CODEN [USA]: IAJPBB ISSN : 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCES
SJIF Impact Factor: 7.187
http://doi.org/10.5281/zenodo.4273883

Avalable online at: http://www.iajps.com *Research Article*

STUDY OF VITAMIN D DEFICIENCY IN HEPATITIS C VIRUS INFECTION IN A TERTIARY CARE HOSPITAL LAHORE

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Article Received: September 2020 **Accepted:** October 2020 **Published: November** 2020

Abstract:

In the past few years, a growing body of clinical evidence has highlighted the risk of vitamin D deficiency in patients with chronic hepatitis C and that vitamin D levels are associated with the course of hepatitis C virus (HCV) infection, adverse effects, and treatment response to peginterferon/ribavirin. Recently, studies have found that vitamin D status is related to drug resistance and increased risk of infection in patients with liver cirrhosis. Vitamin D-related gene polymorphisms have been found to explain the interactions between vitamin D deficiency and HCV infection, offering a new perspective toward understanding the current problems such as the development of insulin resistance and racial differences in sustained virological response. Studies have been conducted to determine whether vitamin D supplementation as an adjuvant yields a better result compared with traditional HCV treatment. Here, we provide a brief review of the past and present knowledge of vitamin D in HCV infection.

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Please cite this article in press Ayesha Mubarik et al, ***Study Of Vitamin D Deficiency In Hepatitis C Virus Infection In A Tertiary Care Hospital Lahore.,*** *Indo Am. J. P. Sci, 2020; 07(11).*

INTRODUCTION:

More than 180 million people are estimated to be infected with the hepatitis C virus (HCV) worldwide; ~ 20% of those with chronic HCV infection progress to cirrhosis [1], and the median survival for HCV-infected patients who develop hepatocellular carcinoma (HCC) is as short as 13.1 months from the time of HCC diagnosis [2]. HCV causes ~ 700 000 deaths annually [3]. Vitamin D is an important seco-steroid hormone with pleiotropic effects and is known to play a key role in calcium and bone homeostasis. Most vitamin D is converted from 7-dehydrocholesterol (7-DHC) in the skin through sunlight, and then metabolized in the liver to 25-hydroxyvitamin D [25(OH)D], which is mediated by 25-hydroxylases, including the microsomal 25-hydroxylase (CYP2R1) and the mitochondrial cholesterol 27-hydroxylase (CYP27A1) enzymes. Finally, the biologically active agonist for vitamin D receptor (VDR), 1,25-dihydroxyvitamin D3 or calcitriol, is produced from circulating renal or extra-renal 25 (OH)D by 1a-hydroxylase (CYP27B1); calcitriol is also highly bound to vitamin D-binding protein (DBP), which is also known as vitamin D-binding globulin (GC), and is the ligand that activates the VDR. Recently, evidence has emerged that vitamin D has antifibrotic, anti-inflammatory, and immuno-modulatory properties. These extra skeletal effects are relevant in the pathogenesis and treatment of many causes of chronic liver disease. Vitamin D deficiency was observed in most hepatitis B virus-infected patients [4] and in patients with non-alcoholic fatty liver disease compared with healthy persons.

In fact, recent studies have found that vitamin D deficiency is also related to HCV progression [6–8], and the response to peginterferon/ribavirin (peg-IFN/RBV) therapy plays a role as a predictor of the response [6,9,10]. However, the current understanding of the pathogenic mechanisms underlying the high prevalence of vitamin D deficiency and the explanation of its effects in chronic hepatitis C (CHC) are insufficient. Neither an agreed upon definition of vitamin D deficiency nor an application standard of vitamin D supplementation has been established, especially in HCV-infected patients, and interactions between vitamin D and HCV are direct and indirect, which are far from complete to form a theoretical system. The purposes of this article are to discuss recent data on the role of vitamin D in HCV-infected patients.

Vitamin D deficiency in chronic hepatitis C infection:

Presently, vitamin D deficiency and insufficiency are seen among more than one-third of the adults worldwide [11–13]. The most recent consensus concerning hypovitaminosis D in the general population, according to the guideline of the Institute of Medicine's 2011 report, defined vitamin D deficiency as less 20 ng/ml [14], and the published Endocrine Society's Practice Guidelines [15] adopted vitamin D deficiency as less than 20 ng/ml, insufficiency as 21–29 ng/ml, and sufficiency as at least 30 ng/ml for maximum musculoskeletal health. The purported purpose of the guideline did not specifically consider diseased populations; thus, there still lacks an optimal and clinically relevant vitamin D level cut-off value to define the decrease of serum vitamin D levels in patients with CHC. Debate over what blood levels of 25(OH)D are considered deficient and sufficient continues. Simultaneously, almost more than 60% patients with HCV infection have hypovitaminosis D in different areas over the past decade, including Asia [16,17], Australia [18], Europe [6,9,19,20], and the USA [21,22]. In particular, previous reports have shown that African-Americans have significantly lower serum 25(OH)D levels than European Americans [23,24].

Vitamin D and hepatitis C virus-related fibrosis:

Over the past decade, many publications have assessed vitamin D status and fibrosis stage in CHC, but conflicting conclusions have been reached [6,19,25–28]. Several cross-sectional studies have been conducted, most of which have focused on genotype 1 patients, and low 25(OH)D levels were independently related to severe fibrosis [6,28]. Several studies did not find significant associations between vitamin D level and fibrosis [19,25–27]. Two were randomized controlled trials (RCTs), the largest of which included 516 patients living in France who were infected with genotype 1, and it found no effect of 25(OH)D on virological response or fibrosis progression upon receiving peg-IFN/RBV [27]; another cohort of 274 treatment-naive patients with HCV-1 [26].

Furthermore, to detect the overall effects of vitamin D on populations with different genetic backgrounds, a recent meta-analysis involved 8321 HCV-infected patients from Europe, the USA, and Australia and showed an inverse association with the severity of liver fibrosis. However, the results from the odds ratio (OR) data extracted studies showed that there was no significant association between serum vitamin D status and the severity of liver fibrosis, although stratifying analyses were conducted by geographic region; the pooled ORs of the studies were 1.33 (95%CI: 0.35–5.08; P = 0.052; I^2 = 66.2%) for those conducted in the

USA and 0.88 (95%CI: 0.694–1.116; P = 0.096; I^2 = 64.0%) for those conducted in Europe [8]. In contrast, to further investigate the relationship between vitamin D and liver fibrosis, a meta-analysis of hepatitis C-mono infected or HCV co-infected patients, including 2521 patients greater than or equal to 18 years old, found that nine of the 12 studies correlated advanced liver disease, defined as a Metavir value of F3/4, with 25(OH)D insufficiency (OR = 1.88; 95%CI: 1.27–2.77; I^2 = 66.94%), thus indicating a significant association across studies [7].

Vitamin D and hepatitis C virus-related hepatocellular carcinoma:

Several studies have shown that vitamin D deficiency and sufficiency are associated with the presence of various types of cancer, including HCC [29,30]. Four independent cohorts of HCV-infected individuals, including 1279 white and Japanese CHC-infected patients with HCC and 4325 without HCC, were adopted to investigate the association between genetic variations in CYP2R1, DBP, and 7-dehydrocholesterol reductase (DHCR7) gene and HCV-induced HCC. In the combined analyses of these cohorts, the strongest associations were found with GC (OR = 1.56; 95%CI: 1.12–2.15; P = 0.007) and DHCR7 (OR = 1.42; 95%CI: 1.13–1.78; P = 0.003), whereas CYP2R1 was almost significantly associated with HCV-induced HCC (OR = 1.13; 95%CI: 0.99–1.28; P = 0.07), suggesting a causal role of vitamin D metabolism in HCV-induced HCC [31]. Population-based studies have been limited in investigating the relationship between HCC and vitamin D levels, and there is currently no published evidence that supplementation of vitamin D or its analogues translate into a benefit in HCV-infected patients with HCC.

Vitamin D and hepatitis C virus treatment:

Several factors likely affecting the response to pegIFN/ RBV therapy have been reported, including factors in both the virus and host, such as HCV genotype 1, male sex, human immunodeficiency virus and hepatitis B virus coinfection, advanced liver fibrosis, insulin resistance, and high viral load (≥600 000 UI/ml) [32,33]. Since the first observation in 2010 that low vitamin D serum levels correlate with negative response to pegIFN/RBV-based therapy in genotype 1 chronic hepatitis C (G1CHC) [6], increasing studies have analysed the relationship between treatment response in CHC with vitamin D status, deter-mining that they are not affected by hepatitis C genotype or geographical distribution.

Pre-treatment vitamin D deficiency is reportedly an independent predictor of failure to achieve a sustained virological response (SVR) in both HCV genotype 1 (HCV-1) and HCV-2/3 patients from Europe [6,9,10] and Asia [10,17] and HCV-4 patients from Africa [34], whereas other studies conducted mostly in HCV-1 patients found no clear association [20,22,26,27]. It is plausible that differences within the patient populations in each study could explain the discordant results.

The first meta-analysis of serum 25(OH)D levels and HCV infection summarized eleven studies, which included 1575 cases with hepatitis C; high rates of SVR were observed in HCV individuals with vitamin D levels above 30 ng/ml (OR = 1.57; 95%CI: 1.12–2.20; P = 0.3799; I^2 = 6.5%) and those supplemented with vitamin D (OR = 4.59; 95%CI: 1.67–12.63; P = 0.2395; I^2 = 30.0%), regardless of genotype [35]. To provide a further reliably quantified relationship, another meta-analysis was per-formed in 2014 [36] that showed an association between low vitamin D status and a lower odd of achieving SVR following pegIFN/RBV therapy in patients with CHC. However, in the same year, Kitson et al. [37] evaluated 11 studies comprising 2605 patients with chronic HCV infection and found no significant association between the baseline mean 25(OH)D level and SVR (OR = 1.44; 95% CI: 0.92–2.26; P = 0.11), regardless of genotype. In addition, it is controversial whether in African-Americans there exists an association between vitamin D concentrations and the possibility to attain SVR in individuals infected with HCV genotype 1 based on pegIFN/RBV therapy [22,38].

To date, only one study has evaluated this influence in patients with direct-acting antivirals (DAAs) treatment, but the results showed that vitamin D levels increased mildly but not significantly in all patients after DAAs treatment. Furthermore, neither the pre-treatment level nor the change in levels during DAAs therapy was associated with SVR [21].

Genetic influence explains vitamin D deficiency in patients with chronic hepatitis C infection

Cholesterol metabolism in the first step of vitamin D synthesis may be a possible cause of vitamin D deficiency. Lower baseline distal cholesterol and 7-DHC were found in patient with HCV-3 infection [39], which could be reversed after treatment with sofosbuvir and ribavirin [38], indicating that HCV-3 virus eradication may affect the cholesterol biosynthesis pathway. Furthermore, in 260 Italian

patients with G1CHC infection, the DHCR7 GG genotype was independently linked to lower vitamin D serum levels and more severe liver fibrosis [28]. A prospective cohort of 398 genotype 1-infected patients from Germany showed a higher prevalence of DHCR7 TT related to SVR [40]. Another study including 623 Thai patients also found an association with lower SVR rates compared with those with the DHCR7 TT/TG genotype, whereas the SVR rate did not differ in HCV non-genotype 1-infected patients [41].

A genetic influence in the second step was found in G1 HCV-infected patients from Germany, whereby polymorph-isms of CYP27B1-1260, such as AA or CA genotype, were related to a higher SVR rate compared with those with the AC and CC genotype [42]. Meanwhile, in a cohort of 238 white patients with CHC infection treated with pegIFN/RBV, there was no correlation between CYP27B1-1260 rs10877012 polymorphism and response to therapy [43], which is in agreement with Thanapirom et al. [41].

In the final step, a genome-wide association study cohort of ~ 30 000 European individuals identified the GC variants associated with lower 25(OH)D concentrations and strongly correlated with lower levels of DBP [44], whereas no association was found between the polymorphisms of GC and treatment outcome, no matter the genotype, in a study of 623 Thai patients [41]. Recently, the first cross-sectional study on the quantitative hepatic expression of VDR in G1CHC reported that VDR expression was reduced according to the severity of liver fibrosis and necro inflammatory activity after correcting for well-known metabolic and histological risk fac-tors [45]. Garcia-Martin et al. [43] observed that the CCA haplotype and the carrier state of the VDR rs2228570 T allele were related to a higher probability of pegIFN/RBV therapy success in a cohort of 238 white patients with CHC infection. Similarly, the bAt (CCA) haplotype and ApaI CC genotype were associated with rapid fibrosis progression [46], and those carrying the bAt (CCA) haplotype, ApaI CC genotype, and TaqI AA genotype had a nonsignificant trend toward lower rates of achieving rapid virological response and SVR [47]

Furthermore, favourable VDR variants (rs7975232-C, rs2239185-T, and rs11574129-T) might contribute to decreased susceptibility to HCV infection in a high-risk HCV genotype 1-infected Chinese population [48].

However, it is worth noting that, based on pegIFN/RBV therapy combined with a protease inhibitor, Arai et al. [49] showed a different result in that none of the vitamin D-related gene polymorphisms GC (rs2282679), DHCR7 (rs7944926), CYP2R1 (rs10741657), CYP27B1 (rs10877012), and VDR gene (rs2228570) had an effect on serum 25(OH)D3 levels in 177 genotype 1b-infected CHC patients from Japan. This might be owing to a higher treatment response of the protease inhibitor that covered up the role of vitamin D-related gene polymorphisms. Above all, these studies may offer a potential mechanism of vitamin D deficiency and its role in influencing the treatment response in HCV-infected patients (Table 1). model of assessment for insulin resistance index. The GC1s/ GC1s phenotype variant of DBP was found to be a risk factor of insulin resistance in a CHC group containing 85.5% genotype 1 (mostly 1b) [51], and CYP27B1-1260 genotype appeared to have an increased risk of developing abnormal fasting plasma glucose levels [52]. Therefore, the determinants of vitamin D may contribute to the development of insulin resistance in HCV-infected patients. Furthermore, African-American patients with HCV-1 infection attained SVR at only approximately one-half the rate of whites after pegIFN/RBV treatment, and it was found that the former expressed a high-affinity variant (the GC1f protein isoform expressed from the rs7041T/rs4588C allele) rather than lower-affinity variants (the GC1s and GC2 isoforms), whereas most white Americans did not [53]. The GC1f allele was also found to be a risk factor of chronic obstructive pulmonary disease compared with the GC1s allele [54]. Whether such racial differences in vitamin D physiology are associated with the achievement of SVR has not been studied yet.

Potential mechanisms for the hypothesized link between vitamin D and hepatitis C virus infection:
In-vitro studies have been conducted to evaluate the antiviral effect of vitamin D. In Huh7.5 hepatoma cells, biological evidence demonstrated for the first time that the level of 1,25 (OH)2D3 directly suppresses HCV-RNA replication in a dose-dependent manner through increased expression of interferon-β (IFN-β) and the IFN-stimulated gene MxA [55]; in specific HCV genotype 1b or 2a replicons, 1,25(OH)2D3 and its receptor VDR were modulators of IFN-β-induced signalling through the Jak–STAT pathway, which provides a dynamic and tissue-specific or cell-specific method of con-trolling IFN-β signalling [56]. Furthermore, it is known that DAAs play their roles through the non-structural protein (NS) 3/NS4A protease and NS5A and NS5B polymerase inhibitors, and 25(OH)D3 was found to have a direct antiviral effect by inhibiting the virus assembly step and perhaps by targeting NS3-4A, influencing the

steps of HCV entry and replication [57]. Patients whose vitamin D levels were below 20 ng/ml were more likely to have pre-existing Y93 RAVs (drug resistance-associated variants) at the HCV NS5A region [58], and patients who developed NS5A multi-RAVs were likely to fail to respond to sofosbuvir/ledipasvir therapy [59].

Table 1. Vitamin D-related gene polymorphisms influence sustained virological response in patients with chronic hepatitis C infection

Factors	Country	Patients	References
DHCR7	Germany	398 G1CHC	Grammatikos et al. [40]
	Thailand	623 G1CHC	Thanapirom et al. [41]
CYP27B1-1260	Germany	468 HCV-1, HCV-2, HCV-3	Lange et al. [42]
	Spain	238 CHC	Garcia-Martin et al. [43]
	Thailand	G1CHC and non-G1CHC	Thanapirom et al. [41]
GC	Thailand	G1CHC and non-G1CHC	Thanapirom et al. [41]
CYP2R1	Thailand	G1CHC and non-G1CHC	Thanapirom et al. [41]
VDR	Germany	CHC	Garcia-Martin et al. [43]
	China	139 G1CHC	Hung et al. [47]

CHC, chronic hepatitis C; HCV, hepatitis C virus; VDR, vitamin D receptor

Studies have identified the serum levels of IFN-γ inducible protein-10 (IP-10), also called CXC motif chemokine 10 (CXCL-10), and of the enzyme dipeptidyl peptidase-IV (DPP IV) as markers involved in inflammatory responses and predictors of treatment outcome in CHC [60–62]. Higher levels of CXCL-10 and activity of DPP IV predicted poorer outcomes. CXCL chemokines primarily attract Th1 lymphocytes and neutrophils, and CXC receptors are found predominantly on Th1 lymphocytes [63]; thus, IP-10 is a key chemokine in inflammation that selectively recruits Th1 lymphocytes into tissues [64]. It has been reported that carcinogenesis may occur in patients with chronic HCV infection with an increased level of Th2 cells, losing the dominance of Th1 cells [65]. Furthermore, vitamin D significantly suppresses the expression of Th1-associated IP-10 in a dose-dependent manner in patients with asthma [66] and increases the angiogenic capacity of myeloid angiogenic cells by down-regulating CXCL-10 in systemic lupus erythematosus [67].

In patients with CHC treated with vitamin D, pegylated IFN/ribavirin showed significant reduction of serum IP-10 within 4 weeks of treatment and lower IFN stimulating gene mRNA expression in hepatocytes compared with the control arm without vitamin D [68]. Recently, a randomized double-blinded, placebo-control trial in Thailand observed a significant reduction of IP-10 and DPP IV levels compared with the placebo group upon correction of vitamin D deficiency in patients with CHC within 6 weeks without the influence of IFN, whereas the serum levels of Th1-related and Th2-related cytokines remained unchanged [62]. Further investigations are required to reveal the relationships between CXCL-10/IP-10 and Th1/Th2 cells in HCV-infected patients.

Oxidative stress has been proposed as a key step in the development and progression of liver damage. In 2010, experimental models showed that vitamin D, via its interaction with the VDR, protects against oxidative stress

[69]. Recently, a study from Iran showed the relationship between hypovitaminosis D and oxidative stress in patients with HCV through a higher oxidant stress index, advanced oxidation protein products, and NOx levels, which are oxidative stress markers [70], and similar results were also observed in Brazil, Japan, and Egypt [71–73].

Vitamin D supplementation: a supplement to ongoing therapy for hepatitis C virus infection:

In biological studies, vitamin D supplementation showed its ability to improve SVR in 1b patients whether they were treatment-naive [74] or with refractory factors based on simeprevir with pegIFN/RBV from a RCT [75]. A cross-sectional study of 108 Spanish genotype 1 patients with CHC found that vitamin D deficiency was common in patients but was not related to virological variables and also had no effect on HCV-RNA serum levels [19]. Vitamin D supplementation was also related to higher SVR rates in HCV-infected individuals (OR = 4.59; 95% CI: 1.67–12.63), regardless of genotype, where the highest level was observed among genotype 1 HCV-infected individuals [35]. No adverse events related to vitamin D supplementation were observed during the study period (6 weeks) in all patients [62], but it is unknown whether there could be related risks in the future. However, a prospective, randomized controlled, open-labelled, two group assignment study consisting of 101 chronic HCV-4 Egyptian patients found that vitamin D supplementation showed no effect on SVR [76]. A recent meta-analysis of Kim et al. [77] confirmed an improved effect on SVR rates of vitamin D supplementation in combination with conventional antiviral therapy in patients with CHC infection. It is interesting that a vitamin D RCT in patients with cirrhosis showed that vitamin D supplementation in patients with cirrhosis is as effective as in the general population, considering the vitamin D doses needed to achieve certain target levels of 25(OH)D [78]. However, more RCTs and meta-analyses are highly needed to better understand the total effect of vitamin D supplementation.

In summary, vitamin D can easily be supplemented and plays a role as a pre-treatment predictor of SVR to standard therapy, with infrequent adverse effects and few costs. However, consensus is still missing on optimal 25(OH)D target levels and dosing strategies. The doses adopted for vitamin D supplementation mainly vary from 1000 to 2000 IU/day [10,17,74,75]. Drug administration intervals, which influence drug effects, also need to be considered [79], as no study has examined this factor or set up different drug intervals. Furthermore, the form of administration mainly refers to 25(OH)D3, although there are other types, such as cholecalciferol, a nonactivated vitamin-D3 supplement, and alfa-calcidol, an activated 1(OH)D3, showing similar results as 25(OH)D combined with SVR to pegIFN/ RBV therapy [72,80,81]. There have been few studies comparing the strength of the effect of various forms adopted for vitamin D [72].

CONCLUSION:

The adjunction of new direct antiviral agents is changing the therapeutic approach in chronic HCV infection. However, many patients are treated with the classic combination therapy of pegIFN/RBV where these new therapies cannot be afforded. One of the most important targets is to obtain SVR after treatment, which is associated with reduced HCC at any stage of fibrosis among HCV-infected persons [11]. With this standard of care, SVR is achieved in ~ 80% of patients with HCV genotypes 2 and 3. However, only half of patients with HCV genotype 1 responded to the treatment. In the quest to enhance treatment response, there has been significant interest in the association of serum 25-vitamin D levels and supplementation during the natural history and treatment of chronic HCV infection. Even in the era of DAAs, we should consider supplementation with vitamin D deficiency for patients with CHC infection.

Recommendations:

Although, recent findings showed the relationship between vitamin D and HCV infection, which comes first? What is the difference in the regulation of vitamin D in patients with CHC infection? How does one make clear guidelines for correcting vitamin D deficiency? Additional clinical data from large and well-defined patient cohorts is also required to verify the safety and efficacy of nutritional vitamin D therapy in this unique patient population and also as a strategy for physicians, medical specialists, and healthcare policy makers.

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