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**Vitamin D deficiency in chronic liver disease**

Iruzubieta P *et al.* Vitamin D and liver disease

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**Abstract**

Vitamin D is an important secosteroid hormone with known effect on calcium homeostasis, but recently there is increasing recognition that vitamin D also is involved in cell proliferation and differentiation, has immunomodulatory and anti-inflammatory properties. Vitamin D deficiency has been frequently reported in many causes of chronic liver disease and has been associated with the development and evolution of non-alcoholic fatty liver disease (NAFLD) and chronic hepatitis C (CHC) virus infection. The role of vitamin D in the pathogenesis of NAFLD and CHC is not completely known, but it seems that the involvement of vitamin D in the activation and regulation of both innate and adaptive immune systems and its antiproliferative effect may explain its importance in these liver diseases. Published studies provide evidence for routine screening for hypovitaminosis D in patients with liver disease. Further prospectives studies demonstrating the impact of vitamin D replacement in NAFLD and CHC are required.

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**Key words:** Cholecalciferol; Vitamin D; Hepatitis C; Liver fibrosis; Liver disease; Interferon; Sustained virological response; Nonalcoholic fatty liver disease; Nonalcoholic steatohepatitis

**Core tip:** (Vitamin D and liver disease) Vitamin D deficiency has been frequently reported in many causes of chronic liver disease and has been associated with the development and evolution of non-alcoholic fatty liver disease (NAFLD) and chronic hepatitis C (CHC) virus infection. The role of vitamin D in the pathogenesis of NAFLD and CHC is not completely known, but it seems that the involvement of vitamin D in the activation and regulation of both innate and adaptive immune systems and its antiproliferative effect may explain its importance in these liver diseases.

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**INTRODUCTION**

Vitamin D insufficiency and deficiency are prevalent in almost half the healthy population of developed countries[1]. Most experts define vitamin D insufficiency as a 25(OH)D level below 75 nmol/L (30 ng/mL) and deficiency as levels below 50 nmol/L (20 ng/mL). It is estimated that one billion people suffer from deficiency or insufficiency of vitamin D[2]. In the United States, between 25% and 50% of the adult population has vitamin D deficiency[3]. In patients with chronic liver diseases, the prevalence of vitamin D deficits is much higher and practically universal[4]. Up to 93% of patients with chronic liver disease have insufficient vitamin D levels, and almost one-third of these show severe deficiency[5].

The outcome of vitamin D deficiency in terms of osteoporosis, osteomalacia and increased fracture risk is well known[6,7]. Furthermore, the association between vitamin D deficiency and the development of infections, cardiovascular, autoimmune and degenerative diseases and several types of cancer (colon, prostate and breast cancer) has also been reported[8]. Vitamin D is important in calcium homeostasis and has also been implicated in the mechanisms of cellular proliferation, differentiation and immunomodulation[9]. These effects are noted in the pathogenesis and treatment of many chronic liver diseases. In this review, we will focus on vitamin D functions involved in the development of chronic liver disease and on the relationship between vitamin D deficiency and the two main causes of chronic liver disease: chronic hepatitis C (CHC) virus infection and non-alcoholic fatty liver disease (NAFLD).

An evidence-based approach was used for this review. MEDLINE search was performed to September 2014 using the following MeSH terms: liver diseases, vitamin D, cholecalciferol, hepatitis C, Chronic, nonalcoholic fatty liver disease. Searches were limited to English language articles. References of suitable articles were searched for other appropriate articles.

**VITAMIN D SYNTHESIS**

Under normal conditions, biogenesis from epidermal cells is the main source of vitamin D. In the skin, ultraviolet radiation from sun exposure transforms 7-dehydrocholesterol, a metabolite of cholesterol, into pre-vitamin D3, which is transformed into vitamin D3 (cholecalciferol). A small portion of vitamin D comes from dietary sources, such as milk and eggs, in the form of vitamin D2 (ergocalciferol) and D3 that is absorbed in the intestine by biliary acids[1,10].Vitamin D synthesized from skin and from dietary sources may be stored in the adipocytes, or it may undergo hepatic 25-hydroxylation. This latter process is mediated by isoforms of the P450 cytochrome (CYP2R1, CYP27A1), the 25-hydroxylases, which produce 25-hydroxyvitamin D [25(OH)D] or calcidiol. The metabolite 25(OH)D, most abundant in blood, is an inactive form of vitamin D. It has a half-life of 2-3 wk and is a useful measure of vitamin D levels because it reflects the total amount of vitamin D from dietary sources, sun exposure and conversion from fatty deposits of the liver, and its concentration in plasma is the most reliable indicator of vitamin D status[11]. This vitamin D metabolite, like others, is a low-solubility lipophilic molecule that moves through the bloodstream attached to plasmatic proteins, the most prevalent of which is vitamin D-binding protein (DBP), also known as Gc. Up to 88% of serum 25(OH)D is attached to a DBP, a protein synthesized mainly in the liver that has anti-inflammatory and immunomodulating functions independent of its role as a vitamin D transporter[12,13]. 25(OH)Dishydroxylated in the proximal tubules of the kidney by 1α-hydroxylase (CYP27B1) that form 1α,25(OH)2D or calcitriol, the most biologically active and powerful metabolite of vitamin D[1]. CYP27B1 activity has been observed in the kidney and other tissues, including the liver, fat tissue and the cells of the innate immune system[14]. Finally, 24-hydroxylase, which is most abundant in the intestine and the kidney, catabolizes the calcitriol into an inactive metabolite that is excreted in bile[15] (Figure 1).

1α,25(OH)2D has a half-life of 4 h. It is transported *via* attachment to plasmatic proteins such as DBP and, as mentioned previously, conducts most of the biological effects of vitamin D by directly and indirectly controlling the expression of over 200 genes linked to angiogenesis, apoptosis, proliferation, differentiation and immunomodulation[1,16,17]. The biological effects of vitamin D are mediated by binding to the vitamin D receptor (VDR), belongs to the superfamily of nuclear steroid hormone receptors, which is expressed in more than 30 tissues, including the liver, the pancreatic islet cells, the epithelial cells of the gastrointestinal tract and the immune system cells[18]. Hence, vitamin D deficiency may be involved in several processes, such as cancer, diabetes mellitus (DM) and cardiovascular and autoimmune diseases[19-26] . Furthermore, the immune system cells, including macrophages, dendritic cells, and T and B lymphocytes, express CYP27A1 or CYP27B1 enzymes and thus can metabolize 25(OH)D to calcitriol. Calcitriol will then have an autocrine or paracrine function[19,20]. Vitamin D favors the innate response of the immune system and has a “self-regulatory” effect by limiting the adaptive response. On one hand, it stimulates the synthesis of antimicrobial peptides (cathelicidin and beta-defensin) and the chemotaxis and phagocytosis of the macrophages. On the other hand, it decreases the expression of class II HLA complex molecules, co-stimulating molecules and the synthesis of Th1, Th2 and Th17 cytokines[19,20]. Finally, in addition to acting as a transcription factor, VDR seems to induce fast non-genomic responses by activating cellular signaling pathways. In this sense, has been shown presence of VDR in plasma membranes of intestinal, lung, kidney, muscle cells and osteoblasts, where it efficiently binds 1α,25(OH)2D[16,27,28].

**REGULATORY MECHANISMS OF VITAMIN D SYNTHESIS**

The synthesis process of vitamin D includes regulatory mechanisms in each step, as follows: (1) in the skin, excess of vitamin D3 is destroyed by sunlight, thus preventing vitamin D3 intoxication from excessive sun exposure[29]; (2) the 25-hydroxylation of vitamin D is under-regulated. The levels of 25(OH)D increase according to the intake of vitamin D; thus, plasmatic levels of 25(OH)D are used to regulate vitamin D status; (3) in contrast, 1α-hydroxylase is highly regulated. Different factors are involved in its activity and expression, including serum calcium and phosphate, parathyroid hormone (PTH) and fibroblast growth factor 23 (FGF23). An elevated calcium serum concentration suppresses 1α-hydroxylase directly and indirectly by decreasing the PTH levels[30]; elevated plasmatic phosphate also decreases the expression and activity of 1α-hydroxylase through a mechanism that is not yet understood. This increase in serum phosphate seems to trigger an increase of FGF23 that inhibits 1α,25(OH)2D synthesis[31]. Furthermore, the synthesis and degradation of 1α,25(OH)2D is also controlled by local factors such as cytokines and growth factors, although this local production has no effect on the blood levels[32,33]. In the case of the macrophages, the expression of CYP27B1 and synthesis of 1α,25(OH)2D are induced by inflammatory cytokines, such as IFNγ, and by toll-like receptor (TLRs) ligands, such as the lipopolysaccharide (LPS); (4) the 25-hydroxyvitamin D-24-hydroxylase (CYP24A1) catabolizes 1α,25(OH)2D to calcitroid acid , a biologically inactive bile-excreted metabolite[15]. The activity and expression of this enzyme, which is most abundant in intestine and kidney, is controlled by the levels of 1α,25(OH)2D, phosphate and PTH[34,35]; (5) the DBP protein may buffer the levels of free vitamin D which is correlated with the levels of active vitamin D, this prevents intoxication[36]. Additionally, DBP prevents catabolism and excretion of the hormone. The DBP levels decrease in liver disease, nephrotic syndrome and malnutrition; despite this modification, the concentration of 1α,25(OH)2D remains constant; and (6) 1α,25(OH)2D controls its own synthesis not only through the increase of CYP24A1 expression, as mentioned above, but also by directly or indirectly inhibiting CYP27B1 expression and providing a negative feedback pathway.

Therefore, we can conclude that multiple factors regulate vitamin D metabolism. The intake of vitamin D through diet or sun exposure is only one of many variables that determine its activity, another of these variables are DBP levels, the local synthesis of 1α,25(OH)2D (the autocrine or paracrine effect) and VDR expression.

**VITAMIN D AND CHRONIC LIVER DISEASE**

As discussed previously, vitamin D plays an important role in reducing the risk of chronic diseases, including DM type 2, several types of cancer, and cardiovascular, autoimmune and infectious diseases. This role most likely results from the local production of 1α,25(OH)2D and its autocrine and paracrine actions in cellular proliferation and differentiation, apoptosis, insulin and renin secretion and interleukin (IL) and bactericidal protein production[1,16,17,19-23]. These effects may also be relevant in the pathogenesis of chronic liver diseases.

Vitamin D deficiency is extremely common in chronic liver disease patients. Up to 93% of these patients have some degree of vitamin insufficiency[4,5]. Even patients with mild liver disease are affected, although liver cirrhosis patients more commonly suffer from severe deficiency.

Several studies in general populations have shown that low levels of 25(OH)D significantly increase the risk of mortality from all causes, including cardiovascular diseases[37,38]. Regarding patients with chronic liver disease of varying etiologies, vitamin D deficiency has been associated with increased mortality[39,40], bacterial infections[41], portal hypertension complications[42] and fibrosis severity[43,44]. However, because the liver plays an important role in the metabolism and pleiotropic functions of vitamin D, the question is whether vitamin D deficiency is a consequence of liver disease or a contributor to the liver dysfunction.

Severe liver disease decreases vitamin D hydroxylation and albumin and DBP production, all of which are linked to low levels of 25(OH)D. Nevertheless, the vitamin D deficiency in chronic liver disease is only partly the result of a synthesis dysfunction of the liver, as evidenced by the fact that vitamin D deficiency is highly prevalent in non-cirrhotic patients[4]. The levels of 25(OH)D in cirrhotic patients normalize after vitamin D treatment, which indicates that the 25-hydroxylation is preserved[45,46]; and although DBP is moderately decreased in cirrhosis[47], vitamin D metabolites require only 5% of the DBP binding sites[48], indicating that liver dysfunction must be severe to decrease the DBP levels and contribute to vitamin D deficiency. Therefore, vitamin D deficiency in chronic liver disease requires several causes in addition to those mentioned above, including inadequate sun exposure, insufficient food intake, steroid use, jaundice-related deterioration of vitamin synthesis on the skin and decreased vitamin D absorption caused by intestinal edema secondary to portal hypertension or to cholestasis-induced bile salt disruption.

The observed association between vitamin D and liver disease is insufficient to establish a causal effect between vitamin D deficiency and the severity of chronic liver disease. Recent systematic and umbrella reviews has cast doubt on any causal link between vitamin D deficiency and non-skeletal health outcomes, suggesting that vitamin D deficiency is a marker of ill-health, rather than an important factor implicated in the pathogenesis of disease[49]. However, there is growing evidence that vitamin D is involved in the decrease of inflammation and fibrosis[43,50,51]. Proinflammatory signals in monocytes and macrophages may regulate the local metabolism of vitamin D, auto-inducing the expression of CYP27B1 and the local production of 1α,25(OH)2D, and thus controlling the excessive inflammatory response[33,52]. Almost 90% of the tissue macrophages are in the liver[53], which suggests that the liver production of active vitamin D is affected during inflammatory diseases of the liver. Furthermore, VDR is expressed in both macrophages and other non-parenchymal cells and biliary epithelial cells[54]. After activation, these cells increases the expression of cathelicidin, an antimicrobial peptide with anti-endotoxin activity[55], and inhibits the synthesis of biliary acids, thus protecting the hepatocytes from these acids[56,57]. Therefore, the relationship between vitamin D and hepatic physiopathology may result from signaling disruptions in non-parenchymal liver cells or extrahepatic cells[58].

It is important to mention that, together with diet intake and sun exposure, genetic factors substantially contribute to variations in 25(OH)D levels[59,60]. Several simple nucleotide polymorphisms (SNPs) of genes involved in the metabolism of VDR and vitamin D, such as DHCR7 (encode the 7-dehydrocholesterol reductase enzyme), CYP2R1, CYP24A1 and GC (encode DBP), have been strongly linked with the serum levels of 25(OH)D and its efficacy[59-62]. A recent study community-dwelling black Americans, as compared with whites, had low levels of total 25(OH)D and DBP, resulting in similar concentrations of estimated bioavailable 25(OH)D. Racial differences in the prevalence of common genetic polymorphisms provide a likely explanation for this observation[63]. Therefore, such genetic variations may be associated with the severity of chronic liver disease, and several polymorphisms of the VDR gene associated with primary biliary cirrhosis, autoimmune hepatitis, CHC and hepatocellular carcinoma have been identified[64-69].

The available data suggest that vitamin D supplements could be beneficial in terms of morbimortality[70,71]. Most experts consider of at least 75 nmol/L (30 ng/mL) as the most advantageous 25(OH)D level for reducing the risk of fractures, prevention of cancer and the risk of hypertension, and between 90-120 nmol/L (36-48 ng/mL) as the most optimal level[71]. In fact, a recent meta-analysis that included 73 cohort studies (849412 participants) and 22 controlled and randomized studies with over 30716 participants showed that vitamin D3 supplements significantly reduced mortality from any cause among older adults[72]. Few published prospective studies have examined the effects of supplements in chronic liver disease, and the results to date are contradictory, most likely because of issues with study designs, the quantity of vitamin D administered, the pre- or post-treatment measurements used and the presence of genetic polymorphisms that influence the biological activity of vitamin D. Nonetheless, vitamin D supplements are currently recommended to decrease the skeletal effects of vitamin D deficiency. In fact, the latest recommendation suggest that a 25(OH)D level over 20 ng/mL is sufficient to meet the vitamin D requirement[73]. However, the Endocrine Society Clinical Practice Guideline (ESCPG) suggested that vitamin D requirements may be greater for sick patients than for healthy individuals and blood level above 30 ng/mL may have additional health benefits in reducing the risk of various disease conditions[74]. In addition, the ESCPG suggest that 25(OH)D should be measured in chronic liver disease patients to identify those with levels under 20 ng/mL who would benefit from vitamin D supplements to reduce the risk of bone fracture[74]. Similarly, the guidelines of the European Association for the Study of the Liver (EASL) recommend calcium (1000-1200 mg/d) and vitamin D (400-800 UI/d) supplements for cholestatic liver disease patients, although supplement use is supported by limited clinical data[75]. In fact, despite the frequency of vitamin D deficiency in liver disease patients, their calcium and PTH serum concentration levels are normal, which contradicts the possibility that regulatory mechanism of calcium metabolism is affected[76,77]. Our group has confirmed these results in cirrhotic patients of different etiologies; these patients showed vitamin D deficiencies[78] but had free vitamin D levels similar to those of healthy subjects (unpublished data). Consequently, the unaffected free vitamin D may be involved in the lack of correlation between the levels of 25(OH)D and calcium and PTH and may maintain calcium homeostasis without causing secondary hyperparathyroidism[79]. For this reason, several authors indicate that the levels of total and free 25(OH)D should be measured to identify the vitamin D status in chronic liver disease patients[76]. Nonetheless, these patients have a high prevalence of bone mass loss that can be explained by the previous data of vitamin D deficiency and by other interfering factors, such as the increase in pro-inflammatory cytokines[80-82], hypogonadism[83], elevated bilirubin levels[84] and steroid treatment[85].

**VITAMIN D FUNCTIONS AND THEIR IMPLICATIONS IN LIVER DISEASES**

Vitamin D maintains the normal skeletal architecture and plays roles in the cardiovascular[86,87] and nervous systems[88,89] and cellular proliferation and differentiation[90,91]. Furthermore, vitamin D may be relevant in the physiopathology of chronic liver diseases because of its effect on the immune system and its anti-fibrotic effect[51,92,93].

Several research lines suggest that vitamin D has beneficial effects in liver diseases by activating and regulating innate and adaptive immunity.Vitamin D increases innate immunity[23], stimulating the mechanisms associated with the elimination of pathogen agents through the secretion of antibacterial proteins, such as cathelicidin and beta-defensin, and favoring chemotaxis and macrophage phagocytosis[19,20,94,95]. An excessive immune response can cause tissue damage; in this sense, vitamin D promotes an adequate innate immune response by regulating the expression of several TLRs and by decreasing the production of proinflammatory cytokines[52]. An inverse relationship between vitamin D levels and the expression of TLR2, TLR4 and TLR9 in monocytes has been observed, as has a decrease in the expression of these innate immunity receptors after the administration of 1α,25(OH)2D[52,96,97]. These three TLRs are primarily related to the inflammation and fibrosis of the liver. A high-fat diet, alcohol consumption and structural changes in the intestinal mucosa resulting from chronic liver diseases (*e.g.*, the loss of epithelial attachment, vascular congestion, defects of the mucosal immune system) alter the permeability of the mucosa, promoting an increase in intestinal bacteria translocation[98-100] and bacterial products, such as LPS, through the bloodstream; there, these bacteria bond to the TLRs, mainly TLR4, that are present such immune cells as hepatocytes, biliary epithelial cells, dendritic cells and hepatic stellate cells, triggering the synthesis of proinflammatory cytokines and fibrogenesis that ultimately result in liver damage[98,101]. However, vitamin D is involved not only in the regulation of TLR expression but also in intestinal permeability; it plays a role in intestine epithelial cell differentiation and in improving cell bonding[102,103], thus decreasing the bacterial products in the liver.

Regarding adaptive immunity, vitamin D seems to control an excessive immune response by decreasing the expression of class II HLA complex molecules and co-stimulator molecules and by modulating the T cell response[19,20,104]. The activation of naïve T cells has been shown to be vitamin D-dependent[105]; furthermore, it inhibits the development of Th1 (IL-2 and interferon-gamma proinflammatory cytokine producers) and Th9 and increases the number of Th2 cells (IL-4, 5 and 10 anti-inflammatory cytokine producers), thus affecting the polarization of T helper cells[106-108]. Additionally, 1α,25(OH)2D prevents the development of Th17 cells by inhibiting IL-6 and IL-23 production from the dendritic cells, and it induces the differentiation and expansion of regulatory T cells (Treg) that secrete the anti-inflammatory cytokines IL-10 and transforming growth factor beta (TGF-β)[107,109,110]. This ability to modulate the adaptive immune system may explain the association between vitamin D deficiency and the risk of autoimmune diseases and liver damage.

Moreover, *in vitro* and *in vivo* studies of mouse models with liver fibrosis have reported that vitamin D has an anti-fibrotic effect due to ability to affect the pathological process of liver fibrosis at several stages, such as: inhibition of injury trigger, suppression of hepatic stellate cells activation and proliferation, reduction in accumulation of extracellular matrix and even degradation of collagen metalloproteinases activation and TIMPs inhibition[92,93]. Moreover, Ding *et al*[111] revealed an intersecting VDR/SMAD genomic circuit that regulates hepatic fibrogenesis and define a role for VDR as an endocrine checkpoint to modulate the wound-healing response in liver and VDR ligands as potential therapy for liver fibrosis[111]. In this regard, a recent study in mice showed that the active metabolite of vitamin D-1α,25(OH)2D may prevent liver fibrosis in the in-vivo model. However, it cannot ameloriate establish cirrhosis in an animal model[112].

**VITAMIN D AND CHRONIC HEPATITIS C VIRUS INFECTION**

Epidemiological studies show that vitamin D deficiency may increase the risk of acquiring viral infections such as influenza, human immunodeficiency virus (HIV) and respiratory infections[113]. Chronic hepatitis C virus infection is one of the main causes of chronic liver disease; it is estimated to affect 130 to 150 million people worldwide, a significant number of whom also develop cirrhosis and hepatic cancer[114]. A high percentage of these patients (46% to 92%) have low vitamin D levels[50,115-117], and more than 25% suffer from severe deficiency[50,115,117]. It has been hypothesized that the high incidence of vitamin D deficiency in these patients may be caused by HCV’s effect on direct or indirect 25-hydroxylation through cytokine induction or oxidative stress[118,119] and that the virus may suppress 25(OH)D levels due to a disruption in lipid metabolism; as shown a recent study where HCV decreases the production of 7-dehydrocholesterol, the endogenous precursor of vitamin D[120].

As discussed previously, vitamin D inhibits fibrosis and modulates the innate and adaptive immune response, increases the production of antimicrobial peptides and inhibits proinflammatory cytokines. The anti-inflammatory action of vitamin D[19,20,50,94,95,104,106-110] can explain the improved therapeutic results of interferon (IFN) and ribavirin (RBV) after the administration of vitamin D supplements[121-123], as some data indicate that proinflammatory cytokines and chemokines promote the persistence of HCV[124]. In this respect, a low Th1/Th2 ratio is an independent sustained viral response (SVR) factor in the treatment of the HCV genotype 1[125], and 1α,25(OH)2Dfavors Th2 in this balance, as mentioned previously[108]. Furthermore, several in-vitro studies have considered vitamin D a direct HCV antiviral agent[126-128]. Gal-Tanamy *et al*[127]. showed that vitamin D increases VDR expression and inhibits HCV replication in human hepatocytes by inducing the expression of IFN beta and the IFN-stimulated gene (MxA) with different antiviral properties, thus producing a synergic effect with antiviral treatment[127]. In the same study, vitamin D or calcitriol added to the antiviral treatment had a synergic effect in the inhibition of HCV. In addition, in recent clinical studies have described an association between VDR polymorphisms on the response to IFN/RBV therapy in CHC[129,130].

The relevance of vitamin D in CHC has been reported in numerous studies that associated vitamin D deficiency with a greater degree of necrosis and fibrosis[40,50,68,131,132] and with a lower likelihood of a SVR to IFN-based therapies[50,115,121,123,133-135]. In fact, all of the patients who showed severe vitamin D deficiency had hardly any SVR, while 50% of those with normal levels or almost normal levels had SVR[50,121,123,136]. However other studies failed to find ant relationship between baseline vitamin D level and SVR and fibrosis[116,137-140] (Table 1). In addition, conflicting conclusions have been reached in two recent meta-analysis[130,141]. This may be due to limitations of the studies included: (1) the small number of patient; (2) mayority had a cross-sectional studies that are subject to bias due to the possibility of reverse causation; (3) lack of vitamin D level assessment during therapy; and (4) characteristic of vitamin D assessment (seasonality, cut off values, methodology of vitamin D determination, ethnicity). In contrast, vitamin D has been shown to increase the probability of SVR when it is added to the antiviral treatment[121-123,142] (Table 1). Thus, futher clinical investigation on the effect of vitamin D supplementation in treating CHC are needed to confirm this item.

Furthermore, Bitteto and colleagues provided additional information in their study of the rs12979860 C/T polymorphism of IL28B. In their study, vitamin D levels were complementary to the rs12979860 C/T polymorphism of the IL28B for predicting SVR in CHC patients infected with difficult-to-treat genotypes (1, 4, 5)[136]. Another polymorphism, the CYP27B1-1260 polymorphism is also known to decrease the intracellular concentration of calcitriol in mononuclear cells and T lymphocytes[134] and is a known cofactor in immune response disruption in these cells. In fact, the study by Lange and colleagues confirms the lack of SVR in patients infected with the HCV 1, 2 and 3 genotypes who have this polymorphism[115]. This study also hypothesized that genotype 3 patients had low 25(OH)D levels, in contrast with previously published data[50,136]. We should, however, note that the definition of vitamin D deficiency differed among the three studies, a factor that should be considered when interpreting these results.

Vitamin D also favors the HCV response by improving the sensitivity to insulin[143-145]. Insulin resistance (IR) is considered one of the most important factors in predicting HCV patients’ response to IFN and RBV[146], and vitamin D is known to prevent DM type 2[144]. As β-pancreatic cells contain VDR, vitamin D deficiency may alter the balance between the intra- and extracellular calcium and interfere with insulin release[147].

Therefore, in theory, vitamin D deficiency may be linked to a lack of response to anti-viral treatment, while vitamin D supplementation may potentiate SVR.

**VITAMIN D AND NONALCOHOLIC FATTY LIVER DISEASE (NAFLD)**

NAFLD is a pathological clinical entity that includes a broad spectrum of liver conditions from steatosis to nonalcoholic steatohepatitis (NASH) and cirrhosis[148] and NAFLD is one of the main causes of chronic liver disease in developed countries, affecting 20% to 30% of the population[149,150]. Some NAFLD patients develop NASH and cirrhosis, while most others do not experience disease progression; however, the reason for these differences in progression are not known. NAFLD is generally related to at least one metabolic syndrome characteristic; in fact, liver conditions are considered part of the syndrome, and although their pathogenesis is not yet known, IR is a key factor in its development[151,152]. Several studies show a negative correlation between vitamin D levels and obesity, glucose intolerance, IR, metabolic syndrome and body mass index (BMI)[24-26,153-155] Furthermore, vitamin D deficiency stimulates PTH, which has been linked to IR and an increase in the acute-phase reactant[156]. In support of this hypothesis, some studies show that vitamin D administration improves insulin secretion[145,157-160] and that its use decreases IR in patients with end-stage renal disease[161]. Moreover, VDR polymorphisms have been associated with IR and have an effect on insulin secretion and on the fasting glucose concentration[162]. Additionally, previous studies have shown that VDR knock-out mice developed hepatic steatosis[163]. Finally, studies have shown that vitamin D administration in mice activates the fibroblastic intestinal growth factor 15 (Fgf15) (human ortholog FGF19). This intestinal hormone prevents IR and high-fat diet-induced obesity by inhibiting CYP7A1, an essential enzyme in the physiopathology of liver dyslipidemia[164]. This evidence suggests that vitamin D is linked to the development of NAFLD *via* its role in glucose metabolism by accelerating the conversion of proinsulin to insulin, while vitamin D deficiency has been associated with pancreatic β cell dysfunction and a greater prevalence of type 2 DM[153,164-167].

As in the case of CHC, vitamin D levels are lower in patients with NAFLD compared with healthy controls[43,167-174]. In addition, vitamin D deficiency in obese patients has been attributed to the accumulation of the vitamin D in adipose tissue[175-177]. Furthemore, vitamin D levels are inversely correlated with the severity of steatosis, necroinflammation and fibrosis independent of age gender, BMI, Homeostatic Model Assesment of Insulin Resistance (HOMA-IR) score and presence of metabolic syndrome[43,168,178]. In a recent clinical study of adults with NAFLD, Targher and colleagues showed that the vitamin D levels had an effect on the development of hepatic steatosis and in the severity of the histological lesion. In fact, their hypothesis stated that patients with greater inflammation and fibrosis had lower vitamin D levels[43] independent of other components of the metabolic syndrome. This observation was later confirmed in pediatric patients[179,180] (Table 2). Still, an association between vitamin D and NAFLD has been demonstrated that is independent of BMI or IR and metabolic syndrome[43,157,162]. Although causal conclusions are difficult to obtain from these studies, their results suggest that vitamin D deficiency plays a role in the development and progression of fatty liver, especially in terms of its anti-inflammatory potential. In fact, vitamin D reduces the risk for NAFLD in healthy men[181] and attenuates high fat diet-induced hepatic steatosis in rats by modulating lipid metabolism[182].

Vitamin D deficiency has been linked to a systemic increase in inflammation markers[183,184], and systemic inflammation may play a central role in the pathogenesis and progression of NAFLD[185,186]. Increases in visceral adiposity promote the release of fatty acids and proinflammatory cytokines and activate inflammation pathways in the liver, prompting proinflammatory cytokine secretion that leads to liver damage[187]. Moreover, the obesity promotes the onset of NAFLD due to increased hepatic lipid synthesis secondary to excess free fatty acids; subsequent association with oxidative stress on mitochondrial and with the increase of proinflammatory cytokines can definitely trigger a progression of steatosis to NASH and cirrhosis[188]. Studies *in vivo* and *in vitro* have clearly documented that steatosis reduces oxidative activity controlled by cytochrome P450[189]. These inflammatory processes may be blocked by increasing the levels of 25(OH)D, and the development and progression of NAFLD may stop. In fact, vitamin D supplements have been shown to decrease inflammation markers[190-193] and increase anti-inflammatory cytokines[190]. It is known that vitamin D’s effects in the liver are not only exerted on the hepatocytes, given that these cells express very little VDR mRNA. In contrast, sinusoidal cells, Kupffer cells, hepatic stellate cells and immune system cells express VDR mRNA that is functionally active. Therefore, vitamin D deficiency may affect the activity/expression of macrophages, dendritic cells and T and B lymphocytes by favoring oxidative stress and the production of proinflammatory cytokines that lead to subclinical inflammation[18,19]. Furthermore, fibrosis is induced by TGFβ secretion that results from the increased secretion of the matrix metalloproteinase 9 inhibitor (TIMP-1)[194]. In fact, cell cultures show that vitamin D has an anti-inflammatory and an antifibrinolytic effect on hepatic stellate cells. Finally, animal models show that more severe histological lesions of NAFLD are associated with higher levels of mRNA of TLR2, 4 and 9, proinflammatory cytokines and oxidative stress markers in rats with a high-fat diet and deficient in vitamin D[195]. A recent study of experimentally NAFLD-induced rats showed that ultraviolet light exposure decreased hepatic stellate cell activity and TGFβ synthesis and stimulated the production of apolipoprotein E and adiponectin. Together, these findings translate into a beneficial effect on NAFLD, and a decrease in IR, steatosis, apoptosis, inflammation and intrahepatic fibrosis was hypothesized[196].Thus, given the above-mentioned findings, we can conclude that extrahepatic signaling affects fibrosis and inflammation[187] and that the vitamin D-VDR axis may play a role in the initiation and progression of NAFLD.

Therefore, although the mechanisms of vitamin D’s control over hepatic lipid homeostasis and its link with inflammation are not fully known, recent research lines provide a more comprehensive understanding of its immune modulation capacity and of new therapeutic interventions for NAFLD.

**CONCLUSION**

The pleiotropic effects of vitamin D indicate a relationship between its deficiency and numerous chronic diseases, such as DM, cardiovascular, autoimmune and infectious diseases, several types of cancer and chronic liver diseases. In the case of chronic liver diseases, vitamin D seems to modulate the innate and adaptive immune system, which explains the association. Specifically, vitamin D deficiency has been associated with a greater risk of portal hypertension complications, mortality and increased histological severity in NAFLD and CHC, and a lower probability of viral response to HCV treatment with IFN based therapies. In fact, clinical studies suggest that these parameters may improve with vitamin D supplementation; however, prospective, randomized and placebo-controlled studies are required to establish firm conclusions.

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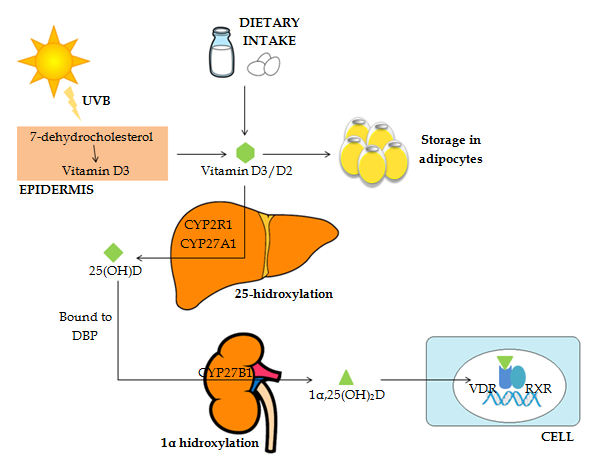
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**Figure 1 Vitamin D synthesis.**

**Table 1 Studies regarding vitamin D and hepatitis C virus**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| **Ref.** | **Year** | **Design** | ***n*** | **HCV genotype** | **Vitamin D deficiency (%)** | **Outcome** | ***P*** |
| **Petta *et al***[50] | 2010 | Cohorts | 197 | 1 | 73% | **Vitamin D levels (ng/mL):**  SVR: 26.6  No SVR: 23.7 | 0.05 |
| **Bitetto *et al***[121] | 2011 | Cohorts | 42 | 1 and no 1 | Not stated | **SVR according to the vitamin D levels (ng/mL):**  ≤ 10 ng/mL: 10%  > 10 and ≤ 20 ng/mL: 30%  > 20 ng/mL: 50% | < 0.05 |
| **Bitetto *et al***[136] | 2011 | Cohorts | 211 | 1-5 | 46.4% | **SVR according to the vitamin D levels (ng/mL):**  ≤ 10 ng/mL: 50%  > 10 and ≤ 20 ng/mL: 60.9%  > 20 ng/mL: 69% | 0.038 |
| **Lange *et al***[115] | 2011 | Cohorts | 468 | 1-3 | 66% | **SVR (genotype 2/3):**  Vitamin D deficit (< 10 ng/mL): 50%  Without deficiency: 81%  **SVR (genotype 1)**  Vitamin D deficit: 60%  Without deficiency: 54% | < 0.0001  0.45 |
| **Nseir *et al***[133] | 2011 | Cohorts | 80 | 1 | Not stated | **Vitamin D levels (ng/mL):**  SVR: 42.1  No SVR: 27.3 | < 0.001 |
| **Jazwinski *et al***[134] | 2011 | Cohorts | 82 | 1 | Not stated | **Vitamin D levels (ng/mL):**  SVR: 23.3  No SVR: 19.3 | 0.82 |
| **Abu-Mouch *et al***[123] | 2011 | Randomized prospective | 72 | 1 | 59% (with vitamin D supplementation)  60% (control group) | **SVR:**  With vitamin D: 86%  Control group: 42% | < 0.001 |
| **Nimer *et al***[122] | 2012 | Randomized prospective | 50 | 2-3 | 60% (with vitamin D)  50% (control group) | **SVR:**  With vitamin D: 95%  Control group: 77% | < 0.001 |
| **Lange *et al***116] | 2012 | Cohorts | 269 | 1-4 | 74% | No significant association between SVR and 25(OH)D serum levels | 0.13 |
| **Kitson *et al***[137] | 2013 | Cohorts | 274 | 1 | 48% | **Vitamin D levels (ng/mL):**  SVR: 76,6  No SVR: 84,7 | 0.03 |
| **Esmat *et al***[140] | 2014 | Randomized prospective | 101 | 4 | 95% | **SVR:**  With vitamin D: 44%  Control group: 68,6% | 0.22 |
| **Yokoyama *et al***[142] | 2014 | Randomized prospective | 84 | 1b | Not stated | **SVR:**  With vitamin D: 64,3%  Control group: 50% | 0.19 |
| **Grammatikos *et al***[138] | 2014 | Cohorts | 398 | 1 | Not stated | **Vitamin D levels (ng/mL)**  SVR: 15.8  No SVR: 17.6 | 0.09 |

HCV: Hepatitis C virus; SVR: Sustained viral response.

**Table 2 Studies regarding vitamin D and non-alcoholic fatty liver disease**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | | | | | | |
| **Ref.** | **Year** | **Design** | **N** | **NAFLD diagnosis** | **Vitamin D levels (ng/ml)** | ***P*** |
| **Targher *et al*[43]** | 2007 | Cohorts prospective | 120 | Liver biopsy | Controls (60): 29.8 ± 6  Steatosis (10): 23.72 ± 8  NASH (50): 14.8 ± 9.2 | 0.001 |
| **Manco *et al*[179]** | 2010 | Cohorts prospective | 64 | Liver US | Without necroinflamation: 26.1 ± 10  With necroinflamation: 19.9 ± 9.8  Without fibrosis: 27.7 ± 10.,3  With fibrosis: 17.1 ± 7.4 | 0.16  < 0.001 |
| **Barchetra *et al*[168]** | 2011 | Cohorts prospective | 262 | Liver US | Without NAFLD (100): 20.5 ± 9.7  NAFLD (162): 14.8 ± 9.2 | < 0.001 |
| **Jablonski *et al*[169]** | 2013 | Cohorts retrospective | 1214 | Liver US | Controls (607): 34 ± 8  NAFLD (607): 30 ± 7 | < 0.001 |
| **Kasapoglu *et al*[171]** | 2013 | Cohorts prospective | 613 | Liver US | Controls (275): 26,4 ± 9,8  NAFLD stage 1 (133): 20 ± 9.2  NAFLD stage 2 (106): 13.3 ± 6.7  NAFLD stage 3 (99): 8.8 ± 7.4 | < 0.05 |
| **Black *et al*[170]** | 2014 | Cohorts prospective | 994 | Liver US | Without NAFLD (838): 30.8 ± 9.6  NAFLD (156): 26.8 ± 8.8 | < 0.001 |
| **Yildiz *et al*[174]** | 2014 | Cohorts prospective | 101 | Liver US | Without NAFLD (43): 16,4 (IQR 12.4-24.8)  NAFLD grade 1 (41): 14.2 (IQR 9.5-21.2)  NAFLD grade 2 (17): 11.5 (IQR 7.5-16.7) | 0.005 |
| **Dasarathy *et al*[178]** | 2014 | Cohorts prospective | 148 | Liver biopsy | Controls (39): 35.7 ± 6  Steatosis (67): 25 ± 11,3  NASH (81): 18.1 ± 8.4 | < 0.01 |
| **Nobili *et al*[180]** | 2014 | Cohorts prospective | 73 | Liver biopsy | NASH (49) was  associated with lower VD levels, *i.e.,* -9.0 pg/mL when compared with that in children without  NASH (24) | < 0.001 |
| **Küçükuzman *et al*[173]** | 2014 | Cohorts prospective | 211 | Liver US | Without NAFLD (57): 20 ± 13.6  NAFLD (154): 12.3 ± 8.9 | < 0.001 |

US: Ultrasonography; IQR: Interquartile range; NAFLD: Non-alcoholic fatty liver disease; NASH: Nonalcoholic steatohepatitis.