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META-ANALYSIS

Association between vitamin D and hepatitis C virus infection: A meta-analysis

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Abstract

AIM: To evaluate the association between 25-hydroxyvitamin D [25(OH)D] and sustained virological response (SVR) in hepatitis C virus (HCV) infected individuals.

METHODS: Relevant studies were identified by systematically searching MEDLINE databases up to March 2012 and abstracts of the European and American Congress of Hepatology conducted in 2011. Studies must provide information on SVR and the levels of 25(OH)D_3 and/or 25(OH)D_2 [henceforth referred to as 25(OH)D] in sera samples from HCV infected individuals. The inclusion criteria were: clinical studies that included HCV infected patients aged older than 18 years regardless of HCV genotype or ethnic group; provided information on SVR rates; and were reported in the English language as full papers. Due to the heterogeneity of studies in categorizing serum vitamin D levels, a cut-off value of 30 ng/mL of serum 25(OH)D was used. Heterogeneity was assessed using I^2 statistics. The summary odds ratios with their corresponding 95%CI were calculated based on a random-effects model.

RESULTS: Overall, 11 studies (8 observational and 3 interventional) involving 1575 individuals were included and 1117 HCV infected individuals (71%) showed low vitamin D levels. Most of the studies included mono-infected HCV individuals with the mean age ranging from 38 to 56 years. Four studies were conducted in human immunodeficiency virus/HCV infected individuals. Regarding vitamin D measurement, most of the studies employed radioimmunoassays (n = 5) followed by chemiluminescence (n = 4) and just one study employed high performance/pressure liquid chromatography (HPLC). Basal vitamin D levels varied from 17 to 43 ng/mL in the studies selected, and most of the HCV infected individuals had genotype 1 (1068/1575) with mean viral load varying from log 4.5-5.9 UI/mL. With regard to HCV treatment, most of the studies (n = 8) included HCV individuals without previous treatment, where the pooled SVR rate was 46.4%. High rates of SVR were observed in HCV individuals with vitamin D levels above 30 ng/mL (OR = 1.57; 95%CI: 1.12-2.2) and those supplemented with vitamin D (OR = 4.59; 95%CI: 1.67-12.63) regardless of genotype.

CONCLUSION: Our results demonstrated high prevalence of vitamin D deficiency and high SVR in individuals with higher serum vitamin D levels or receiving vitamin D supplementation.

Key words: Vitamin D; Hepatitis C; Therapy; Meta-analysis; Sustained virological response

Core tip: High vitamin D levels (above 30 ng/mL) or

supplementation are associated with sustained virological response in hepatitis C virus infected individuals.

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INTRODUCTION

Viral hepatitis C is a serious public health problem worldwide infecting more than 130 million individuals[1]. Treatment of hepatitis C virus (HCV) infection is usually carried out using pegylated interferon (PEG-IFN) and ribavirin (RBV) for 24 wk for HCV genotypes 2 or 3, or 48 wk for HCV genotype 1 and the main objective of HCV therapy is a sustained virologic response (SVR), defined as an undetectable serum HCV-RNA level at 24 wk after the end of therapy. Rates of SVR range from 60%-70% in chronic hepatitis C (CHC) patients with genotypes 2 and 3, but is less than 50% in patients with genotype 1 using conventional therapy[2].

Recently, studies were conducted to analyze the influence of genetic and metabolic factors in antiviral response[3-5], and a recent review showed that vitamin D levels can influence HCV treatment[6]. Vitamin D itself is considered biologically inactive and is hydroxylated to 25-hydroxyvitamin D [25(OH)D] in the liver. 25(OH)D is the main circulating vitamin D metabolite and is used for classification of the vitamin D status[7,8]. In the kidney, 25(OH)D is converted to 1,25-dihydroxyvitamin D [1,25(OH)D] by 1-alpha-hydroxylase, however, it has been demonstrated that this conversion can occur in many extra-renal tissues including the liver[7,9]. Finally, 25(OH)D or 1,25$(OH)_2$D bind to the ubiquitously expressed vitamin D receptor (VDR), which regulates approximately 3% of the human genome[10]. In this context, vitamin D deficiency has been associated with an increased risk of cancer[7,11], cardiovascular[12,13], autoimmune[14,15] and infectious diseases[6,16].

Due to these facts, there is great research interest in the role of vitamin D status in various infectious diseases. Some studies have shown that high levels of serum vitamin D level are an independent predictor of SVR following anti-viral therapy, and higher SVR is achieved with vitamin D supplementation in CHC individuals[17-22]. However, Lange *et al*[18] found that vitamin D deficiency was associated with a lower SVR rate only in CHC genotype 2/3 patients (treated with PEG-IFN and RBV for 24 wk), but not in CHC genotype 1 patients. Moreover, Jazwinski *et al*[23] found no association between vitamin D levels and SVR in 82 African American genotype 1 CHC-naïve patients, treated with PEG-IFN and RBV.

As vitamin D has an uncertain clinical value in HCV infected individuals and taking into consideration the limitations of previous reviews, we conducted an updated systematic review and meta-analysis to comprehensively assess vitamin D deficiency regarding antiviral therapy and the influence of vitamin D supplementation on SVR.

MATERIALS AND METHODS

Identification of studies

A broad search string was used in MEDLINE in order to identify relevant studies (all languages, all available years, search last completed 31.03.12) using the following search terms: [("vitamin D" [MeSH Terms] or "vitamin D" [All Fields] or "ergocalciferols" [MeSH Terms] or "ergocalciferols" [All Fields]) or ("calcifediol" [MeSH Terms] or "calcifediol" [All Fields] or "calcidiol" [All Fields]) or ("25(OH)D" [All Fields] or "25$(OH)D_2$" [All Fields] or "25$(OH)D_3$" [All Fields]) and [("HCV" [MeSH Terms]) or ("HCV" [All Fields] or "Hepacivirus" [All Fields]) or "Hepacivirus" [MeSH Terms])]. Abstracts from the European and American Association Congress of Hepatology (EASL 2011 and AASLD 2011) were also included in order to give more data on this theme.

Potentially relevant papers were accessed in order to review the abstract and/or full text. Only fully published articles were considered. Duplicate publications were deleted. Two researchers independently performed the literature search and data abstraction with regard to the inclusion and exclusion criteria by reading titles and abstracts. When reading titles and abstracts did not allow identification of eligible studies, articles were read in full. Only original studies conducted in humans were considered for the review. Thus, reviews and letters to the editor were excluded in the analysis, but read in full to identify potential relevant original studies. Disagreements between the two observers were resolved by discussion.

The following data were extracted: year of publication, number of patients, age, vitamin D levels, SVR percentage, method of measurement of vitamin D, HCV genotype, HCV viral load, percentage of naive patients. When such data were not explicitly reported, they were derived from data provided in the articles or requested from the authors through personal contacts, wherever possible.

Eligibility criteria

The study must provide information on SVR against HCV and the levels of 25$(OH)D_3$ and/or 25$(OH)D_2$ [henceforth referred to as 25(OH)D] in sera samples from HCV infected individuals. The inclusion criteria were: clinical studies that included HCV infected patients aged older than 18 years regardless of HCV genotype or ethnic group; provided information on SVR rates; and were reported in the English language as full papers. Studies were excluded if they met the following criteria: they did not provide information on 25(OH)D level, HCV status and/or SVR; basic studies; letters / case reports, or articles not reporting outcomes of interest or

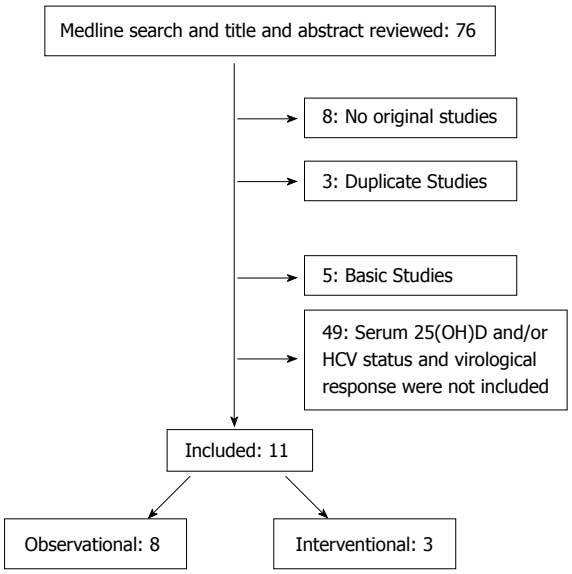

Figure 1 Prisma flowchart for the selection of publications for the systematic review and meta-analysis. HCV: Hepatitis C virus; 25(OH)D: 25-hydroxyvitamin D.

primary data (editorials, reviews).

Statistical analysis

Data were extracted from each paper and compiled for hypovitaminosis D and HCV antiviral response. Statistical analysis was performed using the Meta-Disc software 1.4[24], considering: (1) a summary of data from individual studies; (2) an investigation of the homogeneity of the studies both graphically and statistically; (3) calculation of clustered indices; and (4) exploration of heterogeneity. The meta-analysis was performed using the random-effect model by the Der Simonian and Laird method. Heterogeneity was tested for each planned analysis using the Cochran-Q heterogeneity test and measured using χ^2 and I^2 tests, and statistical significance was considered to be present when $P < 0.05$.

RESULTS

Description of studies included in the meta-analysis

A flow diagram of the search process is shown in Figure 1. The total search yielded 61 articles and 15 abstracts, after accessing the title and abstract, 65 studies were excluded for the following reasons: 49 did not provide data on vitamin D level, HCV status and/or SVR; 5 were basic studies; 8 were reviews, letters or editorials; 3 were duplicate studies.

Eleven studies involving 1575 individuals were included in this study[17,18,20-23,25-29]. The main characteristics of these studies are shown in Tables 1 and 2. Most of the studies were conducted in Europe and only one in North America. Eight studies evaluated vitamin D levels before and after antiviral therapy[17,18,21-23,25,28,29], while three were interventional studies where vitamin D supplementation was conducted[20,26,27]. Most of the studies included mono-infected HCV individuals with the mean age ranging from 38 to 56 years. Four studies were conducted in human immunodeficiency virus/HCV infected individuals[22,25,28,29]. With regard to vitamin D measurement, most of the studies employed radioimmunoassays (n = 5) followed by chemiluminescence (n = 4) and just one study employed HPLC. Basal vitamin D levels varied from 17 to 43 ng/mL in the studies selected, and most of the HCV infected individuals had genotype 1 (1068/1575) with mean viral load ranging from log 4.5-5.9 UI/mL. With regard to HCV treatment, most of the studies (n = 8) included HCV individuals without previous treatment, where the pooled SVR rate was 46.4%.

Vitamin D levels and sustained virological response

Different cut-off values for vitamin D were employed and in order to reduce this heterogeneity, a value of 30 ng/mL was used as the cut-off value, as most of the studies used this value to define vitamin D. Among the observational studies, a total of 1411 individuals were included. Using 30 ng/mL as cut-off value, the χ^2 test of heterogeneity was high (P = 0.3799). There was a significant difference regarding vitamin D levels and SVR, where individuals with values higher than 30 ng/mL had a higher level of SVR. Using the random effects model by the Der Simonian and Laird method, the odds ratio was 1.57 (95%CI: 1.12-2.2) regardless of genotype (Figure 2).

A total of 1117 HCV infected individuals had low vitamin D levels (cut-off value of 30 ng/mL) representing 71% of the population studied, and most of these individuals were in the interventional studies (79.3%) as compared with the observational studies (69.9%). The highest association between vitamin D levels and SVR was observed in the study by Petta *et al*[17] as demonstrated by the OR and CI (OR = 1.96; 95%CI: 1.02-3.79).

Vitamin D supplementation and sustained virological response

With regard to vitamin D supplementation in HCV infected individuals in the interventional studies, the pooled estimation from 3 different studies indicated that SVR rates were higher in treated HCV individuals compared with non-treated HCV individuals. In the meta-analysis of SVR in the interventional studies where the cut-off value was 30 ng/mL, the OR was 4.59 (95%CI: 1.67-12.63) regardless of genotype (Figure 3). The test of heterogeneity (Cochran-Q = 2.86; df = 2; P = 0.2395), inconsistency I^2 = 30%, and t = 0.2454. Of these studies, the OR values were higher in the study where only genotype 1 HCV individuals were included[27] (8.68) compared to the other 2 studies, one study included genotypes 1 and non-1[20] (1.90) and the other study recruited genotype 2 and 3 HCV infected individuals (5.78)[26].

Quality of the studies

Low heterogeneity was observed in the studies included in this meta-analysis according to the Q value for the observational (7.49) and interventional studies (2.86). The possible sources of heterogeneity across the studies were

Table 1 Summary of the general characteristics of the included studies regarding vitamin D and hepatitis C virus (mean ± SD)

Study	Country	Mean age (yr)	Sample Size	Design	25(OH)D measurement	Basal mean vitamin D levels (ng/mL)
Nimer *et al*[26]	Israel	Treated: 48 ± 14 Non treated: 45 ± 10	Treated: 20 HCV infected individuals Non treated: 30 HCV infected individuals	Prospective randomized study	Radioimmunoassay (Diasorin)	Treated: 20 ± 8 Non treated: 19 ± 6
Milazzo *et al*[25]	Italy	45	93 HIV/HCV	Retrospective case-control study (clinical samples)	Radioimmunoassay (IDS)	Cases: 23.1 (15.3-35.3)
Abu-Mouch *et al*[27]	Israel	Treated: 47 ± 11 Non treated: 49 ± 7	Treated: 36 HCV infected individuals Non treated: 36 HCV infected individuals	Prospective randomized study	Radioimmunoassay (Diasorin)	Treated: 19 ± 6 Non treated: 20.5 ± 9
Bitetto *et al*[20]	Italy	Treated: 56 (42-61) Non treated: 52 (23-67)	Treated: 15 HCV infected individuals Non treated: 27 HCV infected individuals	Prospective randomized study	Chemiluminescence immunoassay (Diasorin)	NA
Soumekh *et al*[28]	United States	NA	88 HIV/HCV infected individuals	Prospective study (clinical samples)	Chemiluminescence immunoassay (Diasorin)	NA
Reiberg *et al*[29]	Austria	38	84 HIV/HCV infected individuals	Cohort (clinical sample)	NA	21.9 ± 13.8
Jazwinski *et al*[23]	United States	NA	82 HCV infected individuals	Cohort (clinical sample)	Chemiluminescence immunoassay (Diasorin)	NA
Lange *et al*[18]	Germany	45	468 HCV infected individuals	Cohort (clinical sample)	Radioimmunoassay (Diasorin)	17 (3-80)
Terrier *et al*[22]	France	39.5	189 HIV/HCV infected individuals	Cohort (clinical samples)	Radioimmunoassay (Diasorin)	18.5 ± 9.8
Bitetto *et al*[21]	Italy	47	211 HCV individuals	Cohort (clinical samples)	Chemiluminescence immunoassay (Diasorin)	20.7 (2.1-59.6)
Petta *et al*[17]	Italy	52	Cases: 196 HCV infected individuals	Transversal case-control (clinic and community sample)	HPLC	25.0 ± 9.9

NA: Not available as mean value; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; HPLC: High performance/pressure liquid chromatography; 25(OH)D: 25-hydroxyvitamin D.

also explored using meta-regression analysis with the following co-variates as predictor variables: HCV genotype (1 and non-1); previous treatment (yes or no); Origin (Europe or America); method of vitamin D determination (HPLC, chemiluminescence or radiomunoassay). None of these variables interfered with the levels of vitamin D according SVR (data not shown). It is likely that this occurred because most of the studies were from Europe, including HCV genotype I individuals without previous treatment.

Although low heterogeneity was found, it was not possible to ensure high quality of all studies included in this meta-analysis. Some studies did not provide relevant data such as, mean age of the population included[23,28], mean basal vitamin D measurement[20,23,28], or mean HCV viral load[23,26-28].

DISCUSSION

Our review and meta-analysis summarize the results of eleven studies, which included a total of 1575 cases with hepatitis C, where basal 25(OH)D levels and 25(OH)D supplementation were associated with SVR in HCV patients. This updated review confirms and extends earlier results of a systematic review conducted by Cholangitis[6], who reported that vitamin D deficiency is very frequent before liver transplantation and ranges between 51% and 92%, whereas, in the liver transplantation setting, the prevalence of vitamin D deficiency is also high.

Vitamin D is metabolized by the liver and converted to 1,25-dihydroxyvitamin D_3, which is the active form of the vitamin[29,30]. Individuals with chronic liver disease may have poor conversion from vitamin D3 or any of its other biologically active metabolites[31]. Severe liver disease may increase the risk of vitamin D deficiency and/or there might be a relationship between vitamin D deficiency and fibrosis. Putz-Bankuti *et al*[32] and Baur *et al*[33] also showed that low levels of 25(OH)D are associated with fibrosis and suggested that low 25(OH)D levels may predict hepatic decompensation and mortality in patients with chronic liver failure. More recently, Gal-Tanamy *et al*[34] showed that vitamin D_3 increased the expression of the VDR and inhibited viral replication in cell culture.

Due to the observation of vitamin D deficiency in chronic liver disease patients, some studies have been conducted to evaluate vitamin D supplementation in these patients[20,26,27]. In some of these studies, it is reported that higher sunlight exposure or vitamin D supplementation should be recommended in patients with CHC[20,26,27]. In the present meta-analysis, vitamin D supplementation was related to higher SVR rates in HCV infected individuals, where the highest level was observed among genotype 1 HCV infected individuals. Although only a few studies regarding vitamin D supplementation

Table 2 Summary of included studies regarding vitamin D and hepatitis C virus aspects

Study	Sample size	HCV genotype	Mean viral load log, (UI/mL, average)	SVR (*n*)	SVR[1] (above/ below 30 ng/mL)	Previous HCV treatment
Nimer *et al*[26]	50 HCV infected individuals	Ⅱ:28 Ⅲ:22	NA	Treated: 19/20 Non treated: 23/30	19/23	None
Milazzo *et al*[25]	93 HIV/HCV infected individuals	Ⅰ:66 Non Ⅰ:27	5.8 (5.3-6.2)	21	7/14	Naïve: 31 Non responder or relapser to a previous anti-HCV therapy: 20
Abou-Mouch *et al*[27]	72 HCV infected individuals	Ⅰ:72	NA	Treated: 31 Non treated: 15	31/15	None
Bitetto *et al*[20]	42 HCV infected individuals	Ⅰ:32 Non Ⅰ:10	Treated: 5 (3-7) Non treated: 5 (3-7)	Treated: 8/15 Non treated: 5/27	6/7	All
Soumekh *et al*[28]	88 HIV/HCV infected individuals	Ⅰ or Ⅳ:77 Non Ⅰ:11	NA	13	6/7	All
Reiberg *et al*[29]	84 HIV/HCV infected individuals	Ⅰ:47 Non Ⅰ:37	4.5 (1.4-7.6)	39	11/28	None
Jazwinski *et al*[23]	82 HCV infected individuals	Ⅰ:82	NA	74	39/35	None
Lange *et al*[18]	468 HCV infected individuals	Ⅰ:317 Ⅰ:43 Ⅰ:108	5.9 (2.3-7.7)	280	17/152	None
Terrier *et al*[22]	189 HIV/HCV infected individuals	Ⅰ:84 Ⅱ or Ⅲ:73 Ⅳ:31 Other 1	5.9 (0-7)	61	9/52	None
Bitetto *et al*[21]	211 HCV individuals	Ⅰ:95 Ⅱ:63 Ⅱ:38 Ⅳ-Ⅴ:15	5 (2-7)	134	78/56	None
Petta *et al*[17]	196 HCV infected individuals	Ⅰ:196	5 (2-8)	82	26/56	None

[1]According to basal vitamin D cut-off or supplementation. NA: Not available as mean value; HCV: Hepatitis C virus; HIV: Human immunodeficiency virus; SVR: Sustained virological response.

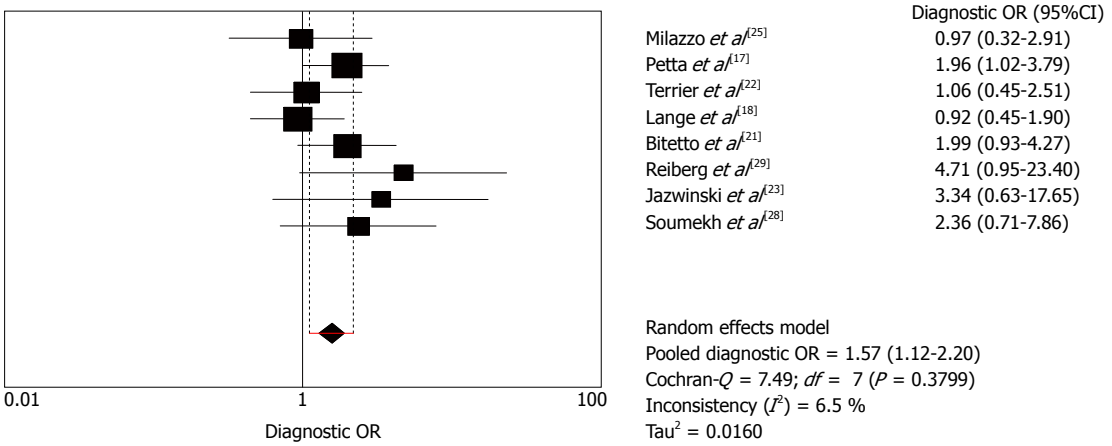

Figure 2 Meta-analysis of 8 observational studies regarding vitamin D levels and sustained virological response against hepatitis C virus infection.

fulfilled the eligibility criteria, different patterns were observed. The first study included only genotypes 2 and 3, the second included only genotype 1 and the third study involved genotypes 1, 2 and 3. Moreover, two of these studies were prospective and one was retrospective. Some limitations of these studies included the small number of patients, lack of vitamin D level assessment during therapy in the treatment and control groups, the design of prospective and randomized studies which were not placebo-controlled in one study[27], and the retrospective design of the study where immunocompromised HCV patients were supplemented with low-dose vitamin D (800 IU/d) after liver transplantation and most of the HCV patients (75%) had low vitamin D levels despite treatment[20].

In this meta-analysis, the levels of vitamin D were also associated with SVR, although different methods of vitamin D determination were used. Lai *et al*[8] demonstrated bias and variability in 25(OH)D measurements between laboratories and between different assays [qui-

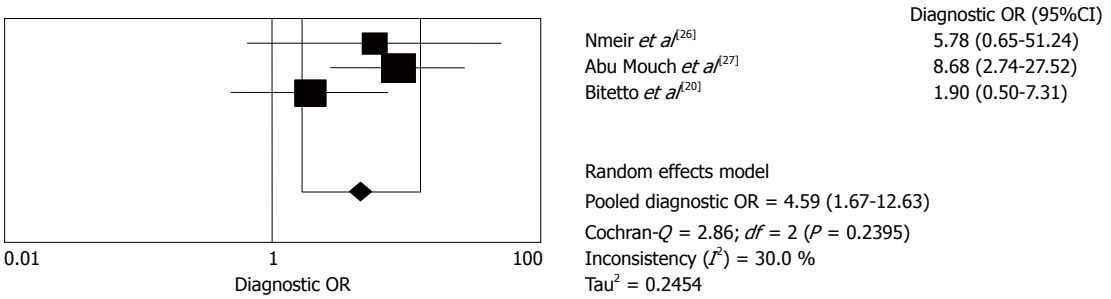

Figure 3 Meta-analysis of 3 interventional studies regarding vitamin D levels and sustained virological response against hepatitis C virus infection.

mioluminescence and liquid chromatography-tandem mass spectrometry (LC-MS/MS)] which can significantly affect clinical decision-making. In this situation, the adoption of common standards to allow assay calibration is urgently required.

Our study is the first meta-analysis of serum 25(OH)D levels and HCV infection in observational and interventional studies. Given the very small numbers of studies available to date, additional studies, ideally from different countries and populations are needed to assess potential differences in the associations between 25(OH)D and SVR for HCV. Large differences can be observed in different populations, depending on exposure to sunlight or vitamin D supplementation, and genetic differences[23]. Moreover, patients of African and Hispanic descent are less likely to respond to standard therapy[23] probably due to polymorphisms of the interleukin (IL)-28B gene, polymorphism of the VDR or vitamin D deficiency[17,35,36]. In this meta-analysis, all the individuals were Caucasian and most lived in Europe, which could explain vitamin D deficiency in this population resulting from possible low exposure to sunlight.

Meta-analysis is an important tool for revealing trends that may not be apparent in a single study. Pooling of independent, but similar studies increases precision and therefore the confidence level of the findings. A particular strength of our study is the application of advanced statistical techniques which allowed a summary of adjusted associations across studies and over the entire range of serum 25(OH)D values, despite the very heterogeneous categorization of 25(OH)D levels in the individual studies. Our study also has important limitations. First, as data on serum 25(OH)D in individuals were not available in each study, median, midpoints and mean of the groups were used for pooling. As a result, estimates of risk may have been less accurate than if data points on each individual had been used. Second, our meta-analysis was limited by the data provided in the individual studies, and although the authors tried to obtain the raw data from the articles, not all were available. Finally, although our review searched the MEDLINE database, recent Congress of Hepatology and Gastroenterology articles, and extensive checks for completeness by cross-referencing were employed, we cannot exclude the possibility that relevant studies may have been missed.

Despite its limitations, our review and meta-analysis support previous suggestions and provide the most comprehensive empirical evidence to date that basal serum 25(OH)D levels and vitamin D supplementation improves SVR in HCV infected individuals. However, available data are still sparse and in-depth analyses of these associations, in the context of additional longitudinal and prospective studies, are highly desirable to enable more precise estimates and a better understanding of the role of vitamin D in HCV infection.

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COMMENTS

Background

Hepatitis C virus (HCV) is a serious public health problem worldwide infecting more than 130 million individuals. Recently, studies have been conducted to analyze the influence of genetic and metabolic factors on antiviral response, and a recent review showed that vitamin D levels can influence HCV treatment.

Research frontiers

Vitamin D itself is considered biologically inactive and is hydroxylated to 25-hydroxyvitamin D [25(OH)D] in the liver. Some studies have suggested that vitamin D deficiency is associated with an increased risk of cancer, cardiovascular, autoimmune and infectious diseases. However, due to the limitations of previous reviews, the authors conducted an updated systematic review and meta-analysis to comprehensively assess vitamin D deficiency with regard to antiviral therapy and the influence of vitamin D supplementation on sustained virological response.

Innovations and breakthroughs

Previous individual studies demonstrated that high levels of vitamin D (above 30 ng/mL) or supplementation are associated to sustained virological response (SVR) in HCV infected individuals. In the present study, a meta-analysis of observational and interventional studies was conducted which proved that high levels of vitamin D (above 30 ng/mL) or supplementation are associated with SVR in HCV infected individuals.

Applications

By showing that basal vitamin D levels or suplementation are important for high rates of SVR in HCV patients, this study may provide a future strategy for therapeutic intervention in the treatment of HCV patients.

Terminology

HCV is an infection caused by a virus transmitted by the parenteral route. Vitamin D itself is considered biologically inactive and is hydroxylated to 25(OH)D in the liver. In the kidney, 25(OH)D is converted to 1,25(OH)$_2$D by 1-alpha-

hydroxylase, however, it has been demonstrated that this conversion can occur in many extra-renal tissues including the liver. Finally, 25(OH)D or 1,25(OH)$_2$D bind to the ubiquitously expressed vitamin D receptor, which regulates approximately 3% of the human genome.

Peer review

The authors examined the influence of vitamin D levels or supplementation among HCV infected individuals. It was observed that high levels of vitamin D or supplementation are strongly associated to SVR among HCV infected individuals. The results are interesting and may represent the role of metabolic factors in HCV infection.

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