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The role of vitamin D3 deficiency in hepatitis C treatment: a systematic review

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Abstract

Hepatitis C virus (HCV) infection remains a major global health burden, often leading to liver fibrosis, cirrhosis, and hepatocellular carcinoma. Vitamin D3 plays a crucial role in immune regulation, liver metabolism, and inflammation, with deficiency frequently observed in patients with chronic liver disease, including HCV. This systematic review explores the prevalence and impact of vitamin D3 deficiency in HCV infection, its association with disease progression, and its potential influence on treatment outcomes. While some studies suggest that low vitamin D3 levels may impair antiviral responses, findings remain inconclusive, especially with current direct-acting antivirals. Genetic polymorphisms and interactions with other micronutrients may further modulate these effects. Although vitamin D supplementation shows promise, its therapeutic value in HCV management requires further investigation through large-scale, genotype-specific clinical trials.

Keywords: *HCV. Hepatitis C. Vitamin D3 deficiency. DAAs.*

Introduction

According to the World Health Organization (WHO), hepatitis C virus (HCV) infection remains a significant global health concern. It is estimated that approximately 50 million people worldwide are living with chronic HCV infection, with 1 million new cases occurring each year. In 2022 alone, hepatitis C was responsible for approximately 242,000 deaths globally (Fig. 1)[1]. HCV infection stands as a potential cause of severe liver conditions, accounting for 27% of cirrhosis cases and 25% of hepatocellular carcinoma (HCC) diagnoses[2,3]. Vitamin D exhibits multifaceted biological activities in the context of chronic diseases. It modulates human physiology through epigenetic regulation, influencing the expression of over 2000 genes[4]. One of its key physiological functions involves facilitating the intestinal absorption of calcium and phosphorus, thereby contributing to the maintenance of bone mineral density and the prevention of bone mass loss. In addition, vitamin D enhances immune function by suppressing pro-inflammatory cytokines while promoting the production of anti-inflammatory cytokines[5]. *In vitro* studies have demonstrated that vitamin D exerts a synergistic effect with interferon (IFN)-alpha and may inhibit HCV replication[6]. Furthermore, genetic studies support a relationship between vitamin D signaling pathways and susceptibility to viral infections[5]. Vitamin D deficiency is highly prevalent, affecting up to 92% of individuals with chronic liver disease (CLD), regardless of the underlying etiology[7], with severe deficiency reported in approximately one-third of these patients[5]. Among individuals with chronic HCV infection, more

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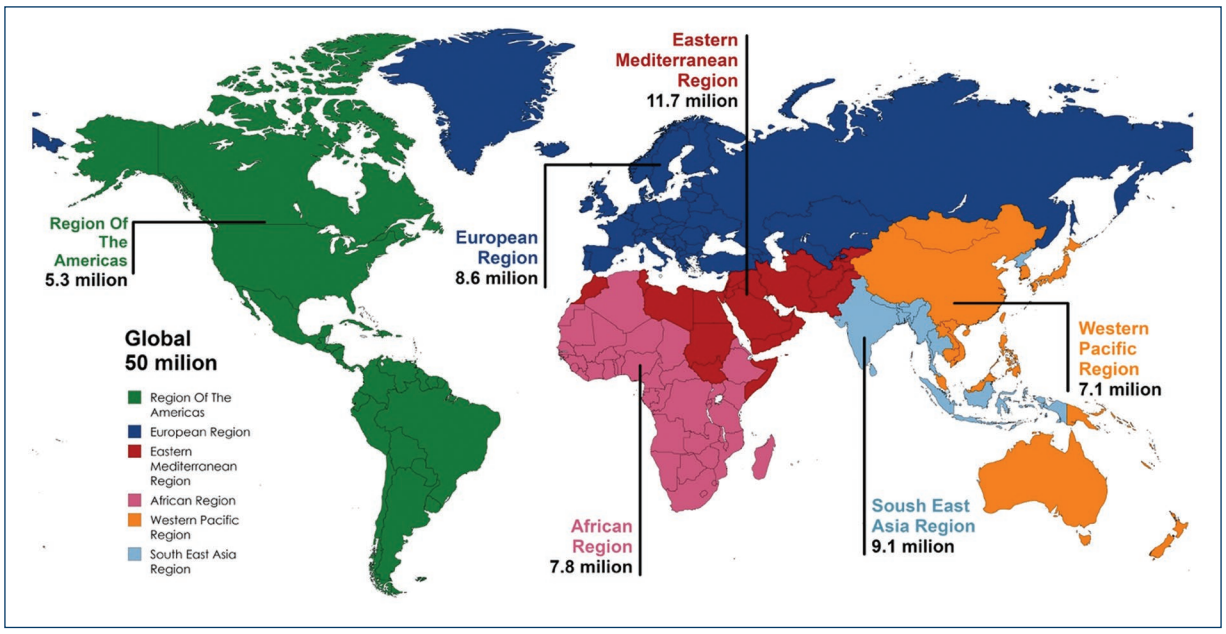


Figure 1. Hepatitis C prevalence by World Health Organization region.

than 60% present with vitamin D deficiency. This deficiency correlates with the degree of hepatic dysfunction and is recognized as a contributing factor to the development and progression of hepatic fibrosis in chronic HCV infection[8]. Moreover, vitamin D deficiency has been associated with reduced responsiveness to antiviral treatment regimens[5]. Prospective studies have also suggested that lower circulating vitamin D levels may elevate the risk of HCC in HCV-infected patients, implying a potential preventative role for vitamin D supplementation[2]. Importantly, vitamin D deficiency may persist even after successful HCV eradication through direct-acting antiviral agents (DAAs), underscoring the importance of ongoing monitoring and possible supplementation in this patient population[8,9]. In this review, we explore the physiological role of vitamin D in liver function, examine the association between vitamin D deficiency and the progression of HCV-related liver disease, and assess the potential therapeutic benefits of supplementation in affected individuals.

Materials and methods

A comprehensive literature search was conducted across multiple databases, including PubMed, Scopus, Web of Science, and EMBASE, to identify studies examining the role of vitamin D3 in the progression and treatment of HCV infection. The search strategy included combinations of the following keywords: ("vitamin D" OR "vitamin D3" OR "cholecalciferol" OR "25-hydroxyvitamin D" OR "calcitriol") AND ("hepatitis C" OR "HCV" OR "liver fibrosis" OR "antiviral therapy" OR "direct-acting antivirals" OR "immune response"). The literature search was limited to articles published between 2010 and 2025, in the English language. In addition to peer-reviewed journal articles, national and international health reports, and clinical guidelines from institutions such as the WHO and the Centers for Disease Control and Prevention were reviewed to provide context on the global burden of HCV and the clinical significance of vitamin D deficiency in liver disease. Studies were included if they met one or more of the following criteria: 1. Evaluated the prevalence of vitamin D deficiency in patients with chronic HCV infection; 2. Assessed the association between vitamin D status and liver disease progression, including fibrosis, cirrhosis, or HCC; 3. Explored the immunological or antiviral mechanisms of vitamin D in the context of HCV; or 4. Investigated the effects of vitamin D supplementation on antiviral treatment outcomes, including sustained virological response (SVR). Exclusion criteria included studies focusing exclusively on animal models or *in vitro* data without clinical relevance, non-peer-reviewed sources, editorials, opinion articles, or studies lacking specific data on clinical outcomes. After applying these criteria, 60 eligible studies were selected and reviewed for qualitative synthesis.

Vitamin D3 metabolism and hepatic activation

Vitamin D3 (cholecalciferol) is synthesized in the skin from 7-dehydrocholesterol following exposure to ultraviolet B radiation or obtained from dietary sources. After entering the circulation, cholecalciferol, which is still biologically inactive, is transported bound to vitamin D-binding protein (DBP) and albumin. To exert physiological effects, it requires two enzymatic hydroxylation steps[10]. The first hydroxylation occurs in the liver, where vitamin D3 is converted into 25-hydroxyvitamin D [25(OH)D] by the cytochrome P450 enzymes CYP2R1 and CYP27A1. Although 25(OH)D is not biologically active, it represents the predominant circulating form of vitamin D and is widely used as a clinical biomarker to assess vitamin D status[11]. The second hydroxylation step takes place primarily in the kidneys, where CYP27B1 converts 25(OH)D into its active form, 1,25-dihydroxyvitamin D [1,25$(OH)_2$D], also known as calcitriol (Fig. 2). Calcitriol functions by binding to the vitamin D receptor (VDR), a nuclear hormone receptor expressed in a wide array of tissues beyond those involved in calcium and phosphate metabolism. These include the liver, intestines, pancreas, prostate, and various immune cells such as macrophages and dendritic cells[12]. Notably, immune cells also express CYP27B1, enabling them to locally convert 25(OH)D into calcitriol, thereby exerting autocrine and paracrine effects within the immune system[10,13].

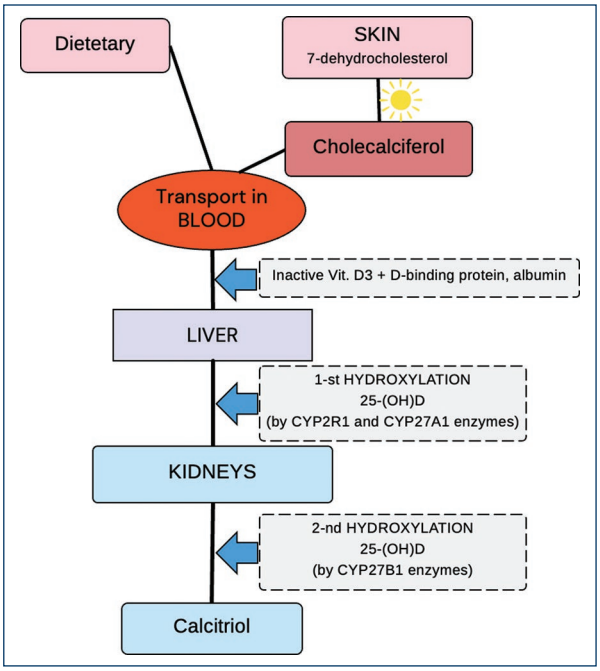


Figure 2. Vitamin D3 synthesis. Vit: vitamin; 1st: first; 2nd: second; 25-(OH)D: 25-hydroxyvitamin D; CYP2R1: cytochrome P450 2R1; CYP27A1: sterol 27-hydroxylase cytochrome P450 27A1; CYP27B1: cytochrome p450 27B1.

Immunomodulatory and hepatic roles of vitamin D3

Vitamin D3 plays a critical role in the modulation of the immune response. It influences both innate and adaptive immunity by acting on T-helper lymphocytes. Specifically, it suppresses pro-inflammatory Th1 and Th17 responses, reducing the production of interleukin (IL)-2, tumor necrosis factor-alpha (TNF-α), and IFN-γ, whereas simultaneously promoting the differentiation and function of regulatory T cells (Tregs), which are essential for immune tolerance and the resolution of inflammation. In addition, VDR expression in Th2 cells stimulates the production of anti-inflammatory cytokines such as IL-4 and IL-10, further contributing to immune regulation[14,15]. Vitamin D3 also enhances innate immune defenses by inducing the expression of antimicrobial peptides, including cathelicidins and defensins, which possess broad-spectrum activity against bacterial and viral pathogens[16]. This antiviral capacity is particularly relevant in chronic viral liver diseases such as hepatitis B and C[17]. Clinical evidence suggests a strong link between vitamin D deficiency and liver disease progression. Patients with autoimmune hepatitis and primary biliary cholangitis demonstrate significantly lower serum vitamin D levels and decreased VDR expression compared to healthy controls, with greater deficiency correlating with more advanced disease[12]. Similarly, in non-alcoholic fatty liver disease, Kumar et al. reported that vitamin D deficiency is highly prevalent and associated with increased hepatic steatosis, inflammation, and fibrosis[18]. Vitamin D3 appears to influence hepatic lipid metabolism by regulating genes involved in fatty acid oxidation and *de novo* lipogenesis. Its anti-inflammatory properties are also believed to mitigate hepatic injury and fibrosis, further highlighting its potential therapeutic relevance in liver disorders[19].

Genetic determinants of vitamin D metabolism

Genetic factors have been shown to contribute to both vitamin D3 deficiency and the progression of HCV infection. In a study by Yang et al.,[20] polymorphisms in

genes involved in vitamin D3 metabolism, specifically CYP27A1, CYP2R1, and CYP27B1, were analyzed. The researchers identified four single-nucleotide polymorphisms within the *CYP2R1* gene that were significantly associated with increased susceptibility to HCV infection, while no such association was observed for CYP27A1 or CYP27B1. In addition to genetic predisposition, elevated levels of HCV replication have been implicated as a contributing factor to reduced circulating vitamin D3 concentrations[20]. However, a separate study found that these genes did not exhibit clinical relevance during the course of treatment[21]. Variations in the VDR gene may also modulate disease progression. Notably, specific VDR polymorphisms, such as TaqI TT, ApaI/TaqI GG/TT, and TG/TT genotypes, may enhance the receptor's antifibrotic effects, potentially influencing the clinical course of HCV-related liver disease[22]. Previous studies conducted in Italian, Egyptian, and Thai populations have reported distinct findings regarding the role of genetic and molecular factors in HCV progression and treatment response. In an Italian cohort, individuals with the VDR FokI CC genotype showed no progression from HCV infection to HCC, suggesting a potential protective effect[23]. In contrast, among Egyptian HCV patients, the FokI single-nucleotide polymorphism was identified as a potential risk marker for HCC development[23]. In Thai patients infected with HCV genotype 1, the presence of DHCR7 rs12785878 GT or TT alleles was associated with significantly better responses to pegylated IFN therapy compared to other genotypes[21]. Furthermore, a combined effect of microRNA-130a and calcitriol has been observed, with evidence supporting enhanced IFN expression and inhibition of HCV RNA replication through their interaction[24]. These findings highlight the complex and sometimes conflicting role of genetic and molecular factors in vitamin D metabolism and HCV progression, underscoring the need for further large-scale, population-specific studies to clarify their clinical significance and therapeutic potential.

Epidemiological patterns of vitamin D deficiency in hepatitis C

Vitamin D deficiency is generally defined as a circulating level of 25(OH)D below the normal range, although the exact threshold varies between studies[25]. Some sources define hypovitaminosis D as levels below 20 ng/mL or 30 ng/mL, with severe deficiency described at 10-12 ng/mL[26,27]. Multiple studies have investigated the association between hypovitaminosis D and the progression of HCV infection, consistently highlighting a link between insufficient vitamin D3 levels and adverse clinical outcomes. These include genetic predispositions, compromised clinical status, and the development of secondary complications such as hepatic fibrosis, cirrhosis, and HCC[26]. Vitamin D deficiency is widely recognized as a common comorbidity in patients with CLD, regardless of its underlying etiology, with reported prevalence rates ranging from 64% to 92%[28]. Among individuals infected with HCV, the deficiency appears to be even more pronounced, affecting approximately 30% of patients with cirrhosis and 14% of those without cirrhosis[28]. Global epidemiological studies have also revealed substantial regional variation in hypovitaminosis D, with serum levels below 30 ng/mL observed in 77% of patients in Spain, 66.2% in Brazil, 56.9% in Caucasian populations in the United States, and 85.8% among African-American populations in the United States[29]. These disparities are further reflected in the global distribution of dietary vitamin D supply (Fig. 3), where many low- and middle-income countries, particularly across Africa, South Asia, and parts of Latin America, exhibit critically low per capita intake levels, underscoring the widespread nutritional vulnerability that may exacerbate liver disease outcomes in HCV-infected populations. A study by Falak et al. involving 74 participants, 51 of whom were infected with HCV, evaluated vitamin D status in comparison to healthy controls. The findings revealed that 76.5% of HCV-infected individuals had suboptimal vitamin D levels. Interestingly, no significant difference in vitamin D3 concentrations was observed between patients with compensated and decompensated liver disease[30]. Other studies corroborate these findings, reporting a 49% prevalence of hypovitaminosis D among HCV patients[31], and rates increasing markedly to 70.5-89.6% in those with advanced hepatic fibrosis or cirrhosis[32]. Similarly, Jafar et al. identified low vitamin D levels in 78.3% of patients with chronic hepatitis[33]. Additional studies have also demonstrated associations between vitamin D deficiency and complications such as hepatic encephalopathy (HE) in the context of HCV-related liver damage[34,35]. Interestingly, low serum levels of vitamin D3 may also result from enhanced viral replication. *In vitro* studies have reported that the replication of HCV can be inhibited by both calciferol and cholecalciferol[36]. Moreover, Shi et al. demonstrated that HCV non-structural protein 3-transactivated protein 1 (NS3TP1) contributes to hepatic fibrosis and is modulated by calcitriol[37]. However, findings are not uniformly consistent across the literature. For example, Basile et al.[38] assessed the

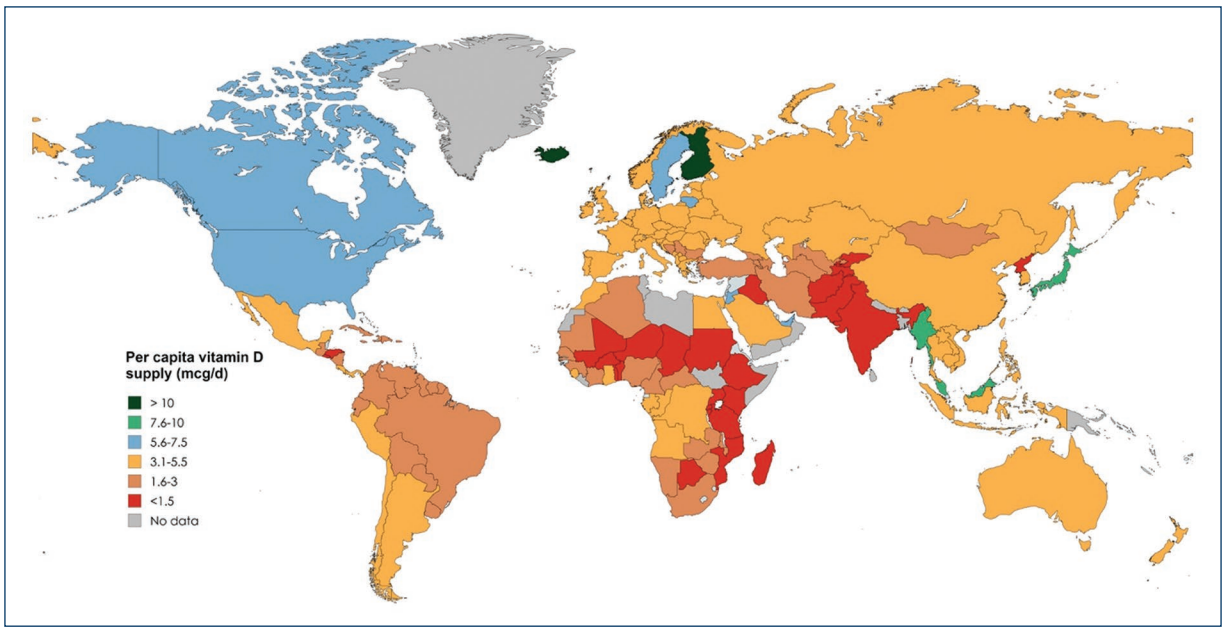


Figure 3. Global map of vitamin D intake.

potential of serum vitamin D and DBP as biomarkers for distinguishing between stages of HCV-related liver disease. However, they concluded that neither marker reliably reflected disease severity. Similarly, a Korean study found no significant association between vitamin D3 supplementation and SVR in HCV-infected individuals, despite an observed SVR rate of 84.5% in those receiving supplementation. In addition, serum vitamin D levels did not increase following successful antiviral therapy, suggesting that factors other than supplementation, such as environmental exposure or metabolic regulation, may play a greater role in chronic hepatitis C patients[39]. It is important to note that both of these studies had notable limitations, including small sample sizes and a lack of adjustment for potential confounding variables such as sunlight exposure[38,39]. To provide a broader perspective, several studies across diverse geographic regions and clinical settings have explored the relationship between vitamin D3 levels and HCV-related outcomes, highlighting variability in prevalence, patient characteristics, and clinical correlations. The summary of reviewed studies can be found in table 1.

Influence of vitamin D3 deficiency on antiviral treatment

Before the DAAs, IFN-based therapy was the standard of care for chronic hepatitis C, despite limited efficacy and a substantial side effect burden. Early treatment with IFN was associated with low SVR rates, frequent relapses, and more adverse events[40]. A recent meta-analysis involving 1083 patients treated with pegylated IFN-α and ribavirin therapy suggested that vitamin D deficiency may serve as an independent predictor of treatment failure, with lower vitamin D levels being associated with reduced SVR rates. Notably, significant heterogeneity was observed across studies, with a meaningful association between vitamin D status and SVR identified only when a cutoff level of 20 ng/mL was applied. Furthermore, low vitamin D levels were also correlated with an increased risk of acute liver failure[41]. However, other studies found no significant association between vitamin D levels and treatment outcomes in patients receiving IFN-based therapy, regardless of HCV genotype[42]. Despite major advances in HCV therapy, most notably the development of DAAs, which have made HCV the only chronic infectious disease that is curable, evidence regarding the role of vitamin D in the context of DAA-based treatment remains limited. Ali et al. reported that vitamin D deficiency was significantly associated with poor treatment outcomes in patients receiving DAAs, with lower vitamin D levels observed in non-responders. Serum 25(OH)D levels below 21 ng/mL were predictive of treatment failure and were also associated with increased risk of HCC following unsuccessful therapy[43]. In contrast, Gayam et al. found no significant correlation between vitamin D status and SVR across three DAA

Table 1. Association of vitamin D deficiency and HCV progression

Location	Sample size	Age range	Patient characteristics	Findings
Pakistan	74	20-65 years (mean 36.1)	22 with cHCV, 29 with dHCV, 23 healthy controls; 29 females, 45 males	76.5% of HCV patients had suboptimal vitamin D levels. No significant difference between control and cHCV. Deficiency is more common in dHCV.
Pakistan	115	18-60 years (mean 41.9)	HCV genotype 3; 61 females, 54 males	78.3% had below-normal vitamin D levels; 42.6% were deficient, 35.6% insufficient. Low vitamin D is associated with treatment failure.
Egypt	135	≥ 18 years	Cirrhosis due to HCV with/ without HE or SBP; no vitamin D in the past 2 months	Low vitamin D is linked to HE and SBP. 25(OH) D may serve as a prognostic marker for cirrhosis severity.
Greece	81	18-70 years	Previously untreated; 54 males, 27 females; mostly genotypes 1 and 3	TaqI TT genotype linked to enhanced VDR expression and potentially less fibrosis progression.
Nordic countries	331	Mean 41.9 years	Genotypes 2 or 3; 13% cirrhotic; 313 Caucasians; 60% male	Weak correlation of vitamin D with fibrosis, stronger with cirrhosis (not significant in multivariate analysis). Seasonal variation observed.
Egypt	160	40-60 years (mean 47.8-48.2)	80 CHC patients, 80 controls; 20 males and 60 females per group; genotypes 2 and 4	vitamin D deficiency correlated with fibrosis severity and 70.5-89.6% malnutrition prevalence in advanced liver disease.
Korea	148	20-75 years (mean 51.5-51.6)	HCV-RNA positive; genotypes 1, 2, 3; 71 received treatment only, 77 received vitamin D with treatment	SVR was 84.5% in the supplemented group, but not statistically significant. Vitamin D did not increase SVR.
Italy	65	-	Untreated CHC; excluded patients who received vitamin D in the prior 2 years.	No significant difference in 25(OH) D or DBP. Only FLCs were elevated. None served as reliable biomarkers for HCV-related disease stage.

CHC: chronic hepatitis C; cHCV: compensated HCV; dHCV: decompensated HCV; DBP: vitamin D binding protein; FLCs: free light chains; HCV: hepatitis C virus; HE: hepatic encephalopathy; SBP: spontaneous bacterial peritonitis; SVR: sustained virological response; VDR: vitamin D receptor.

regimens, with overall response rates exceeding 95% regardless of baseline vitamin D levels[44]. Similarly, Backstedt et al. reported that neither baseline vitamin D status nor its changes during therapy predicted treatment outcomes in patients receiving either IFN-based or IFN-free regimens[6]. Moreover, short-term vitamin D supplementation following DAA therapy did not improve serum fibrogenesis markers, suggesting it may have a limited impact on accelerating the resolution of residual liver fibrosis[8]. In addition, another study demonstrated that although insufficient 25(OH)D levels are frequently observed in patients with chronic hepatitis C or B, these deficiencies are not associated with adverse virological parameters. Notably, the only factor significantly influencing vitamin D levels in these patients was seasonal variation[45]. In conclusion, although vitamin D deficiency has been linked to reduced treatment efficacy during the IFN era, its role in DAA-based HCV therapy remains unclear. Current evidence suggests that vitamin D status is unlikely to significantly influence the achievement of SVR in patients treated with DAAs.

Potential benefits of vitamin D supplementation in HCV patients

Vitamin D, owing to its immunomodulatory and antiviral properties, has emerged as a potentially cost-effective adjunctive or standalone option in the prevention and treatment of various viral infections. Although still preliminary, growing evidence suggests a therapeutic role for vitamin D in modulating the course of HCV infection[46,47]. In HCV-infected individuals, vitamin D2 has been shown to inhibit viral RNA replication, possibly through the induction of oxidative stress pathways. Notably, advanced hepatic fibrosis, which is often accompanied by vitamin D insufficiency, is associated with increased mortality in patients with chronic HCV infection[47]. DBP has been proposed as a non-invasive biomarker of hepatic fibrosis, with higher serum levels correlating with preserved liver function or early fibrosis, and lower levels indicating advanced disease[46]. Several studies have demonstrated that vitamin D may exert anti-HCV effects via multiple mechanisms (Fig. 4)[48,49]. Furthermore, vitamin D exhibits both antifibrotic and

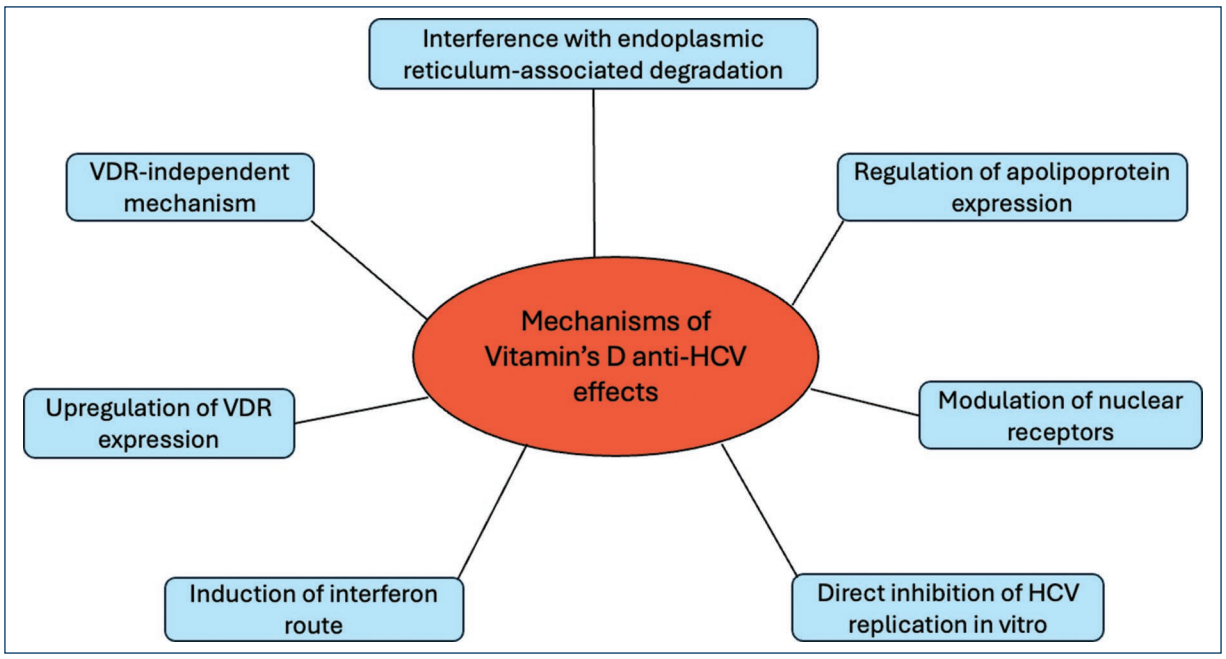


Figure 4. Mechanisms of vitamin D's anti-HCV effects. HCV: hepatitis C virus; VDR: vitamin D receptor.

anti-inflammatory properties, modulating key immunological and fibrogenic pathways implicated in the progression of HCV-related liver disease[31,50]. Early studies suggested that vitamin D supplementation could improve biomarkers of hepatic fibrogenesis in patients with chronic HCV. However, short-term supplementation following DAA therapy did not result in significant changes in fibrogenesis markers[8]. Meta-analyses indicate a positive correlation between higher serum vitamin D levels and improved virological response rates, although the direct impact of supplementation on clinical outcomes remains inconclusive[8]. Notably, some studies have failed to observe significant improvements in fibrogenesis markers in DAA-treated patients receiving vitamin D supplementation[8]. While vitamin D supplementation in HCV patients shows potential benefits due to its antiviral and antifibrotic properties, the current body of evidence is insufficient to draw definitive conclusions, highlighting the need for further well-designed clinical studies.

Interaction between vitamin D3 and other micronutrients in liver health

Vitamin D3 interacts with several micronutrients, most notably calcium, magnesium, and other fat-soluble vitamins, affecting both hepatic function and overall physiological balance. Adequate magnesium levels are essential for vitamin D metabolism, serving as a cofactor in its transport and enzymatic activation. Magnesium deficiency can upregulate 24(OH)ase activity, accelerating the degradation of active vitamin D and potentially impairing its immunoregulatory effects within hepatic tissue[51]. The connection between vitamin D and calcium is equally critical. The active form, 1,25-dihydroxyvitamin D, enhances calcium absorption by stimulating receptor-mediated transport and calcium-binding protein synthesis in the intestine. In vitamin D deficiency, this active transport is impaired, leading to reduced calcium availability, secondary hyperparathyroidism, and hypophosphatemia. In vitamin D deficiency, impaired calcium homeostasis may exacerbate hepatic inflammation and fibrosis, especially in CLD[52-54]. Although high doses of vitamin D may acutely increase bone resorption, long-term use does not appear to significantly worsen bone turnover, as shown in extended studies[55,56]. Calcitriol also plays a compensatory role by mobilizing calcium from bone stores to maintain serum levels[52]. Combined supplementation with calcium and vitamin D3 has demonstrated anti-inflammatory effects, including reductions in systemic markers such as IL-6 and TNF-α, which are also elevated in CLD[57]. Vitamin D facilitates the intestinal absorption of minerals such as magnesium, iron, phosphate, zinc, and copper, all of which are essential cofactors in hepatic enzymatic

reactions. Conversely, high levels of 25(OH)D3 may increase the uptake of toxic metals such as cadmium and lead, which are known to contribute to hepatic oxidative stress and impair vitamin D activation by damaging renal and hepatic mitochondria[58]. In hepatic tissue, the synergistic actions of fat-soluble vitamins are particularly important. Vitamin D3 and vitamin K together promote proper calcium handling and may help prevent ectopic calcification in fibrotic livers. In addition, vitamin D3 and vitamin A support hepatic immune surveillance and epithelial barrier integrity, both of which are compromised in CLDs[59]. Deficiencies in fat-soluble vitamins are frequently observed in obesity-related metabolic disorders, including metabolic dysfunction-associated steatotic liver disease. These deficiencies can accelerate steatosis, oxidative damage, and hepatic inflammation, highlighting the need for comprehensive micronutrient assessment and correction in patients with liver disease[60].

Conclusion and future directions

vitamin D3 deficiency is common in HCV patients and is associated with liver disease progression, including fibrosis, cirrhosis, and HCC. Although some studies suggest that adequate vitamin D levels or supplementation may improve treatment outcomes, evidence remains inconclusive in the era of DAAs. Genetic polymorphisms in vitamin D metabolism and receptor pathways may further influence susceptibility and disease severity. Vitamin D also interacts with other micronutrients, potentially affecting liver health through broader metabolic and immunological pathways. Future research should clarify the clinical relevance of supplementation, particularly post-DAA therapy, and explore individualized strategies based on genetic and nutritional profiles.

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Conflicts of interest

The authors declare no conflicts of interest.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. The study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. The SAGER guidelines do not apply.

Declaration on the use of artificial intelligence. The authors declare that no generative artificial intelligence was used in the writing or creation of the content of this manuscript.

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