D-β-

hydroxybutyrate) as terminal products. Simultaneously, the high concentration of acetyl CoA is synthesized through β-oxidation, which in turn, participates to induce an excessive Krebs cycle. In addition, plasma membrane NOX (NADPH oxidase) catalyzes the conversion of NADPH to $NADP^+$, and the conversion of oxygen to superoxide anion ($O_2^{-\bullet}$), which ultimately leads to the activation of myofibroblasts, inducing liver fibrosis.[138] NOX-induced high ROS may lead to hypoxia-induced hepatocyte apoptosis and necrosis.[139,140] Simultaneously, high rates of gluconeogenesis would take place to meet the energy demand, while the uncoupling of the electron transport chain would occur, which may lead to less ATP production.[141] Vitamin D significantly reduces oxidative stress parameters. It was reported that vitamin D supplementation (50,000 IU every 14 days for four months) can reduce the level of malondialdehyde in NAFLD patients.[142] In addition, vitamin D supplementation can increase cellular glutathione biosynthesis, and reduce ROS production.[143] A clinical trial conducted for intensive care unit patients revealed that a high dose of vitamin D supplementation (300,000 IU) can improve the total antioxidant capacity.[144] Furthermore, an *in vivo* study revealed that vitamin D supplementation can potentially upregulate superoxide dismutase type 1 (SOD1), and prevent cellular damage.[145] The overexpression of SOD has been shown to prevent alcohol-induced liver injury in a rat model.[146] In another *in vivo* study, it was shown that SOD1 acts to protect hepatocytes from type-1 interferon-mediated oxidative damage.[147] Vitamin D is an important regulator of mitochondrial function. It was reported that vitamin D is capable of enhancing the mitochondrial biogenesis and membrane potential by increasing Ca^{2+} accumulation[148] In addition, vitamin D interacts with hydroxyacyl-CoA dehydrogenase trifunctional multienzyme complex subunit alpha, and suppresses the biosynthesis of carnitine, which limits the fatty acid transport to the mitochondria, and impairs β-oxidation.[149] As mentioned earlier, the regulation of NOX is important in NAFLD pathogenesis.[150] The role of vitamin D in NOX expression has been reported in cerebral ischemia. The pre-treatment of mice with vitamin D potentially reduced the expression of NOX-2, and minimized the high ROS-induced brain injury.[151,152] However, the role of vitamin D in downregulating NOX-2 remains to be explored for NAFLD.

Pitfalls and future directions

The primary diagnosis of NAFLD generally relies on imaging techniques, such as abdominal ultrasonography and computed tomography. However, these non-invasive techniques often lead to a poor diagnosis, in the case of mild steatosis.[153–155] In this context, non-invasive biomarkers for the detection of fibrosis, combined with imaging, may be helpful to arrive at a proper diagnosis. However, a liver biopsy warrants further confirmation. In addition, patients with liver injury and comorbidities represent inconsistencies in clinical findings.[156]

The emergence of inadequate vitamin D levels has become a serious clinical issue worldwide. As mentioned earlier, extensive research has been carried out on the low vitamin D status in NAFLD. It has been reported that vitamin D supplementation can significantly improve NAFLD-related abnormalities. However, there is an urgent need to investigate the role of vitamin D in the regulation of MAFLD. Furthermore, there is a need to explore the vitamin D-associated molecular interactions, in order to obtain a better understanding of the progression of the disease. Vitamin D is actively involved in regulating cells, such as adipocytes, hepatocytes, pancreatic β-cells, liver macrophages, and their cellular processes. Hence, the effect of vitamin D needs to be closely monitored using *in vitro* cell lines, and *in vivo* animal models. Besides, the effect of vitamin D needs to be checked on the gut microbiota, in order to explore the role of vitamin D in the regulation of the gut-liver axis in NAFLD progression.

Conclusions

The global incidence of NAFLD is increasing. Metabolic disorders and lifestyle significantly impact the NAFLD progression. The underlying molecular mechanism of NAFLD is multifactorial and complex to understand. In addition, prominent and targeted therapeutic strategies to treat NAFLD are presently being developed. After the careful analysis and consideration of relevant published data, the results suggested that WATs play an initiative role in NAFLD progression. The generation of high FFA flux and cellular trafficking may be correlated with the associated downstream events of NAFLD pathogenesis, such as inflammation, high ROS, fibrosis, and liver damage, while metabolic abnormalities and the gut microbiota aggravate the disease progression.

Recently, vitamin D deficiency and increasing incidents of NAFLD cases have been reported. Extensive research has been carried out through *in vitro* and *in vivo* studies, and clinical trials to elucidate the beneficial effect of vitamin D supplementation on NAFLD. The present review highlights the possible molecular targets of vitamin D to diminish the NAFLD pathogenesis. Vitamin D is capable of regulating molecular pathways linked to obesity, insulin resistance and diabetes, which are the major risk factors of NAFLD. Vitamin D tremendously acts on adipocytes to control the FFA trafficking, lipogenesis, and inflammation. Similarly, vitamin D acts on hepatocytes to reduce *de novo* lipogenesis and cellular FFA trafficking. This potentially acts on pancreatic β-cells to improve insulin secretion, cell survival, and cellular functions. In addition, this improves the glucose uptake and insulin sensitivity. Moreover, vitamin D decreases proinflammatory cytokines, and reduces the chance of liver injury in NAFLD. In addition, vitamin D acts on the mitochondria to control ROS-mediated cellular toxicity. Hence, there is an urgent need to diagnostically screen out vitamin D deficient NAFLD patients, and conduct extensive research at the molecular level, in order to analyze the indispensable role of vitamin D, and control NAFLD. Vitamin D supplementation therapy may be beneficial for the treatment and control of NAFLD in the future.

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Conflict of interest

The author has no conflict of interest to declare.

Author contributions

SS: performed the literature survey, data compilation and interpretation; constructed the study design and diagrams; wrote the manuscript.

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