Vitamin D deficiency and hepatitis viruses-associated liver diseases: A literature review

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Abstract

The secosteroid hormone vitamin D has, in addition to its effects in bone metabolism also functions in the modulation of immune responses against infectious agents and in inhibiting tumorigenesis. Thus, deficiency of vitamin D is associated with several malignancies, but also with a plethora of infectious diseases. Among other communicable diseases, vitamin D deficiency is involved in the pathogenesis of chronic liver diseases caused by hepatitis B and C viruses (HBV, HCV) and high prevalence of vitamin D deficiency with serum levels below 20 ng/mL in patients with HBV and HCV infection are found worldwide. Several studies have assessed the effects of vitamin D supplementation on the sustained virological response (SVR) to interferon (IFN) plus ribavirin (RBV) therapy in HBV and HCV infection. In these studies, inconsistent results were reported. This review addresses general aspects of vitamin D deficiency and, in particular, the significance of vitamin D hypovitaminosis in the outcome of HBV- and HCV-related chronic liver diseases. Furthermore,
current literature was reviewed in order to understand the effects of vitamin D supplementation in combination with IFN-based therapy on the virological response in HBV and HCV infected patients.

**Key words:** Vitamin D; Vitamin D deficiency; Chronic liver disease; Hepatitis B virus infection; Hepatitis C virus infection; Liver cirrhosis; Hepatocellular carcinoma; Sustained virological response; Vitamin D supplementation

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Core tip: Vitamin D deficiency is common and associated with chronic liver diseases. Several studies have ascribed a strong association of vitamin D insufficiency with unfavorable clinical courses and progression of liver disease in hepatitis B virus (HBV) and hepatitis C virus (HCV) infections. However, any causal relation is so far not fully understood. In addition, there are inconsistent results with regard to the impact of vitamin D supplementation on the virological response to IFN-based therapy; this applies particularly to HCV infections. The present review addresses general aspects of vitamin D deficiency and focuses on its association with HBV and HCV infection. Furthermore, the effects of vitamin D supplementation in combination with IFN-based therapy on the virological response in HBV and HCV infected patients are reviewed.

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**INTRODUCTION**

Vitamin D deficiency affects almost one billion people globally. Further to its crucial role in bone metabolism by supporting enteric absorption of calcium, magnesium, phosphate, iron and zinc, vitamin D has important non-skeletal functions which are involved in many biological processes. In addition to insufficient sun exposure, seasonality, place of residence, diet and the extent of skin pigmentation, which all affect vitamin D bioavailability, hepatitis B and C, the major causes of liver cirrhosis (LC) and hepatocellular carcinoma (HCC), may also contribute to vitamin D deficiency. Low vitamin D serum levels are associated with many human diseases and frequently observed in chronic liver diseases; vitamin D constraints contribute to disease progression in chronic hepatitis B and C, but also to non-alcoholic fatty liver disease (NAFLD). Protective properties of vitamin D in preventing HBV and HCV replication and in retarding clinical progression of HBV/HCV-related liver diseases have been reported.

The prevalence of vitamin D insufficiency in patients with HBV and HCV infection covers the broad range from 16% up to 100%. Several studies have demonstrated a strong association between vitamin D insufficiency and the clinical outcome and disease progression of HBV and HCV infections. This applies in particular to the onset of LC. However, the causal relation and applying pathophysiological mechanisms are not fully understood. Although increasing numbers of studies describe the influence of vitamin D deficiency on either the outcome of HBV/HCV-related liver disease or on the virological response to interferon (IFN)/ribavirin (RBV) treatment, the findings are still inconsistent. (Ref. 19: ClinicalTrials.gov; identifier NCT01277601). Conflicting observations and conclusions apply also to several randomized clinical trials in which the effects of vitamin D supplementation were evaluated.

Here, we address general aspects of vitamin D deficiency and, in particular, focus on its association with HBV and HCV-related chronic liver disease. We also review the effects of vitamin D supplementation in combination with IFN-based therapy on the virological response in HBV and HCV infected patients.

**LITERATURE SEARCH**

A systematic literature search was conducted using PubMed, MEDLINE and ClinicalTrials.gov (identifiers given where applicable). Search terms used in various combinations were "vitamin D", "vitamin D deficiency", "hepatitis B virus infection", "hepatitis C virus infection", "chronic liver disease", "liver cirrhosis" and "hepatocellular carcinoma". We did not restrict the search to a certain period of time. Thus, articles written in English and published in peer-reviewed journals describing associations of vitamin D deficiency with clinical outcomes or the effects of vitamin D in combination with IFN-based therapy on the virological response in HBV and HCV infected patients were included. Abstracts, letters and posters presented in conferences were not considered.

**VITAMIN D: METABOLISM AND FUNCTION**

Vitamin D was first identified as a prohormone early in the 20th century. It is a fat-soluble secosteroid and regulates skeletal and non-skeletal functions. Adequate vitamin D levels are required for bone growth and remodeling of osseous structures by osteoblasts and osteoclasts, thus protecting from osteoporosis. Vitamin D promotes the absorption of calcium, magnesium, phosphate, iron and zinc from the gut and maintains essential serum calcium and phosphate concentrations to warrant normal bone mineralization and to prevent hypocalcaemia.

Since the discovery of the vitamin D receptor (VDR)
the non-skeletal functions of vitamin D have gained attention. VDR is a member of the nuclear receptor family of transcription factors and is expressed on more than 35 types of solid tissues\(^\text{[32]}\), but also on macrophages as well as on T and B cells\(^\text{[33,34]}\). Vitamin D is involved in physiological processes through VDR activation, including the regulation of immune responses, cell growth and cell differentiation\(^\text{[35,36]}\). Therefore, vitamin D is considered a powerful modulator of pathophysiological mechanisms in several infectious diseases, cancers and metabolic disorders\(^\text{[6,37-39]}\).

Vitamin D occurs as vitamin D3 (25(OH)D\(_3\); cholecalciferol) and vitamin D2 (25(OH)D\(_2\); ergocalciferol). More than 90% of vitamin D3, the prevailing form of vitamin D, are produced in the skin by means of sunlight exposure, while the remainder is retrieved from dietary components\(^\text{[2,30]}\). Vitamin D2 does not depend on sunlight and only minute amounts of vitamin D2 are derived from plants\(^\text{[40]}\). Both vitamin D3 and D2 are inert. To become biologically active they need to be sequentially converted to their intermediate metabolite [calcidiol, 25(OH)D] and the final active form [calcitriol, 1,25(OH)\(_2\)D] by hydroxylation in the liver and the kidney\(^\text{[41]}\). Hydroxylation of vitamin D is a process that introduces a hydroxyl group (-OH) into vitamin D2 and D3 in the liver to form 25-hydroxyvitamin D [25(OH)D]. The metabolites are further hydroxylated in the kidney to produce the active form calcitriol. The active form circulates as a hormone in the blood stream to regulate the concentrations of calcium and phosphate and to promote healthy growth and remodeling of bones\(^\text{[41]}\).

Precise quantification of calcitriol is problematic due to its short half-life and the serum concentrations that are 1000 times less compared to those of 25(OH)D. In contrast, 25(OH)D has a half-life of approximately three weeks, making it an appropriate and largely reliable indicator of the individual vitamin D status\(^\text{[1,42]}\).

An appropriate duration of exposure to ultraviolet B (UVB) radiation is crucial in cutaneous vitamin D production\(^\text{[1,43]}\), and a strong correlation exists between vitamin D serum levels, UVB exposure and geographical residence\(^\text{[1,44,45]}\). As latitudes increase, disposable amounts of vitamin D decrease\(^\text{[44]}\). At latitudes > 37°N and < 37°S, sunlight does not sufficiently induce vitamin D synthesis in the skin, in particular during the winter months\(^\text{[46]}\). Latitude and UVB exposure are, however, not exclusive indicators of vitamin D deficiency. Other factors are age, nutritional components and skin pigmentation as well as certain chronic pathological conditions\(^\text{[1,43,45]}\).

**VITAMIN D DEFICIENCY**

A standard definition of vitamin D deficiency does not exist. Formerly, the vitamin D status was assessed empirically, *e.g.*, through overt diagnoses of childhood rickets and osteomalacia in adults\(^\text{[47,48]}\). Today, the recognition of deficiency relies on quantification of vitamin D serum levels, representing the current supply rather than functional activity and, thus, not sufficiently supporting a standard definition of vitamin D deficiency.

Serum 25(OH)D levels are inversely correlated with parathyroid hormone (PTH) levels. Low levels of vitamin D stimulate PTH production and, consequently, PTH may be considered a surrogate marker in the diagnosis of vitamin D deficiency. However, high vitamin D levels do not always lead to decreased PTH levels. If vitamin D values are above approximately 30 ng/mL, serum PTH levels will be at a low steady level\(^\text{[49,50]}\). Thus, current and widely accepted definitions of vitamin D levels include deficiency (< 20 ng/mL), insufficiency (20–30 ng/mL), and sufficiency (> 30 ng/mL)\(^\text{[1]}\).

Vitamin D deficiency is associated with a wide spectrum of diseases including not only bone disorders, but also several autoimmune and infectious diseases, asthma and malignancies as well as psychiatric conditions\(^\text{[1,51,52]}\). Vitamin D inadequacy involves both deficiency and insufficiency and constitutes an underestimated health factor in many populations\(^\text{[53]}\). In developed countries, vitamin D deficiency is very common, with almost half of the population affected\(^\text{[1]}\). Moreover, global assessment of the vitamin D status in postmenopausal women with osteoporosis showed that 24% had severe deficiency (< 10 ng/mL), with the highest prevalences reported in central and southern Europe\(^\text{[42]}\). A similar trend was reported in a cross-sectional, observational study conducted at 61 sites across the United States, indicating that 52% and 18% among 1536 postmenopausal women receiving osteoporosis treatment had 25(OH)D levels of less than 30 ng/mL and 20 ng/mL\(^\text{[60]}\), respectively.

Vitamin D deficiency is common in western and northern countries, but also in Africa and Asia\(^\text{[54-58]}\).

Serum levels in Asian populations were assessed in three large cross-sectional studies in China (\(n = 3262\))\(^\text{[56]}\), South Korea (\(n = 6925\))\(^\text{[52]}\), and in Thailand (\(n = 2641\))\(^\text{[54]}\). These studies defined deficiency as levels of < 20 ng/mL and indicated highest prevalences of deficiency in China (69%) and in South Korea (males 47%; females 65%)\(^\text{[55]}\). In contrast, a significantly lower prevalence of deficiency of 6% only was observed in Thailand\(^\text{[54]}\). This results most likely from its geographical location close to the equator. In Vietnam, recent studies with, however, smaller sample sizes found that vitamin D deficiency prevalences range from 16 to 63%\(^\text{[4,59,60]}\).

Vitamin D deficiency in African populations may be attributed to the skin pigmentation, traditional full-length clothing, and the occurrence of infectious diseases (tuberculosis, HIV/AIDS, malaria) which are associated with deficiency\(^\text{[61-65]}\). A cross-sectional analysis of adults in a National Health and Nutrition Examination Survey (\(n = 8415\)) conducted in the United States reported that vitamin D insufficiency among African Americans was as high as 81%, but only 28% in individuals of European descent\(^\text{[66]}\). Other studies also consistently indicate that vitamin D deficiency is more prevalent in immigrants from Africa to the United States and to Europe\(^\text{[67,68]}\). These reports underline that skin pigmentation is an
important factor in reducing vitamin D production.

Sub-Saharan Africa and several parts of Asia bear a heavy burden of communicable diseases, which may affect the vitamin D status. Several studies investigated the causal effect of vitamin D deficiency on the severity and progression of infectious diseases, in particular of tuberculosis[49-51] and respiratory tract infections[72-74]. Recently, vitamin D deficiency has also been implicated in susceptibility to viral hepatitis and the severity and progression of viral hepatitis-associated chronic liver diseases[4,12,75-77].

VITAMIN D DEFICIENCY IN CHRONIC HEPATITIS B AND C

Whether low vitamin D levels are the cause or the result of certain diseases, including chronic viral liver diseases, is not clear. Based on 290 prospective and intervention studies, a systematic review has recently concluded that vitamin D deficiency might be a result and a biological marker of deteriorating health, driving 25(OH)D to low concentrations, rather than a cause of disease[2,9]. Vitamin D deficiency may contribute to liver damage through increased inflammation and fibrosis[9,39]. Other studies have shown that vitamin D deficiency is clearly associated with unfavorable clinical outcomes and accelerated progression of chronic liver diseases due to viral hepatitis, alcohol consumption and NAFLD[4,6,8,10,12,60,78-82]. Although vitamin D is associated with NAFLD, a recent study showed that vitamin D insufficiency was not associated with the presence of NAFLD[83]. Relationship between vitamin D deficiency and the pathogenesis of NAFLD has been systematically reviewed[10], and that vitamin D could be used as a supplement in the management of NAFLD. However, clinical trials concluded that vitamin D supplementation has a less impact on the NAFLD pathogenesis such as hepatic fat, injury, and hepatic steatosis[94,85]. Notably, vitamin D deficiency may also contribute to reduced antiviral responses in IFN/RBV treatment of hepatitis B and C[6,19,28,80]. Comparable studies with regard to more recent treatment regimens such as IFN-free and direct-acting antiviral agents are not available so far.

Worldwide, approximately 257 and 130-150 million people are affected by chronic hepatitis B and C, respectively, making it a significant cause of viral infection-related fatality[87,88]. A high prevalence of vitamin D deficiency occurs in almost all chronic liver diseases and their progression, irrespective of their etiology[79,19,78]. Based on results of studies on vitamin D insufficiency and deficiency in chronic hepatitis B and C, serum vitamin D levels of < 20 ng/mL range from 16%-100%[5,15,16] (Tables 1 and 2). Although high prevalences of vitamin D insufficiency/deficiency are observed both in healthy populations and in patients with viral hepatitis, significantly higher rates of deficiency were found in hepatitis patients compared to controls in several studies[94,8,80].

Vitamin D deficiency and chronic hepatitis B

So far, most studies on associations of HBV-related liver diseases with vitamin D deficiency were cross-sectional studies (Table 1). In such study designs, any fluctuation of vitamin D levels over the course of HBV infection cannot be assessed and a causative association of vitamin D levels with HBV-related liver diseases cannot reliably be established.

Vitamin D is significantly associated with virus replication in chronic HBV infection. Recently, several studies have shown that insufficient vitamin D levels most likely fail to suppress HBV replication and contribute to poor clinical courses[4,11,12,89]. Vitamin D levels are positively correlated with albumin levels and platelet counts and, inversely, with ALT levels during the active phase of hepatitis B[19,39,78]. Serum levels of < 10 ng/mL can be predictive for low serum albumin levels and the severity of chronic liver disease[22,75]. However, other studies have reported that vitamin D insufficiency was not correlated with liver function parameters, possibly due to the fact that vitamin D levels depend also on the composition of study cohorts and the study designs[4,11]. Liver disease progression in patients with chronic hepatitis B appears also to be influenced crucially by distinct viral factors, in particular by the infecting HBV genotypes. Genotypes C and B are the major causes of chronic hepatitis B and subsequent LC and HCC in East Asia[90-92]. Recent studies indicate that patients infected with genotype B had a higher prevalence of vitamin D insufficiency than those infected by the C genotype[21,93].

To the best of our knowledge, there are only two studies which have investigated the association of baseline vitamin D levels with sustained virological response (SVR) to nucleoside/nucleotide analogues (NUC) or IFNα in addition to treatment with NUC in chronic hepatitis B. It was shown that the baseline levels (cutoff value: 30 ng/mL) can predict the virological response at week 104 (67% in the insufficiency group vs 82% in the sufficient group, P < 0.001) in patients with chronic hepatitis B treated with NUC[29]. Chan et al[19], however, concluded, inconsistent with the findings given in Ref. 29, that baseline vitamin D levels are not associated with more favorable treatment outcomes in patients treated with either tenofovir disoproxil fumarate (TDF) plus Peg-IFNα or TDF or Peg-IFNα monotherapy[19]. Further prospective studies assessing associations of baseline vitamin D levels and treatment outcomes in chronic hepatitis B, particularly in the IFNα-based therapy, are worth to be conducted.

Association of vitamin D deficiency with SVR to antiviral therapy in chronic hepatitis C patients

In several studies the role of the vitamin D status as well as the effects of vitamin D supplementation on the efficacy of IFNα plus RBV in the treatment of chronic hepatitis C have been investigated (Table 2). Most studies showed high prevalences of vitamin D deficiency and significant associations of low baseline
Table 1 Representative studies on vitamin D deficiency in chronic hepatitis B virus patients

| Study population | Diagnosis | Sample size (n) | Study design | Length of follow-up | Vitamin D cutoff (ng/mL) (%) | Main results | Ref. |
|------------------|-----------|----------------|-------------|---------------------|-----------------------------|--------------|------|
| China | CHB (n = 560) | Multicenter, randomized, controlled | 104 wk from initiation of antiviral treatment | < 20: deficiency | Vitamin D insufficiency highly prevalent in treatment-naive patients with chronic hepatitis B | Yu et al., 2017 |
| Vietnam | CHB (n = 165) | Cross-sectional | NA | < 10: severe deficiency | Vitamin D insufficiency frequent among HBV patients | Hoan et al., 2016 |
| China | CHB (n = 115) | Cross-sectional | NA | < 10: deficiency | Vitamin D levels significantly lower in LC compared to CHB and HC groups (P < 0.001) | Zhao et al., 2016 |
| South Korea | CHB (n = 110) | Cross-sectional | NA | < 10: deficiency | Vitamin D insufficiency independently associated with advanced liver fibrosis | Ko et al., 2016 |
| China | CHB (n = 84) | Cross-sectional | NA | < 10: deficiency | Reduced vitamin D levels highly prevalent among untreated CHB patients | Sali et al., 2016 |
| Multicenter in Europe, Asia and North America | CHB (n = 737) | Randomized, open-label, controlled clinical trial | 48 wk of PegIFN TDF or PegIFN followed by TDF PegIFN | < 20: deficiency | Low baseline levels of vitamin D associated with high HBV DNA loads, abnormal ALT at week 48 independent of treatment groups | Chan et al., 2015 |
| China | CHB (n = 426) | Cross-sectional | NA | < 32 insufficiency | Vitamin D deficiency common among patients with CHB and associated with adverse clinical outcomes | Wong et al., 2015 |
| China | CHB (n = 242) | Cross-sectional | NA | < 20: deficiency | Higher prevalence of vitamin D insufficiency in HBV genotype B patients than in genotype C patients | Yu et al., 2015 |
| China | CHB (n = 133) | Cross-sectional | NA | < 14: deficiency | Vitamin D levels not associated with HBV DNA levels or the stage of fibrosis in CHB patients | Zhu et al., 2016 |
| Germany | CHB (n = 203) | Cross-sectional | NA | < 10: deficiency | Vitamin D levels not associated with other clinical parameters | Farnik et al., 2013 |

Vitamin D deficiency significantly associated with HBV genotype B
Low baseline levels of vitamin D associated with high HBV DNA loads, abnormal ALT at week 48
Vitamin D levels significantly lower in LC compared to CHB and HC groups (P < 0.001)
Vitamin D insufficiency highly prevalent in treatment-naive patients with chronic hepatitis B
Vitamin D insufficiency frequent among HBV patients
Vitamin D levels significantly lower in LC compared to CHB and HC groups (P < 0.001)
Vitamin D deficiency independently associated with advanced liver fibrosis
No significant association of vitamin D levels in treated and treatment-naive patients
Low baseline levels of vitamin D associated with high HBV DNA loads, abnormal ALT at week 48 independent of treatment groups
Vitamin D deficiency common among patients with CHB and associated with adverse clinical outcomes
Higher prevalence of vitamin D insufficiency in HBV genotype B patients than in genotype C patients
Vitamin D levels not associated with HBV DNA levels or the stage of fibrosis in CHB patients
Vitamin D levels not associated with other clinical parameters
Baseline vitamin D levels not associated with treatment outcomes
Higher prevalence of vitamin D insufficiency in HBV genotype B patients than in genotype C patients
Vitamin D levels not associated with HBV DNA loads as strong predictor of low vitamin D levels in CHB patients
Baseline vitamin D levels significantly lower in LC compared to CHB and HC groups (P < 0.001)
levels of 25(OH)D at the time of antiviral therapy initiation and lower odds of achieving SVR, which is defined as undetectable serum HCV RNA level at 24 wk after cessation of treatment. However, other studies reported rather inconsistent and partly contradicting results, possibly due to heterogeneity in patient inclusion criteria (HCV infection or HIV/HCV coinfection, ethnicity) and characteristics of vitamin D assessment (seasonality, cutoff values, laboratory methods).

To date, five meta-analyses have described an association of baseline vitamin D levels with SVR (Table 2). One study showed a significant association of SVR with vitamin D deficiency. Low odds of achieving SVR rates were found in patients with vitamin D levels of < 20 ng/mL compared to patients with levels of ≥ 30 ng/mL (OR = 0.5, 95%CI: 0.3-0.9). A similar result was found in another study, which reported high rates of SVR in HCV patients with vitamin D levels of ≥ 30 ng/mL (OR = 1.6; 95%CI: 1.1-2.2) and in patients supplemented with vitamin D (OR = 4.6; 95%CI: 1.7-12.6), regardless of viral genotypes. In contrast, Kitson et al. reported that baseline 25(OH)D levels were not associated with SVR in Peg-IFN/RBV treatment, also regardless of the viral genotype involved. The main differences in these meta-analyses are the study designs and patient selection strategies, as, for instance, studies involving patients with HCV/HIV coinfections were excluded in the third meta-analysis, but included in the other meta-analyses.

When looking at the effect of vitamin D supplementation as an adjuvant to IFNα/RBV therapy for treatment of chronic HCV infections, some evidence indicates that vitamin D supplementation improves the SVR (Table 2). SVR rates in patients supplemented with vitamin D depend on the infecting HCV genotypes, and range from 54%-86% for HCV genotype 1 (18.5% and 42% in the non-supplemented control groups) up to 95% for HCV genotype 2 and 3 infections (77% in the non-supplemented control group). A meta-analysis including eleven studies reported high odds of SVR (OR = 4.6, 95%CI: 1.7-12.6) in vitamin D supplemented groups compared to non-supplemented patient groups, regardless of genotypes. A retrospective study in Italy has assessed the effect of supportive vitamin D treatment in combination with antiviral therapy (IFNα plus RBV) in recurrent HCV infections of patients who had undergone liver transplantation. Vitamin D supplementation could increase SVR rates significantly. In contrast, other studies showed inconsistent results for the HCV genotypes 4 and 1. Randomized prospective studies with small sample sizes and lacking a placebo-controlled arm challenge the application of vitamin D as an adjuvant substance in order to enhance SVR.

VITAMIN D AND VIRAL HEPATITIS-RELATED LIVER CIRRHOSIS

In an assessment of liver cirrhosis (LC) mortality in 187 countries during the period from 1980 to 2010, global fatalities increased from approximately 676,000 in 1980 to more than 1 million in 2010, accounting for approximately 2% of all causes of death. There is growing evidence that vitamin D deficiency is associated with progression of LC caused by various etiologies, mainly by HBV and HCV infection, but also by alcoholic and NAFLD. Vitamin D deficiency reflects also hepatic dysfunction and is associated with mortality in patients with LC, regardless of underlying causes.

The association of vitamin D with LC may be relevant in the treatment of chronic hepatitis C, further randomized, placebo­armed studies are required in order to confirm whether vitamin D supplementation in fact improves the SVR in combination with IFN in HCV infections.
| Study population | Diagnosis | Sample size (n) | Study design | Length of follow-up | Vitamin D cutoff (ng/mL) (%) | Main results | Ref. |
|------------------|-----------|----------------|-------------|--------------------|-------------------------------|--------------|------|
| Italy CHC (n = 197) | HCV genotype 1 controls (n = 49) | Cross-sectional | NA | < 30: deficiency | 73 | Low vitamin D linked to severe fibrosis and low SVR in IFN-based treatment | [161] |
| United States | CHC (n = 216) | Prospective | 12 wk after cessation of antiviral therapy | < 20: deficiency | 43 | Vitamin D deficiency associated with HCV-related LC and with hepatic function | [158], 2017 |
| Switzerland | CHC (n = 269) HCV genotypes 1-4 | Case-control | NA | < 20: deficiency | 36 | No significant association between SVR12 and serum vitamin D levels at baseline | [157], 2013 |
| Spain | CHC genotypes 1-4 (n = 182) | Cross-sectional | NA | < 20: deficiency | 41 | No difference in vitamin D levels in patients with and without progression of HCV-associated liver disease | [159], 2014 |
| Northern Italy | CHC (n = 211) HCV genotypes 1-5 | Prospective | 24 wk after cessation of antiviral therapy | < 20: deficiency | 46.4 | SVR24 rates to IFNα therapy were 50%, 61%, and 69% in CHC patients with baseline vitamin D levels of < 10 ng/mL, 10-20 ng/mL, and > 20 ng/mL, respectively | [160], 2011 |
| Multicenter study, United States | Cases (histological progression or clinical decompensation; (n = 129), controls (n = 129) | Nested case-control study | Over 4 yr | At baseline: cases: 44.8 controls: 44.0 | Not stated | No association between SVR rate and baseline vitamin D levels correlated with liver fibrosis as assessed by FibroTest | [162], 2010 |
| Multicenter study, Japan | CHC (n = 247) HCV genotype 1b | Case-control | NA | < 30: deficiency | Not stated | NS5A Y93H and L31M resistance-associated variants associated with vitamin D deficiency | [163], 2012 |
| Multicenter study, France | HCV-HIV coinfection (n = 189) | Cross-sectional | NA | < 30: deficiency | 85 | Low serum vitamin D levels associated with liver fibrosis and baseline vitamin D levels | [164], 2011 |
| Japan | CHC (n = 619) | Cross-sectional | NA | < 20: deficiency | 47 | Vitamin D levels influenced by gender, age, hemoglobin level, albumin and seasonality | [165], 2015 |
| Egypt | CHC (n = 70) controls (n = 50) | Cross-sectional | NA | < 20: deficiency | 16 | Baseline vitamin D levels not associated with SVR or fibrosis stage in HCV genotype 1 but deficiency associated with high activity | [166], 2013 |
| Australia | CHC (n = 274) HCV genotype 1 | Case-control | NA | < 30: deficiency | 18 | SVR24 rates: 65% in patients with vitamin D levels > 18 ng/mL vs 38.5% in patients with vitamin D levels of < 18 ng/mL | [167], 2014 |

Table 2: Representative studies regarding vitamin D status in chronic hepatitis C virus patients
| Location/ Country | Study Type | Study Design | Time of Measurement | Vitamin D Levels | SVR Rate | Notes |
|------------------|------------|--------------|---------------------|-----------------|----------|-------|
| Egypt CHC (n = 101) | Randomized prospective | Until 72 wk from start of antiviral therapy | < 20: deficiency | 95 No impact of vitamin D supplementation on SVR in HCV genotype 4 patients | Esmat et al(24), 2015 |
| Egypt CHC (n = 50), controls (n = 51) | Randomized prospective | Not stated | < 20: deficiency | 5 No correlation between vitamin D levels and stage of liver fibrosis | Not stated |
| Israel CHC (n = 72) | Randomized prospective | 24 wk after cessation of antiviral treatment | < 10: severe deficiency | 21 Addition of vitamin D to Peg-IFNα/αRBV therapy improves SVR24 (86% vs 42%) | Abu-Mouch et al(31), 2011 |
| Israel CHC (n = 36), controls (n = 36) | Randomized prospective | 24 wk after cessation of antiviral treatment | < 12: deficiency | 26 Addition of vitamin D to Peg-IFNα/αRBV therapy improves SVR24 (95% in treated group vs 77% in controls) | Ninner et al(35), 2012 |
| France CHC (n = 516) HCV genotype 1 | Randomized controlled | Not stated | < 32: insufficiency | 33.3 Vitamin D deficiency correlated with SVR in HCV genotype 2 and 3 patients (50% vs 81%: SVR24 for patients with and without severe vitamin D deficiency) | Belle et al(68), 2017 |
| Egypt CHC (n = 66) | Randomized prospective | 24 wk after cessation of antiviral treatment | < 12: deficiency | 33.3 Addition of vitamin D to conventional Peg-IFNα/αRBV therapy improved SVR24 | Eltayeb et al(69), 2015 |
| Germany CHC (n = 468) HCV genotypes 1-3 | Retrospective | 24 wk after cessation of antiviral treatment | < 30: deficiency | 66 Vitamin D deficiency associated with SVR in HCV genotype 2 and 3 patients (50% vs 81%: SVR24 for patients with and without severe vitamin D deficiency) | Lange et al(80), 2011 |
| Taiwan CHC (n = 132) | Retrospective | SVR was assessed at week 48 (HCV genotype 1) and at week 24 (HCV genotype 2) from initiation of antiviral treatment | Not stated | 34 Vitamin D can suppress HCV replication in hepatic cell lines | Jee-Fu et al(86), 2017 |
| Germany CHC (n = 398) | Retrospective | SVR was assessed at week 24 from initiation of antiviral treatment | At baseline | Not stated | Grammatikos et al(28), 2014 |
| Germany CHC (n = 42) | Retrospective | 24 wk after cessation of antiviral treatment | < 10: deficiency | 57 Low vitamin D levels may impair virological response to Peg-IFNα/αRBV therapy, especially in difficult-to-treat patients | Mandorfer et al(29), 2013 |
| Italy CHC (n = 42) | Retrospective | SVR was assessed at week 48 from initiation of antiviral treatment | < 10: severe deficiency | Not stated | Bitetto et al(30), 2011a |
| Multicenter study, United States CHC (n = 1292) | Retrospective | 24 wk after cessation of antiviral treatment | < 12: deficiency | 19 Higher vitamin D levels not associated with SVR in Peg-IFNα/αRBV therapy | Lofthfield et al(31), 2016 |
| Meta-analysis 1 To assess vitamin D levels related to ALF and/or SVR (n = 3755) (11 studies for SVR, 7 studies for ALF) | Meta-analysis | NA | < 10: severe deficiency | Not stated | Garcia-Alvarez et al(32), 2014 |
Vitamin D is involved in inhibition of inflammation and liver fibrosis, substantiated by the observation that VDR knockout mice spontaneously develop hepatic fibrosis [77,109]. The function of vitamin D in mesenchymal multipotent cells is to decrease expression of collagen and profibrotic factors [transforming growth factor beta 1 (TGFβ1)] and serpin family E member 1 (SERPINE1)] [110], suggesting vitamin D supplementation as preventive and supportive treatment in LC [110]. Furthermore, vitamin D directly inhibits the proliferation and profibrotic phenotype of hepatic stellate cells and reduces thioacetamide-induced liver fibrosis in an animal model [109]. There are several lines of evidence to support an inverse association of vitamin D levels with liver fibrosis induced by chronic viral hepatitis [4,100,111,112]. More specifically, a high expression of hepatic Toll-like receptors (TLR2 and TLR4) can result in the production of tumor necrosis factor alpha (TNFα) in chronic hepatitis C [113]. This cytokine is shown to modulate fibrosis [114,115]. In this context, vitamin D might elicit an anti-inflammatory mechanism by downregulating the expression of TLR2 and TLR4 molecules. Recent in-vivo studies have documented on the reduced production of TNFα by monocytes, macrophages and myeloid dendritic cells treated with vitamin D [116,117]. Corroborating the findings, a yet another study show that circulating vitamin D levels inversely correlate with TLR2 and TLR4 expression [118].

Fibrotic conditions appear to be reversible and even curable [119,120] when interventions are initiated at early stages [121]. Several observations have underlined the importance of vitamin D supplementation in the treatment of chronic liver diseases. However, so far there have been no randomized prospective trials to assess the role of vitamin D supplementation in the treatment of LC.

### VITAMIN D DEFICIENCY AND HEPATITIS-RELATED HEPATOCELLULAR CARCINOMA

Both incidences and mortality rates of certain cancers are higher in northern latitudes, where sunlight exposure is rather scarce [122,123]. Sound epidemiologic studies have shown that vitamin D deficiency is associated with an increased risk of colon, breast, prostate, and ovarian cancers [124–130]. Not much information is, however, available on an association

| Meta-analysis | To clarify any association between baseline vitamin D levels and SVR (n = 2605) (11 studies) | Meta-analysis | NA | Not stated | NA | Baseline vitamin D levels not associated with SVR in Peg-IFNa/RBV therapy, regardless of genotype | Kitson et al [89], 2014 |
| Meta-analysis | To assess the association of vitamin D levels with the severity of liver fibrosis in CHC (n = 8321) (6 studies) | Meta-analysis | NA | Not stated | NA | Lower serum vitamin D is a risk factor for severity of liver fibrosis in chronic HCV patients. | Luo et al [80], 2014 |
| Meta-analysis | To evaluate the association between vitamin D levels and SVR in CHC (n = 1575) (8 observational and 3 interventional studies) | Meta-analysis | NA | At baseline 17-43 ng/mL. | NA | High SVR rates observed in patients with vitamin D levels > 30 ng/mL. | Villar et al [29], 2013 |
| Meta-analysis | To access the association between vitamin D supplementation and SVR rate to PEG-IFN/RBV in CHC (n = 548) (7 studies) | Meta-analysis | NA | NA | NA | Vitamin D supplementation significantly increased SVR rates to Peg-IFNα/RBV at 24 wk | Kim et al [86], 2017 |

CHC: Chronic hepatitis C; LC: Liver cirrhosis; ALF: Acute liver failure; IFNα: Interferon alpha; RBV: Ribavirin; Peg-IFN: Pegylated interferon; SVR: Sustained virological response; RVR: Rapid virological response; NA: Not applicable.
of serum vitamin D levels with either the risk or the incidence and mortality rates of HCC caused by chronic viral hepatitis.

In a recent cross-sectional study from Vietnam a high prevalence of vitamin D deficiency was observed in HBV-related HCC patients compared to healthy individuals, and vitamin D deficiency was associated with unfavorable courses of the disease[4]. In chronic hepatitis C, distinct single nucleotide polymorphisms in genes related to the vitamin D signaling pathway, including cytochrome P450 family 2 subfamily R member 1 (CYP2R1, encoding the liver 25-hydroxylase (rs1993116, rs10741657)), 7-dehydrocholesterol reductase (DHCR7, encoding the 7-dehydrocholesterol reductase (rs7944926, rs12785878)) were investigated and an association between the human genotypes and reduced 25(OH)D3 serum levels in the development of HCC-related HCC was observed[131]. Another study indicated that vitamin D might be a potential biomarker for the development of HCC in patients with chronic hepatitis C[132]. In addition, a large prospective cohort study examined the association between serum vitamin D levels and the incidence of liver cancer among 520000 participants in ten European countries[76]. During more than 10 years of follow-up, a total of 204 HCC cases, mostly due to HBV and HCV infection, were identified. Serum levels of 25(OH)D were inversely associated with the risk of HCC. This finding was in agreement with another prospective study showing that lower serum 25(OH)D3 concentrations in 200 HCC patients, also caused largely by HBV and HCV infection, were associated with poor outcomes and end stages of HCC, classified according to the BCLC (Barcelona Clinic Liver Cancer) staging system and the Cancer of the Liver Italian Program (CLIP) score[133]. Overall survival rates of HCC patients with serum 25(OH)D3 levels of ≤ 10 ng/mL were significantly lower than those of patients with serum levels > 10 ng/mL. In addition, the levels were independently associated with the overall survival in a multivariate analysis[133]. Apparently, vitamin D deficiency is associated with tumor progression and a poor prognosis in HCC patients. Although the results suggest this role of vitamin D in HCC, it remains to be determined further whether the association holds and is causal.

VITAMIN D AND ITS ANALOGUES IN HCC PREVENTION

Vitamin D has numerous additional functions in the prevention of cancer due to its antiproliferative, pro-apoptotic, differentiating, antiangiogenic and antiinvasive properties[134-136]. Several in vitro and in vivo studies have suggested that vitamin D inhibits growth of HCC cell lines and effectively suppresses DNA damage[137-138]. Data from several preclinical studies have assigned an important role of vitamin D in prevention and treatment of certain malignancies[133,140,141]. Furthermore, in a randomized clinical trial (ClinicalTrials.gov; identifier NCT00352170) vitamin D and calcium supplementation have substantially reduced the risk of cancer[142]. These observations have raised increasing awareness of ensuring adequate vitamin D levels in order to reduce the risk of neoplasms.

The vitamin D analogues paricalcitol, doxercalciferol and tacalcitol have meanwhile been approved for application in patients with osteoporosis and psoriasis[143] and analogues of vitamin D receptor activators such as maxacalcitol (OCT), 16-ene analogs, 19-nor analogs, LG190119 have been tested in preclinical studies on diabetes, several cancers (e.g., leukemia, colon, breast, prostate, pancreatic cancer)[144-146]. With regard to HCC, the vitamin D analogue seocalcitol, which has proven effects in animal models of cancer[147-149] has been investigated in patients with inoperable HCC in a phase II clinical trial (ClinicalTrials.gov; identifier NCT00051532)[150]. Seocalcitol may be effective in the treatment of HCC, especially in early stages when prolonged treatment can be instituted. In addition, seocalcitol is 50-200 times more effective in inhibiting proliferation and differentiation of human cancer cell lines than natural vitamin D3[151].

In a phase 1 clinical trial the safety of high doses of vitamin D administered in lipiodol and directly injected into the hepatic artery of 8 patients with refractory HCC was evaluated[152]. Lipiodol is an oily substance consisting of unsaturated esters enriched in iodine used as a vector for chemoembolization or internal radiotherapy in unresectable HCCs[153]. Although this study was not specifically designed as a pilot study of vitamin D efficacy in HCC, the results showed a certain stabilization of tumor marker levels, suggesting some efficacy of vitamin D[152]. Another clinical trial (ClinicalTrials.gov; identifier NCT01575717) is currently performed to assess the effect of two different doses of vitamin D3 (2000 IU vs 4000 IU) on serum 25OHD levels in HCC patients on liver transplant lists. Nevertheless, so far, there are no approved vitamin D analogues available for supportive HCC treatment.

CONCLUSION

Vitamin D deficiency is very common and frequently observed in HBV- and HCV-associated chronic liver diseases. It negatively affects the clinical courses and promotes progression of liver diseases, but causal relations are still not fully understood. Several lines support that sufficient vitamin D levels play an important role during antiviral treatment of HBV and HCV infections. However, the effect of vitamin D supplementation in combination with IFN-RBV based therapy on virological responses is still unclear. Various non-skeletal effects of vitamin D, including antiinflammatory, antifibrotic and antitumor properties have emphasized an association of vitamin D deficiency with unfavorable liver disease outcomes, in particular, liver cirrhosis. There is currently no approved
recommendation for vitamin D supplementation and vitamin D analogues as supportive adjuvant treatment regimes in viral hepatitis and related chronic disorders. Further randomized, placebo-arm studies need to be performed in order to confirm whether supplementation of vitamin D or vitamin D analogues improve SVRs in combination with specific antiviral treatment strategies in HBV or HCV infections.

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