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REVIEW

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 mg/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

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[1]. 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 effects 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[2,3] and frequently observed in chronic liver diseases; vitamin D constraints contribute to disease progression in chronic hepatitis B[4,5], chronic hepatitis C[6,7], but also to non-alcoholic fatty liver disease (NAFLD)[8-10]. 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[11-14].

The prevalence of vitamin D insufficiency in patients with HBV and HCV infection covers the broad range from 16% up to 100%[5,15,16]. 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[6,17-23] (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[24-29].

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[30]. Adequate vitamin D levels are required for bone growth and remodeling of osseous structures by osteoblasts and osteoclasts, thus protecting from osteoporosis[30,31]. 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[32], but also on macrophages as well as on T and B cells[33,34]. Vitamin D is involved in physiological processes through VDR activation, including the regulation of immune responses, cell growth and cell differentiation[35,36]. Therefore, vitamin D is considered a powerful modulator of pathophysiological mechanisms in several infectious diseases, cancers and metabolic disorders[6,37-39].

Vitamin D occurs as vitamin D3 (25(OH)D_3; cholecalciferol) and vitamin D2 (25(OH)D2; 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[3,30]. Vitamin D2 does not depend on sunlight and only minute amounts of vitamin D2 are derived from plants[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[1]. 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[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[1,42].

An appropriate duration of exposure to ultraviolet B (UVB) radiation is crucial in cutaneous vitamin D production[1,43], and a strong correlation exists between vitamin D serum levels, UVB exposure and geographical residence[1,44,45]. As latitudes increase, disposable amounts of vitamin D decrease[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[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[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[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[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)[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[1,51,52]. Vitamin D inadequacy involves both deficiency and insufficiency and constitutes an underestimated health factor in many populations[53]. In developed countries, vitamin D deficiency is very common, with almost half of the population affected[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[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[49], respectively.

Vitamin D deficiency is common in western and northern countries, but also in Africa and Asia[4,54-58]. Serum levels in Asian populations were assessed in three large cross-sectional studies in China (n = 3262)[56], South Korea (n = 6925)[55], and in Thailand (n = 2641)[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%)[55]. In contrast, a significantly lower prevalence of deficiency of 6% only was observed in Thailand[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%[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[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[66]. Other studies also consistently indicate that vitamin D deficiency is more prevalent in immigrants from Africa to the United States and to Europe[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[69-71] 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]. Vitamin D deficiency may contribute to liver damage through increased inflammation and fibrosis[6,39]. 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[4,8,10,12,60,78-82]. 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[84,85]. Notably, vitamin D deficiency may also contribute to reduced antiviral responses in IFN/RBV treatment of hepatitis B and C[6,19,28,86]. 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[9,19,78]. 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[4,6,80].

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[23,93].

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 < 30: insufficiency ⩾ 30: sufficiency	21 55 24	Vitamin D insufficiency highly prevalent in treatment-naïve patients with chronic hepatitis B Baseline levels predict virologic response at week 104 after treatment initiation (67% in the insufficiency group *vs* 82% in the sufficient group)	Yu *et al*[29], 2017
China CHB (*n* = 133)	Cross-sectional	NA	< 14: severe deficiency ⩾ 14: deficiency < 30 sufficiency	27 66 7	Vitamin D deficiency significantly associated with HBV genotype B	Zhu *et al*[93], 2016
Vietnam CHB (*n* = 165) LC (*n* = 127) HCC (*n* = 108)	Cross-sectional	NA	< 10: severe deficiency < 20: deficiency < 30: insufficiency ⩾ 30: sufficiency	10.4 41.5 32.4 15.7	Vitamin D insufficiency frequent among HBV patients Reduced vitamin D levels significantly associated with clinical progression of LC Vitamin D levels and HBV DNA loads strongly and inversely correlated	Hoan *et al*[4], 2016
China CHB (*n* = 115) LC (*n* = 115) HC (*n* = 115)	Cross-sectional	NA	< 10: deficiency < 20: insufficiency ⩾ 20: sufficiency	83 17 0	Vitamin D levels significantly lower in LC compared to CHB and HC groups ($P < 0.001$) Child-Pugh score independently associated with vitamin D deficiency (cutoff < 10 ng/mL)	Zhao *et al*[5], 2016
South Korea CHB (*n* = 110) Other CLD (*n* = 97)	Cross-sectional	NA	< 10: deficiency < 20: insufficiency ⩾ 20: sufficiency	34.8 45.4 19.8	Vitamin D deficiency independently associated with advanced liver fibrosis	Ko *et al*[154], 2016
Iran CHB (*n* = 84)	Cross-sectional	NA	< 10: deficiency < 20: insufficiency ⩾ 20: sufficiency	17.9 34.5 47.6	No significant association of vitamin D levels in treated and treatment-naïve patients	Sali *et al*[155], 2016
Multicenter in Europe, Asia and North America CHB (*n* = 737)	Randomized, open-label, active-controlled clinical trial	48 wk of TDF + PegIFN 16 wk of TDF + PegIFN followed by 32 wk of TDF 48 wk PegIFN or 120 wk of TDF	< 20: deficiency < 30: insufficiency ⩾ 30: sufficiency	58 35 7	Reduced vitamin D levels highly prevalent among untreated CHB patients Low baseline levels of vitamin D associated with high HBV DNA loads, abnormal ALT at week 48 independent of treatment groups Baseline vitamin D levels not associated with treatment outcomes	Chan *et al*[19], 2015
China CHB (*n* = 426)	Cross-sectional	NA	< 32 insufficiency ⩾ 32 sufficiency	82 18	Vitamin D deficiency common among patients with CHB and associated with adverse clinical outcomes	Wong *et al*[78], 2015
China CHB (*n* = 242)	Cross-sectional	NA	< 20: deficiency < 30: insufficiency ⩾ 30: sufficiency	8.7 31.4 60	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	Yu *et al*[23], 2015
China CHB (*n* = 133)	Cross-sectional	NA	< 14: deficiency < 30: insufficiency ⩾ 30: sufficiency	27 66.2 6.8	Higher prevalence of vitamin D insufficiency in HBV genotype B patients than in genotype C patients Vitamin D levels not associated with other clinical parameters	Zhu *et al*[93], 2016
Germany CHB (*n* = 203)	Cross-sectional	NA	< 10: deficiency < 20: insufficiency ⩾ 20: sufficiency	34 47 19	HBV DNA viral loads as strong predictor of low vitamin D levels in CHB patients	Farnik *et al*[12], 2013

Egypt OBI (n = 16) CHB (n = 52)	Cross-sectional	NA	< 10: deficiency < 30: insufficiency ⩾ 30: sufficiency	OBI: 12.5 CHB: 40.4 OBI: 62.5 CHB: 59.6 OBI: 25 CHB: 0	Vitamin D levels significantly higher in OBI than in CHB patients Serum level of vitamin D inversely correlated with HBV DNA loads	Mashaly *et al*[156], 2016
China CHB (n = 128)	Cross-sectional	NA	< 10: deficiency < 20: insufficiency ⩾ 20: sufficiency	13.3 61.7 25	Vitamin D levels negatively correlated with HBV DNA loads Effective antiviral therapy might increase the level of vitamin D in CHB patients	Chen *et al*[11], 2015
Iran CHB (n = 173)	Cross-sectional	NA	< 10: deficiency < 20: insufficiency ⩾ 20: sufficiency	58 39 3	Vitamin D levels inversely correlated with HBV DNA levels	Mohamadkhani *et al*[89], 2015

CHB: Chronic hepatitis B; LC: Liver cirrhosis; HCC: Hepatocellular carcinoma; CLD: Chronic liver disease; OBI: Occult hepatitis B infection; NA: Not applicable.

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[7,16,20,94], 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)[86].

To date, five meta-analyses have described an association of baseline vitamin D levels with SVR[28,86,95-97] (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 ⩾ 20 ng/mL (OR = 0.5, 95%CI: 0.3-0.9)[86]. 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[28]. In contrast, Kitson *et al*[95] reported that baseline 25(OH)D levels were not associated with SVR in Peg-IFN/RBV treatment, also regardless of the viral genotype involved[95]. 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)[17,98] up to 95% for HCV genotype 2 and 3 infections (77% in the non-supplemented control group)[21]. 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[28]. 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[98]. In contrast, other studies showed inconsistent results for the HCV genotypes 4 and 1[15]. 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[15,17,21,26]. Although vitamin D may be relevant in the treatment of chronic hepatitis C, further randomized, placebo-armed studies are required in order to confirm whether vitamin D supplementation in fact improves the SVR in combination with IFN in HCV infections.

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 676000 in 1980 to more than 1 million in 2010, accounting for approximately 2% of all causes of death[99]. 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[4,10,39,75,100-104]. Vitamin D deficiency reflects also hepatic dysfunction and is associated with mortality in patients with LC, regardless of underlying causes[102,104].

The association of vitamin D with LC has been more intensively discussed in chronic hepatitis C and in NAFLD patients, rather than in chronic hepatitis B. A recent meta-analysis included seven studies in order to assess vitamin D serum levels and advanced liver

Table 2 Representative studies regarding vitamin D status in chronic hepatitis C virus patients

Study population Diagnosis Sample size (*n*) Study objective	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 ⩾ 30: sufficiency	73 27	Low vitamin D linked to severe fibrosis and low SVR in IFN-based treatment	Petta *et al*[6], 2010
United States CHC (*n* = 218) LC (*n* = 123) Non-LC (*n* = 95)	Prospective	12 wk after cessation of antiviral therapy SVR12: defined as a viral load undetectable or below the level of detection at week 12 after cessation of antiviral treatment	< 20: deficiency < 30: insufficiency ⩾ 30: sufficiency	43 33 24	Vitamin D deficiency associated with HCV–related LC and with hepatic function No significant association between SVR12 and serum vitamin D levels at baseline	Backstedt *et al*[18], 2017
Switzerland CHC (*n* = 269) HCV genotypes 1-4	Case-control	NA	< 30: deficiency ⩾ 30: sufficiency	74 26	No significant association between SVR and serum vitamin D levels irrespective of genotypes	Lange *et al*[20], 2012
Spain CHC genotypes 1-4 (*n* = 182)	Cross-sectional	NA	< 20: deficiency < 30: insufficiency ⩾ 30: sufficiency	36 41 23	Vitamin D deficiency not related to biochemical and virological variables or to the stage of fibrosis stage	Ladero *et al*[157], 2013
Northern Italy CHC (*n* = 211) HCV genotypes 1-5	Prospective	24 wk after cessation of antiviral therapy SVR24: defined as a viral load undetectable or below the level of detection at week 24 after cessation of antiviral treatment	< 20: deficiency ⩾ 20: sufficiency	46.4 53.6	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	Bitetto *et al*[25], 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 difference in vitamin D levels in patients with and without progression of HCV-associated liver disease	Corey *et al*[158], 2012
Multicenter study, Japan CHC (*n* = 247) HCV genotype 1b	Case-control	NA	< 20: deficiency < 30: insufficiency ⩾ 30: sufficiency At baseline: 22(6–64)	Not stated	NS5A Y93H and L31M resistance-associated variants associated with vitamin D deficiency	Okubo *et al*[159], 2016
Multicenter study, France HCV-HIV coinfection (*n* = 189)	Cross-sectional	NA	< 30: deficiency ⩾ 30: sufficiency	85 15	Low serum vitamin D levels correlated with liver fibrosis as assessed by FibroTest No association between SVR rate to IFN-based therapy and baseline vitamin D levels	Terrier *et al*[7], 2011
Japan CHC (*n* = 619)	Cross-sectional	NA	< 20: deficiency < 30: insufficiency ⩾ 30: sufficiency	47 36.7 16.3	Vitamin D levels influenced by gender, age, hemoglobin level, albumin and seasonality	Atsukawa *et al*[160], 2015
Egypt CHC (*n* = 70) controls (*n* = 50)	Cross-sectional	NA	At baseline Cases: 18.6 Control: 56	NA	Vitamin D decreased in HCV patients	Reda *et al*.[161], 2015
Australia CHC (*n* = 274) HCV genotype 1	Case-control	NA	< 20: deficiency < 30: insufficiency ⩾ 30: sufficiency	16 48 36	Baseline vitamin D levels not associated with SVR or fibrosis stage in HCV genotype 1 but deficiency associated with high activity	Kitson *et al*[16], 2013
Japan CHC (*n* = 177)	Prospective	24 wk after cessation of antiviral therapy	Not stated	NA	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	Atsukawa *et al*[162], 2014

Egypt CHC (n = 101) HCV genotype 4 Vitamin D supplementation group (n = 50), controls (n = 51)	Randomized prospective	Until 72 wk from start of antiviral therapy SVR was assessed at week 72 from initiation of antiviral treatment	< 20: deficiency ⩾ 20: insufficiency ⩾ 30: sufficiency	95 5 0	No impact of vitamin D supplementation on SVR in HCV genotype 4 patients No correlation between vitamin D levels and stage of liver fibrosis	Esmat *et al*[15], 2015
Israel CHC (n = 72) HCV genotype 1 Vitamin D supplementation group (n = 36), controls (n = 36)	Randomized prospective	24 wk after cessation of antiviral treatment	< 10: severe deficiency < 20: insufficiency ⩾ 20: sufficiency	21 59 20	Addition of vitamin D to Peg-IFNα/RBV therapy improves SVR24 (86% *vs* 42%)	Abu-Mouch *et al*[17], 2011
Israel CHC (n = 50) HCV genotype 2 and 3 Vitamin D supplementation group (n = 20), controls (n = 30)	Randomized prospective	24 wk after cessation of antiviral treatment	< 12: deficiency < 32: insufficiency ⩾ 32: sufficiency	26 54 20	Addition of vitamin D to IFNα/RBV therapy improves SVR24 (95% in treated group *vs* 77% in controls)	Nimer *et al*[21], 2012
France CHC (n = 516) HCV genotype 1	Randomized controlled	Until 72 wk from initiation of antiviral therapy	Not stated	Not stated	No impact of vitamin D levels on efficacy of antiviral therapy in naïve genotype 1 HCV patients	Belle *et al*[24], 2017
Egypt CHC (n = 66) Vitamin D group (n = 20) controls (n = 30)	Randomized prospective	24 wk after cessation of antiviral treatment	< 12: deficiency < 32: insufficiency ⩾ 32: sufficiency	33.3 43.3 23.4	Addition of vitamin D to conventional Peg-IFNα/RBV therapy improved SVR24	Eltayeb *et al*[26], 2015
Germany CHC (n = 468) HCV genotypes 1-3	Retrospective	24 wk after cessation of antiviral treatment	< 30: deficiency ⩾ 30: sufficiency	66 34	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)	Lange *et al*[80], 2011
Taiwan CHC (n = 132) HCV genotype 1-2	Retrospective	SVR was assessed at week 48 (HCV genotype 1) and at week 24 (HCV genotype 2) from initiation of antiviral treatment	Not stated	Not stated	Vitamin D can suppress HCV replication in hepatic cell lines Vitamin D serum levels associated with both SRV and RVR to Peg-IFNα based therapy	Jee-Fu *et al*[13], 2017
Germany CHC (n = 398) HCV genotype 1	Retrospective	SVR was assessed at week 24 from initiation of antiviral treatment	At baseline 18.7 (3-84.3)	Not stated	Addition of vitamin D to Peg-IFNα/RBV therapy for treatment-naïve patients with chronic HCV genotype 1: no significant association with SVR	Grammatikos *et al*[94], 2014
Austria HCV-HIV coinfection (n = 65)	Retrospective	24 wk after cessation of antiviral treatment	< 10: deficiency < 30: insufficiency ⩾ 30: sufficiency	57 23 20	Low vitamin D levels may impair virological response to Peg-IFNα/RBV therapy, especially in difficult-to-treat patients	Mandorfer *et al*[163], 2013
Italy CHC (n = 42) Vitamin D supplementation group (n = 15) controls (n = 27)	Retrospective	SVR was assessed at week 48 from initiation of antiviral treatment	< 10: severe deficiency < 20: insufficiency ⩾ 20: sufficiency	Not stated	Vitamin D supplementation improves SVR rate following Peg-IFNα/RBV therapy (54% in vitamin D group *vs* 18.5% in control group)	Bitetto *et al*[98], 2011a
Multicenter study, United States CHC (n = 1292) HCV genotype 1	Retrospective	24 wk after cessation of antiviral treatment	< 12: severe deficiency < 20: insufficiency ⩾ 20: sufficiency	19 48 33	Higher vitamin D levels not associated with SVR in Peg-IFNα/RBV therapy	Loftfield *et al*[27], 2016
Meta-analysis 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 < 20: deficiency < 30: insufficiency ⩾ 30: sufficiency	Not stated	Low vitamin D levels related to ALF Low vitamin D levels at baseline in CHC patients were associated with a higher likelihood of having ALF and lower odds of achieving SVR	Garcia-Alvarez *et al*[86], 2014

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-IFNα/RBV therapy, regardless of genotype Effect of vitamin D supplementation on SVR to be determined	Kitson *et al*[95], 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*[97], 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 High SVR rates observed in CHC patients supplemented with vitamin D, regardless of genotype	Villar *et al*[28], 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*[96], 2017

CHC: Chronic hepatitis C; LC: Liver cirrhosis; ALF: Acute liver fairlure; IFNα: Interferon alpha; RBV: Ribavirin; Peg-IFN: Pegylated interferon; SVR: Sustained virolagical response; RVR: Rapid virological response; NA: Not applicable.

fibrosis in patients with chronic hepatitis C. Low vitamin D levels were related to advanced fibrosis, with two cutoff values set of either 10 ng/mL (OR = 2.5, 95%CI: 1.2-4.7) or 30 ng/mL (OR = 2.2, 95%CI: 1.2-4.0)[86]. With regard to chronic hepatitis B, two studies have recently reported a strong and inverse correlation of serum vitamin D levels with progression of LC[45]. Abnormal vitamin D metabolism in LC was described almost four decades ago[105,106]. It was mainly attributed to impaired hydroxylation resulting from impaired liver function[100]. In LC patients, vitamin D deficiency is also caused by dietary lacks, malabsorption and decreased hepatic production of vitamin D binding protein[75,107,108].

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, prostrate, and ovarian cancers[124-130]. Not much information is, however, available on an association

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 HCV-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[137-139]. Data from several preclinical studies have assigned an important role of vitamin D in prevention and treatment of certain malignancies[135,140,141]. 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 polyunsaturated 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-armed 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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