REVIEW

Vitamin D: A new player in non-alcoholic fatty liver disease?

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Received: August 27, 2014
Peer-review started: August 28, 2014
First decision: September 15, 2014
Revised: October 25, 2014
Accepted: December 5, 2014
Article in press: December 8, 2014
Published online: February 14, 2015

Abstract

Vitamin D through its active form 1a-25-dihydroxyvitamin D [1,25(OH)$_2$D] is a secosteroid hormone that plays a key role in mineral metabolism. Recent years have witnessed a significant scientific interest on vitamin D and expanded its actions to include immune modulation, cell differentiation and proliferation and inflammation regulation. As our understanding of the many functions of vitamin D has grown, the presence of vitamin D deficiency has become one of the most prevalent micronutrient deficiencies worldwide. Concomitantly, non-alcoholic fatty liver disease (NAFLD) has become the most common form of chronic liver disease in western countries. NAFLD and vitamin D deficiency often coexist and epidemiologic evidence has shown that both of these conditions share several cardiometabolic risk factors. In this article we provide an overview of the epidemiology and pathophysiology linking NAFLD and vitamin D deficiency, as well as the available evidence on the clinical utility of vitamin D supplementation in NAFLD.

Key words: Steatohepatitis; Non-alcoholic fatty liver disease; Fatty liver; Vitamin D

Core tip: Non-alcoholic fatty liver disease (NAFLD) is a multifactorial disease and its pathogenesis is closely linked to the metabolic syndrome. Vitamin D deficiency, which also shares similar associations with obesity and sedentary lifestyle, is often found together with NAFLD. As our understanding of the many functions of vitamin D has grown, emerging evidence points to a closely linked and potentially causative relationship between vitamin D deficiency and NAFLD. As such, vitamin D is now emerging as an immunomodulatory and anti-fibrotic agent. However, in order to implement clinical recommendations larger, randomized, placebo-control trials are required to better evaluate the efficacy of vitamin D replacement in NAFLD.

INTRODUCTION

Non-alcoholic fatty liver disease (NAFLD) has become the most common form of chronic liver di-
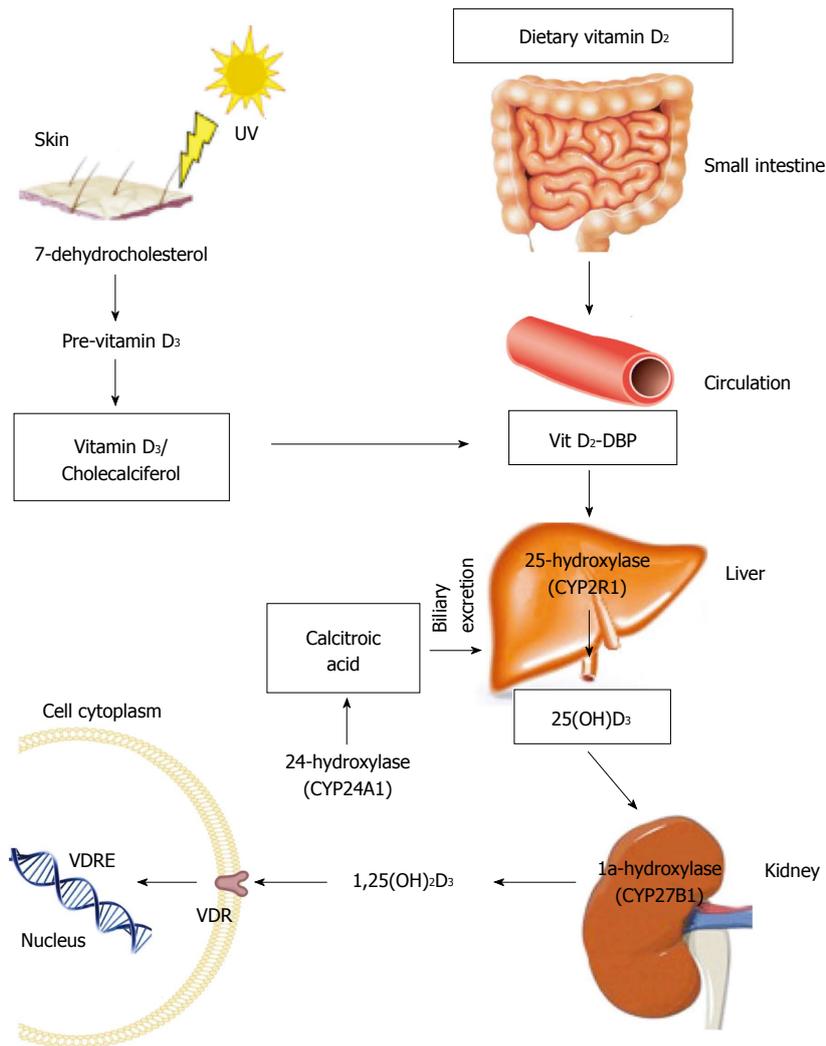
Figure 1 Vitamin D synthesis and metabolism. DBP: D binding protein; VDRE: Vitamin D response element.

sease in Western countries with prevalence as high as 30%[1,2], thus exceeding that of viral hepatitis and alcoholic liver disease. NAFLD represents a continuum of hepatic injuries, which progress from simple fatty liver to steatohepatitis (NASH), cirrhosis or even hepatocellular carcinoma. The metabolic syndrome is universally considered as the key factor in the pathogenesis of NAFLD[3,4]. However, the evolution of liver inflammation in NAFLD and the progression from simple fatty liver to steatohepatitis and hepatic fibrosis is more complex[5]. As our understanding in the pathogenesis of NASH continues to evolve, vitamin D is emerging as an important player in the development and progression of NAFLD. This review will assess the role of vitamin D deficiency in the pathogenesis of NAFLD, explore the epidemiologic evidence that supports a link between vitamin D deficiency and NAFLD and provide available evidence on the clinical utility of vitamin D replacement in NAFLD subjects.

VITAMIN D METABOLISM

Vitamin D is a fat-soluble vitamin. Although, multiple forms of this vitamin exist, vitamin D_2 (ergocalciferol) and vitamin D_3 (cholecalciferol) are the two major forms. Vitamin D_2 is produced by some organisms of phytoplankton, invertebrates and yeast in response to ultraviolet irradiation but it is not constitutively produced by vertebrates. Thus this form of vitamin D has been exploited commercially and is used for fortification and supplementation. Vitamin D_3 on the other hand, originates in the skin of most vertebrates including humans, after irradiation of 7-dehydrocholesterol with ultraviolet light (UVB) (Figure 1). Dietary vitamin D_2 is absorbed by the small intestine and incorporated into chylomicrons where it is transported to the liver bound to vitamin D-binding protein. In the liver, vitamin D from both the skin and diet is then metabolized by 25-hydroxylase (CYP2R1) to 25-hydroxyvitamin D [25(OH)D], which

is the major circulating metabolite and the most widely used indicator of vitamin D stores. 25(OH)D is transported to the kidney where it undergoes hydroxylation by 1a-hydroxylase (CYP27B1) to the biologically active form 1a,25-dihydroxyvitamin D [1,25(OH)$_2$D]. Finally, *via* binding to vitamin D receptor (VDR), 1,25(OH)$_2$D is able to exert its biological actions.

The synthesis of 1,25(OH)$_2$D is tightly regulated by the synthetic activity of 1a-hydroxylase and the catabolic activity of 24-hydroxylase (CYP24A1) which catabolizes 1,25(OH)$_2$D to the water soluble and biologically inactive calcitoic acid which is then excreted in the bile. Parathyroid hormone, 1,25(OH)$_2$D and Fibroblast growth factor 23 (FGF23) are the main regulators of these enzymes. 1,25(OH)$_2$D decreases its own synthesis though negative feedback but also by way of inhibition of parathyroid hormone (PTH) which is the main stimulus for 1a-hydroxylase transcription. Fibroblast growth factor 23, secreted from osteoblasts, acts on the kidneys to suppress renal expression of 1a-hydroxylase and to promote 24-hydroxylase activity which result in reduced production of 1,25(OH)$_2$D.

VITAMIN D TARGETS

The leading and most widely known physiological function of 1,25(OH)$_2$D is to regulate mineral and skeletal homeostasis. However, over the last decades the functions of vitamin D have been broadened beyond those on skeletal tissue and calcium homeostasis. Indeed, the finding of VDR expression in a wide range of tissues such as the immune system (T and B cells, macrophages, and monocytes), the reproductive system (uterus, testis, ovary, prostate, placenta, and mammary glands), the endocrine system (pancreas, pituitary, thyroid and adrenal cortex), in muscles (skeletal, smooth and heart muscles), and in brain, skin, and liver has stimulated considerable interest in understating the putative pleiotropic properties of vitamin D and introduced the idea of a paracrine/autocrine role in regulating cell proliferation, differentiation and apoptosis as well as immune-cells regulation[6,7].

VITAMIN D DEFICIENCY AND NAFLD: THE EPIDEMIOLOGIC EVIDENCE TO DATE

Numerous publications propose that low levels of 25(OH)D are strongly associated with features of the metabolic syndrome[8,9] and may play an important role in modifying the risk for cardio-metabolic outcomes including Type 2 diabetes (T2DM), hypertension and cardiovascular disease[10]. A recent systematic review found that 25(OH)D levels > 25 ng/mL were associated with 43% lower risk of T2DM compared to

levels < 14 ng/mL[11]. In the same study, vitamin D treatment improved insulin resistance among patients with baseline glucose intolerance. Similarly, another meta-analysis showed that vitamin D supplementation improves insulin resistance compared to placebo, albeit the effect was weak[12]. In support of the beneficial role of vitamin D in diabetes and insulin resistance are the findings of various animal studies showing that lack of VDR in mice or vitamin D deficiency impairs insulin secretion from pancreatic beta cells[13]. In contrast to the above findings, are the results of a recent meta-analysis by Seida *et al*[14]. In this study, 35 randomized controlled trials were examined with a total of 43407 patients. No significant effect of vitamin D supplementation on the prevention of diabetes in individuals without diabetes, or on the reduction of insulin resistance and hyperglycemia in those with pre-diabetes or established type 2 diabetes was found. However these results are limited by the presence of moderate heterogeneity between the studies, the associated risks of bias and the short term of follow up.

Given the strong association of NAFLD with obesity and the metabolic syndrome, recent years have witnessed a significant scientific interest into the potential role of vitamin D in NAFLD. Accumulating epidemiological data suggest that low levels of serum 25(OH)D are associated with NAFLD as diagnosed either by biochemistry, imaging or biopsy. These data are summarized in a recently published meta-analysis in which NAFLD subjects were 26% more likely to be vitamin D deficient compared to controls[15]. In US the largest of these studies was by Liangpunsakul *et al*[16] in which the authors reported that in a subset of 1287 adult participants from the NHANES III database, those with unexplained elevation in serum alanine aminotransferase (ALT) levels - a proxy of NAFLD - had lower 25(OH)D levels than those with normal ALT levels (24.7 ± 10.4 ng/mL *vs* 26.8 ± 10.9 ng/mL, *P* < 0.01). Compared to the lowest quartile, patients with the two top quartiles of serum 25(OH)D levels had significantly lower prevalence of unexplained elevation in serum ALT, independently of metabolic syndrome features[16]. In Asia, the largest study was a cross-sectional study of 6567 Korean men which found that subjects in the lowest tertile of 25(OH)D levels had a significantly increased risk for NAFLD compared to thosein the highest tertile, even after adjusting for body mass index and metabolic syndrome (OR = 1.247 and 1.408 *vs* the highest tertile, *P* < 0.001)[17]. A more recent Korean study however, showed contradictory results. In this study the authors analyzed data from the Korean National Health and Nutrition Examination database (KNHANES IV) with more than 16000 individuals and found that obese subjects (BMI > 25) with > 2 components of the metabolic syndrome were more likely to have elevated liver enzymes compared to normal weight subjects; however there was no

Mechanisms	Evidence
Improvement in insulin secretion and insulin resistance	Presence of VDR in pancreatic beta cells[26]
	Expression of 1-α-hydroxylase enzyme in pancreatic beta cells[79]
	Impaired insulin secretory response in mice lacking a functional VDR[13]
	Transcriptional activation of the human insulin gene by 1,25(OH)₂D[80]
	Vitamin D deficiency impairs glucose-mediated insulin secretion from rat pancreatic beta cells *in vitro*[81] and *in vivo*[82]
	Vitamin D enhances insulin responsiveness for glucose transport in muscle cells[83]
	Vitamin D up-regulates glucose transporter 4 (GLUT4) translocation and glucose utilization in adipocytes[44]
Improvement in adipose tissue inflammation	Higher 25(OH)D concentrations were independently associated with higher adiponectin concentrations in a large cohort of men and women[40]
	Reduction of IL-6 in adipocytes after supplementation of vitamin D in mice fed high fat diet[84]
	1,25-dihydroxyvitamin D treatment in human adipocytes inhibits NF-κB pathway and reduces pro-inflammatory cytokine release[85,86]
	1,25-dihydroxyvitamin D inhibits macrophage recruitment and increases adiponectin expression in preadipocytes[87]
Improvement in hepatic inflammation	Vitamin D deficiency causes TLR activation and exacerbates hepatic inflammation[42]
	Artificial sunlight therapy in rats reduced liver inflammation and apoptosis[43]
	VDR expression on cholangiocytes was inversely correlated with steatosis severity and nonalcoholic fatty liver disease score in NASH patients[31]
Improvement in hepatic fibrosis	Presence of VDR in HSC[24]
	Vitamin D treatment suppresses HSC proliferation in cultured HSC from rats[73]
	Vitamin D treatment downregulates pro-fibrotic marker TIMP-1 and collagen type I production in cultured HSCs[73,74]
	VDR knockout mice develop spontaneous liver injury with fibrosis[30]

Table 1 Potential mechanisms and evidence to support a benefit for vitamin D in non-alcoholic fatty liver disease

VDR: Vitamin D receptor; TLR: Toll-like receptor; IL: Interleukin; TLR: Toll like receptor; NASH: Nonalcoholic steatohepatitis; HSC: Hepatic stellate cells.

significant difference in vitamin D levels between the groups[18].

Targher *et al*[19] was the first to study the association between biopsy-proven NAFLD and vitamin D levels. The study confirmed that 25(OH)D concentrations were lower in NAFLD subjects compared to matched controls. Furthermore 25(OH)D levels predicted the histological severity of NAFLD, with NASH patients having lower 25(OH)D levels compared to those with isolated fatty liver. These findings have been confirmed by four other studies with biopsy-proven NAFLD in adults[20,21] and in children[22,23].

Collectively, the data from the published studies indicate that NAFLD subjects are more likely to be vitamin D deficient compared to controls. However, definite directionality of the results cannot be ascertained due to the nature of the above studies (*i.e.*, cross-sectional) and the limitations observed which include the variability in the method of diagnosis of NAFLD, clinical heterogeneity among the study groups and variability in defining vitamin D deficiency.

NAFLD PATHOPHYSIOLOGY

Our understanding of the pathogenesis of NAFLD has evolved from the relatively simplistic "two-hit" hypothesis to the "multiple-hits" hypothesis[5]. In this model, a number of diverse, parallel processes contribute to the development and progression of liver inflammation from simple hepatic steatosis to

steatohepatitis and hepatic fibrosis. A number of these pathways can be affected by vitamin D and relate to the hormonal, immunologic and cellular differentiation "non-classical" effects of vitamin D. Below, we will discuss each of these pathways. A summary of evidence is provided in Table 1 and Figure 2 provides a schematic representation of these mechanisms.

PUTATIVE MECHANISMS LINKING VITAMIN D DEFICIENCY TO NAFLD

Vitamin D signaling

Vitamin D mediates its intracellular signals via its receptor VDR which is constitutively expressed in the liver[24,25]. It has been estimated that VDR regulates over 200 genes involved in glucose and lipid metabolism[13,26], inflammation[27], cellular proliferation and differentiation and apoptosis[28]. In a GWAS study of NAFLD subjects, four single nucleotide polymorphisms (SNPs) were found to have significant association with NAFLD. Among these four SNPs *GC* gene was included which is predominately expressed in hepatocytes and codes for vitamin D binding protein, the main carrier protein for vitamin D[29]. We also know from animal studies that normal functioning of VDR is crucial for liver fibrosis, as VDR knockout mice exhibit spontaneous liver injury with fibrosis[30]. In humans, Barchetta *et al*[31] showed that liver VDR expression is inversely correlated with severity of NAFLD on histopathology, independently
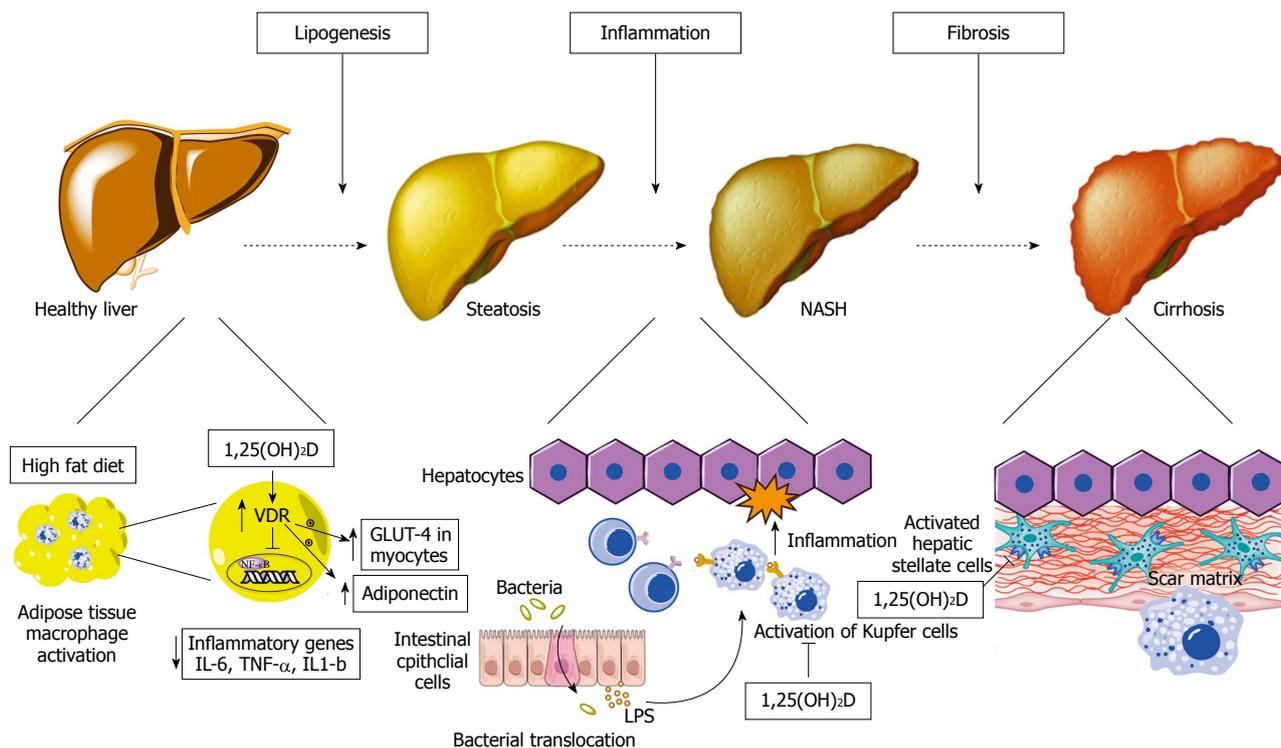
Figure 2 Schematic representation of metabolic, anti-inflammatory and anti-fibrotic effects of vitamin D on hepatocytes and non-parenchymal hepatic cells (hepatic stellate cells, Kupffer cells) in non-alcoholic fatty liver disease. Left: At the initial stage of lipogenesis, 1,25(OH)$_2$D acts on adipocytes and inhibits NF-κB transcription, known as the pro-inflammatory "master switch", and thus inhibits the expression of the inflammatory cytokines IL-6, TNF-α and IL-1β. It also increases adiponectin secretion from adipoycytes and enhances GLUT-4 receptor expression in myocytes, both of which improve insulin resistance; Middle: Increased gut permeability allows translocation of bacterial pathogens which can activate Toll like receptors on Kupffer cells. 1,25(OH)$_2$D downregulates the expression of TLR-2, TLR-4 and TLR-9 in these cells and thus ameliorates inflammation; Right: 1,25(OH)$_2$D acts on hepatic stellate cells by binding to VDR and reduces proliferation of these cells that play a major role in inducing fibrosis. VDR: Vitamin D receptor; TLR: Toll like receptor; LPS: Lipopolysacharides.

from other metabolic parameters such as BMI, insulin resistance or adiponectin.

Adipose tissue, insulin resistance and hepatic inflammation - the role of vitamin D

Insulin resistance, a key risk factor in the pathogenesis of NAFLD, is linked to the development of oxidative stress and lipotoxicity[32,33]. As a result, hepatic steatosis resulting from accumulation of free fatty acids is associated with a state of chronic hepatic inflammation. An important mediator in this process is nuclear factor κ-β (NF-κB) that functions as a pro-inflammatory "master switch" by upregulating the transcription of a wide range of inflammatory mediators. Accordingly, increased NF-κB activity in the livers of high fat diet mice is associated with the increased expression of pro-inflammatory cytokines, including TNF-α, IL-6, IL-1β and activation of Kupffer cells[34]. These cytokines are capable of producing all of the classical histological features of NASH including hepatocyte necrosis/apoptosis, neutrophil chemotaxis and activation of hepatic stellate cells. Moreover, human studies have demonstrated increased cytokine gene expression in the livers of patients with NASH compared to obese controls with normal livers, with the increased expression correlating with histolocical severity[35]. Adiponectin on the other hand, has

been described as the prototypic adipokine by way of its function as an anti-inflammatory agent. In murine models, high levels of adiponectin have been experimentally shown to decrease necroinflammation and steatosis in alcoholic and nonalcoholic fatty liver disease[36] as well as improved insulin resistance[37]. Moreover, studies in humans showing reduced serum levels of adiponectin and reduced hepatic expression of its receptor in patients with NASH compared with body mass index-matched patients with steatosis[38,39], provide strong supportive evidence that reduced adipocyte production of adiponectin plays an important role in the pathogenesis of progressive NAFLD.

The role of vitamin D in adipokine activity is an active area of research. Vaidya *et al*[40] showed a positive association between 25(OH)D concentrations and levels of adiponectin in a large cohort of patients. Interestingly, this relationship was independent of BMI. Furthermore, in a double-blind, randomized, controlled trial of Iranian type 2 diabetic patients, daily intake of 1000 IU vitamin D either with or without extra calcium for 12 wk resulted in a significant increase of serum adipokines including adiponectin and decreased cellular secretion of the inflammatory cytokines IL-6 and IL-1β[41].

Additional evidence from animal studies further support the notion of an immunomodulatory role of

vitamin D in NAFLD. To explore the effect of vitamin D deficiency on inflammatory markers Roth *et al*[42] used a rat model consistent of 4 groups; rats were fed either a low-fat diet alone (LFD) or with vitamin D depletion (LFD + VDD) or high-fat Western diet which was either replete (WD) or deficient in vitamin D (WD + VDD). In VDD groups, blood 25(OH)D levels were reduced compared to the replete diet groups. Mice fed WD/VDD showed increased hepatic steatosis comprared to LFD groups. Liver histology also showed increased lobular inflammation and NAFLD activity score in WD/VDD group compared to the WD alone group. In addition WD/VDD mice had increased hepatic mRNA levels of resistin, IL-4, IL-6 and TNF-α markers known to be implicated in oxidative stress and hepatic inflammation. Accordingly in another rat NASH model[43], phototherapy increased 25(OH)D and 1,25(OH)$_2$D levels while reducing hepatocyte inflammation, fibrosis and apoptosis compared to controls. Phototherapy also improved insulin resistance and increased serum adiponectin in association with reduced hepatic expression of inflammatory genes TNF-α and TFG-β. In total, these findings suggest that vitamin D deficiency worsens NAFLD related to upregulation of hepatic inflammatory and oxidative stress genes.

Another interesting and plausible mechanism underlying the association of diabetes/insulin resistance with low vitamin D levels has been recently showed in an *in-vitro* study where 3T3L1 adipocytes were treated with high glucose in the presence or absence of 1,25-dihydroxyvitamin D. 1,25(OH)$_2$D treatment of adipocytes caused significant up-regulation of GLUT4 receptor expression and its translocation to cell surface, and an increase in glucose uptake as well as glucose utilization[44]. Supplementation also stimulated adiponectin secretion in high glucose-treated cells, lending further weight of a beneficial effect of vitamin D in reducing adipose tissue inflammation.

Intestinal microbiome and innate immunity in NAFLD and the role of viatamin D deficiency

The liver is positioned between the gut and systemic circulation and in addition to its synthetic function it has a key role in degrading and removing toxins, exogenous antigens, and infectious agents responding to exogenous antigenic molecules. This role makes the liver not only a metabolic organ but also a mediator of systemic and local innate and adaptive immunity[45]. The intestinal epithelial cells prevent the translocation of bacterial products to the portal circulation. When this barrier is ineffective the liver cells are exposed to bacterial products and this translocation may impair liver homeostasis and trigger liver inflammation, inducing the innate immune response[46,47]. A study from Italy showed that patients with NAFLD have increased gut permeability and small intestinal bacterial overgrowth (SIBO). Both gut permeability and the prevalence of SIBO correlated with the severity of steatosis but not with presence of NASH in this study[48].

Bacterial lipopolysaccharides (LPS) are activators of the immune system and in animal models were involved in the development of both systemic inflammation and obesity[49]. Toll Like receptor-4 (TLR-4) recognizes a diverse array of pathogen associated molecular patterns including LPS[50]. The role of TLR-4 has been studied and there is a clear association between TLR-4 activation and NAFLD[48,49,51-54]. Interestingly, the development and progression of NAFLD by western diet is exacerbated by vitamin D deficiency through the activation of TLR2 and TLR4 by way of CD14/LBP, and stimulation of downstream inflammatory signaling molecules leading to steatosis and inflammation[42].

Toll-like receptor 5 (expressed in the gut mucosa helping defense against infection) is implicated in the development of metabolic syndrome and alterations in gut microbiota. In a study published in 2010, TLR-5-deficient mice developed hyperphagia, obesity, insulin resistance and hepatic steatosis. In this study, transfer of microbiota from TLR-5-deficient mice to healthy mice led to development of *de novo* disease, indicating a possible connection between TLR-5 and intestinal microbiota in NAFLD[55]. In contrast to this study, Kanuri *et al*[54] found that TLR-5 is significantly overexpressed in patients with NAFLD compared to controls thus making the role of TLR-5 in the development of NAFLD unclear.

A different subtype of TLR, TLR-9 is activated by bacterial/viral DNA and has been implicated in the development of steatohepatitis in animal models[56]. Miura *et al*[57] showed that TLR-9-deficient mice failed to develop inflammation *vs* controls when exposed to IL-1b. In another study mentioned earlier the investigators showed that vitamin D deficient mice following Western Diet had increased levels of messenger RNA of TLR-2, TLR-4, and TLR-9[42]. However, there are no randomized controlled trials studying whether vitamin D replacement is beneficial in suppressing the effects of TLR-4 and TLR-9.

The role of the major components of the innate immunity like macrophages and Kuppfer cells[58-61], neutrophils[62-64], eosinophils[65] and dendritic cells (DC)[66,67] in the pathogenesis of NAFLD and insulin resistance has been studied but a detailed report extends beyond the goals of the current review. It is however interesting to note the immunomodulatory effect of vitamin D in DC. Dendritic cells express VDR[68] and treatment with 1,25(OH)$_2$D inhibits DC maturation and promotes a tolerogenic phenotype in some studies[69,70]. However Henning *et al*[66] showed that DC depletion markedly exacerbates intrahepatic fibroinflammation. Thus the role of vitamin D in the

regulation of this pathway is not clear yet.

Vitamin D and hepatic fibrosis

The development of liver fibrosis in NAFLD indicates advanced disease and is in fact the strongest predictor for disease-specific mortality[71]. It is characterized by an accumulation of extracellular matrix (ECM) with subsequent destruction of the normal liver architecture, leading to liver cell dysfunction. Hepatic stellate cells (HSCs) play a critical role in the development of liver fibrosis, since they are responsible for excessive deposition of ECM proteins, predominantly type I collagen. Two main processes lead to liver fibrosis. First, HSCs become activated, resulting in increased cellular proliferation and bio-transformation to an activated myofibroblast-like cell. Second, there is an increase in ECM protein synthesis and deposition, predominantly type I collagen. TGF-β1 signaling pathway plays a central role in this process, as it is the main stimulating factor for profibrotic ECM synthesis[72].

Although it has been known for some time that vitamin D has anti-proliferative and anti-fibrotic properties and plays an important role in the regulation of ECM, little has been known until recently about the effects of vitamin D on HSCs. Indeed, the finding of a robust VDR expression in HSCs[24] has led to the discovery that VDR signaling can suppress fibrotic gene expression and inhibit proliferation of HSCs[30,73]. Elegant mechanistic studies with VDR knockout mice confirmed the development of spontaneous liver injury with fibrosis in these mice[30]. Moreover, in an experimental mouse model of liver injury, co-treatment with VDR ligand attenuated the progression of liver fibrosis[30]. Consistent with the above studies are the findings of another *in-vitro* study, this time in human HSCs, in which treatment with 1,25(OH)$_2$D caused inhibition of fibrogenesis by inhibiting type 1 collagen formation[74]. The underlying mechanism by which VDR prevents this pathological process has only been recently elucidated and involves the antagonistic action of VDR on SMAD transcription factor - a key transcription factor in the pro-fibrotic process linking TGF-β1[30].

VITAMIN D AS A TREATMENT FOR NAFLD/NASH

In total, the evidence to date suggests that vitamin D may be beneficial in preventing the progression of NAFLD. Therefore, clinical trials that directly evaluate the effect of vitamin D supplementation on disease progression in NAFLD subjects are warranted. Only recently were the results of a small double-blind, placebo-control study in NAFLD subjects published. In this study[75], the investigators randomly assigned NAFLD participants in the vitamin D group (50000 IU every 14 d for 4 mo) and the control group (no

vitamin D supplementation). After a follow-up period of 4 mo, there were no significant differences in the serum levels of liver enzymes, HOMA-IR or grades of hepatic steatosis, measured by ultrasound, between the two groups. However there was a significant decrease in the levels of hsCRP and MDA (malon-dialdehyde) - a marker of lipid peroxidation - in the subjects treated with vitamin D. The negative results of this study on the markers of steatosis and liver injury have to be interpreted carefully given the limited number of participants (n = 53) and the relatively short term of follow up. On the contrary, the confirmation that vitamin D treatment resulted in improvement of inflammatory biomarkers in NAFLD subjects suggests that vitamin D supplementation may be considered as an adjunctive therapy to attenuate systemic inflammation in NAFLD.

CONCLUSION

Vitamin D deficiency is commonly associated with NAFLD and has even been correlated with disease severity. The metabolic, anti-inflammatory and anti-fibrotic properties of vitamin D provide plausible mechanisms by which vitamin D may impact on the various steps of disease progression and severity. Cumulatively, this would suggest that vitamin D replacement might be effective in the treatment of NAFLD. However, controversies exist in the field given the limited number of prospective randomized studies in humans examining the role of vitamin D supplementation in NAFLD, the presence of variability on the methodologies used for detecting vitamin D levels[76] as well as the lack of consensus in the scientific community on defining the optimal levels of vitamin D (> 20 ng/mL *vs* > 30 ng/mL)[77,78].

In conclusion, larger, randomized, placebo-controlled trials are required to better evaluate the efficacy of vitamin D replacement and parameters of therapy in NAFLD. Until then, it is premature to recommend vitamin D supplementation for the specific treatment of NAFLD even though its role seems to be promising.

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