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Association between serum vitamin D and severity of liver fibrosis in chronic hepatitis C patients: a systematic meta-analysis*

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Abstract: To conduct a systematic review of group studies assessing the association of serum vitamin D status with the severity of liver fibrosis in chronic hepatitis C patients using meta-analysis. The relevant research literatures were identified by searching PubMed and EMBASE databases prior to October 2013 with no restrictions. We included group studies that reported odds ratio (OR) estimates with 95% confidence intervals (CIs) or a mean with standard deviation (SD) for the association between serum vitamin D status and the severity of liver fibrosis in chronic hepatitis C patients. Approximately 8321 participants from several countries were included in this analysis. Six studies on serum vitamin D status and the severity of liver fibrosis were included in this meta-analysis. ORs with 95% CIs were extracted from four studies and the pooled ORs were 0.866 (95% CI, 0.649 to 1.157). The means with SDs were extracted from three studies and the pooled means were −0.487 (95% CI, −0.659 to −0.315). There was statistically significant heterogeneity among the mean data extracted studies (P=0.029; I^2=71.8%) but not among the OR data extracted studies (P=0.061; I^2=55.6%). Finally, results from the mean data extracted studies suggest that lower serum vitamin D is a risk factor for the severity of liver fibrosis in chronic hepatitis C patients. However, there is no conclusive evidence on this association because of inconsistencies between the OR data extracted studies and the mean data extracted studies.

Key words: Vitamin D, Fibrosis, Hepatitis C virus, Meta-analysis
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1 Introduction

It is reported that there are 120–180 million hepatitis C virus (HCV) carriers around the world, with the worldwide prevalence estimated at 3% (Shepard *et al*., 2005; Tong *et al*., 2012). Chronic hepatitis C is considered to be a major cause of liver disease, including progressive liver fibrosis, cirrhosis, and hepatocellular carcinoma (Hoofnagle, 2002; Shepard *et al*., 2005; Thomas and Seeff, 2005; Micallef *et al*., 2006; Zhu *et al*., 2014). The risk factors like older age, consumption of alcohol, metabolic alterations, liver necroinflammation, duration of infection and viral co-infections (Poynard *et al*., 2003), and insulin resistance (Romero-Gómez *et al*., 2005) can influence the degree of liver fibrosis. More and more evidence also shows that vitamin D status is very important for the liver disease severity in patients who are infected with chronic hepatitis C (Terrier *et al*., 2012; Kitson *et al*., 2013; Ladero *et al*., 2013; Lange *et al*., 2013). 25-Hydroxyvitamin D or 25(OH) D is a metabolite of vitamin D in liver, and is exported to combine with vitamin D binding protein

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(VDBP). Because the half-life of serum 25(OH) D is long, the serum concentration of 25(OH) D is the most commonly used biomarker for vitamin D status (Wang *et al*., 2004; Stokes *et al*., 2013). Vitamin D plays an important role not only in maintenance of skeletal health, but also in the immune response, wound healing and many other important physiological functions (Cholongitas *et al*., 2012). 1,25-Dihydroxyvitamin D also plays an important role for innate and adaptive immune pathways (von Essen *et al*., 2010).

Recently, studies have reported that the 25(OH) D level decreased in patients with various forms of chronic liver disease and advanced fibrosis (Arteh *et al*., 2010; Geier, 2011). A lower serum 25(OH) D level significantly correlates with an increasing risk of advanced fibrosis and a higher severity of necroinflammatory activity has been related to different populations with individuals infected with chronic hepatitis C (Lange *et al*., 2011; 2013; Kitson *et al*., 2013; Petta *et al*., 2013). However, the results are not consistent in different studies and by race (Kitson *et al*., 2013; White *et al*., 2013). Taking into account that a single study may have been insufficient to detect the overall effects that vitamin D can have on populations with different genetic backgrounds, the accumulated data from different studies and quantitative synthesis were thought to be very important in providing evidence of the association of serum vitamin D levels and the severity of liver fibrosis in the patients who are infected with HCV. So, we carried out this meta-analysis on all published studies to estimate the overall effects of serum vitamin D levels and the severity of liver fibrosis. The heterogeneity between the individual studies and the potential publication bias was also evaluated. This meta-analysis is different from that reported by Villar *et al.* (2013), which focused on the association between 25(OH) D and sustained virological response (SVR) in HCV-infected individuals.

2 Materials and methods

2.1 Literature search strategy

We conducted a literature search of available materials prior to October 2013 in the PubMed and EMBASE databases without restrictions. The search items were "vitamin D or 25(OH) D" and "HCV or chronic hepatitis C or chronic liver disease". The search results also included articles reviewed ahead of publication. Moreover, the references cited by the selected articles and published reviews were scanned for additional relevant studies. We also contacted the authors for additional information if necessary.

2.2 Eligibility criteria

Studies were included in the meta-analysis if they met the following standards: (1) the association between the severity of liver fibrosis and the blood (plasma or serum) vitamin D or 25(OH) D status was evaluated; (2) the results showed interest and relevance to the fibrosis stage of the patients infected with HCV; (3) the results provided the odds ratio (OR) with 95% confidence intervals (CIs) or a mean with standard deviation (SD) or adequate information to calculate them. Abstracts, conference proceedings, case reports, reviews, patients co-infected with HIV, and repeated literatures were excluded. The most complete studies were those selected in which there were several studies available from the same investigators.

2.3 Data extraction

All data from the included studies were independently extracted by two authors. Any disagreements were resolved by discussions according to the selection criteria guidelines. Finally, the data for this meta-analysis were made available from six studies. The following data were extracted: name of the first author, publication year, ethnic background, participant sex and age, sample size (cases and controls or group size), fibrosis stage, measure of vitamin D, OR estimates with 95% CIs, or mean with SD (all of the data are shown in Table 1).

2.4 Statistical analysis

We quantified the relationship between serum vitamin D status and severity of liver fibrosis in chronic hepatitis C patients by using a random-effects model, which considered variation both within and between the studies. Sensitivity analysis was performed by deleting each study which reflected the influence of the individual dataset on the pooled ORs. Subgroup analysis was performed by geographic region and ethnic background. An estimation of potential publication bias was assessed by using Egger's linear regression test (Egger *et al*., 1997).

Table 1 Characteristics of studies on serum vitamin D status and severity of liver fibrosis

Source	Ethnic background	Study	Sex	Age (year)[1]	n_c	n_p	Study quality[2]	Measure of vitamin D
Petta *et al*., 2013	Italy	Consecutive	M/F	52.8±11.9	74	260	7	Chromosystem reagent and HPLC
Lange *et al*., 2011	Germany	Retrospective	M/F	45 (22–72)	146	6567	6	Radioimmunoassay
Arteh *et al*., 2010	55% Caucasian, 45% African American	Consecutive	M/F	53±9	43	118	6	Automated chemiluminescence immunoassay
White *et al*., 2013	African American	Cross-sectional	M	57.4±4.2	63	289	6	Automated immunochemiluminometric assay
	White (non-Hispanic)			55.7±5.5	54		6	Automated immunochemiluminometric assay
Kitson *et al.*, 2013	Caucasian	CHARIOT	M/F	43.9±9.4	44	896	7	LC-MS/MS methodology
Amanzada *et al*., 2013	Germany (Caucasian)	Cohort	M/F	51±10	36	191	6	Chromatographic system and HPLC

Source	OR/relative risk (95% CI)	Mean (95% CI)	HCV type	How fibrosis assessed and diagnosis criteria	Severe fibrosis vs. zero or lesser degrees
Petta *et al.*, 2013	0.958 (0.919, 0.999)	−0.44 (−0.71, −0.16)	G1	Biopsy according to Scheuer numerical scoring system	F3–F4 vs. F0–F1
Lange *et al.*, 2011	0.740 (0.548, 1.000)		G1, 2, 3	Biopsy according to METAVIR model	F2–F4 vs. F0–F1
Arteh *et al.*, 2010	0.681 (0.377, 1.229)		NA	By liver biopsy or by clinical or biochemical evidence of hepatocellular failure and/or portal hypertension	Cirrhosis vs. without cirrhosis
White *et al.*, 2013	12.91 (1.30, 128.16) 0.84 (0.20, 3.59)		G1, 2, 3, 4	By biochemical evidence according to FibroSURE-ActiTest model	F3/F4–F4 vs. F0–F3
Kitson *et al.*, 2013		−0.21 (−0.53, 0.12)	G1	Liver biopsy according to METAVIR model	F3/F4 vs. F0–F2
Amanzada *et al.*, 2013		−0.80 (−1.10, −0.50)	G1	Liver specimens, NA	Severe fibrosis/cirrhosis vs. absent/mild/moderate

[1] Data are expressed as mean±SD or mean (range); [2] Study quality was judged on the basis of the Newcastle-Ottawa scale (1–9 stars). n_c: number of cases; n_p: number of participants; M: male; F: female; CHARIOT: collaborative group hepatitis C study using high-dose Pegasys RBV induction dose in genotype one; HPLC: high performance liquid chromatography; LC: liquid chromatography; MS: mass spectrometry; G1, 2, 3, 4: hepatitis C genotype 1, 2, 3, or 4 infection; NA: not available

All statistical tests were performed with the STATA software 12.0. $P<0.05$ was considered statistically significant.

3 Results

3.1 Literature search

A flow diagram of our literature search is shown in Fig. 1. Our total search yielded 775 entries. We identified six eligible publications (Arteh *et al*., 2010; Lange *et al*., 2011; Amanzada *et al*., 2013; Kitson *et al*., 2013; Petta *et al*., 2013; White *et al*., 2013) concerning the association between vitamin D and severity of liver fibrosis in patients infected with chronic hepatitis C. Among these studies, two (Arteh *et al*., 2010; Petta *et al*., 2013) were consecutive studies, one (Lange *et al*., 2011) was a retrospective study, one (White *et al*., 2013) was a cross-sectional study, one (Kitson *et al.*, 2013) was a CHARIOT study, and one was a cohort study (Amanzada *et al*., 2013).

3.2 Study characteristics

The six studies concerning the relationship between serum vitamin D and the severity of liver fibrosis were published between 2010 and 2013 (Table 1), which involved a total of 8321 patients. Of these six studies, three (Lange *et al*., 2011; Amanzada *et al*., 2013; Petta *et al*., 2013) were conducted in Europe, two (Arteh *et al.*, 2010; White *et al*., 2013) in the

United States, and one (Kitson *et al*., 2013) in Australia. The five (Arteh *et al*., 2010; Amanzada *et al*., 2013; Kitson *et al*., 2013; Petta *et al*., 2013; White *et al*., 2013) studies assessed included a review of serum 25(OH) D status, and one (Lange *et al*., 2011) on $25(OH)D_3$ and $1,25(OH)_2D_3$ status. Three studies (Amanzada *et al*., 2013; Kitson *et al*., 2013; Petta *et al*., 2013) included patients with chronic hepatitis C genotype 1 infection, one (Lange *et al*., 2011) with chronic hepatitis C genotype 1, 2, or 3-infection, one (White *et al*., 2013) with chronic hepatitis C genotype 1, 2, 3, or 4-infection, and one (Arteh *et al*., 2010) did not specify the kind of HCV type. Four studies (Baur *et al*., 2012; Corey *et al*., 2012; Weintraub *et al*., 2012; Ladero *et al*., 2013) were excluded because they did not report usable data. One study (Petta *et al*., 2010) was excluded because it reported on the same author.

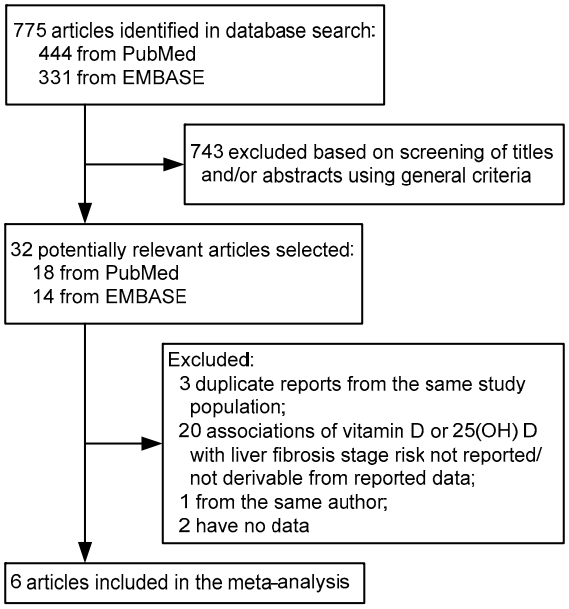

Fig. 1 Flowchart of the literature search

3.3 Serum vitamin D status and severity of liver fibrosis

The overall results for the serum vitamin D status associated with the severity of liver fibrosis are shown in Fig. 2. Results from studies concerning the relationship between serum vitamin D status and severity of liver fibrosis were inconsistent with inverse or positive associations reported. The pooled OR was 0.866 (95% CI, 0.649 to 1.157) and mean was −0.487 (95% CI, −0.659 to −0.315). There was statistically significant heterogeneity among mean data extracted studies (P=0.029; I^2=71.8%) but not among OR data extracted studies (P=0.061; I^2=55.6%).

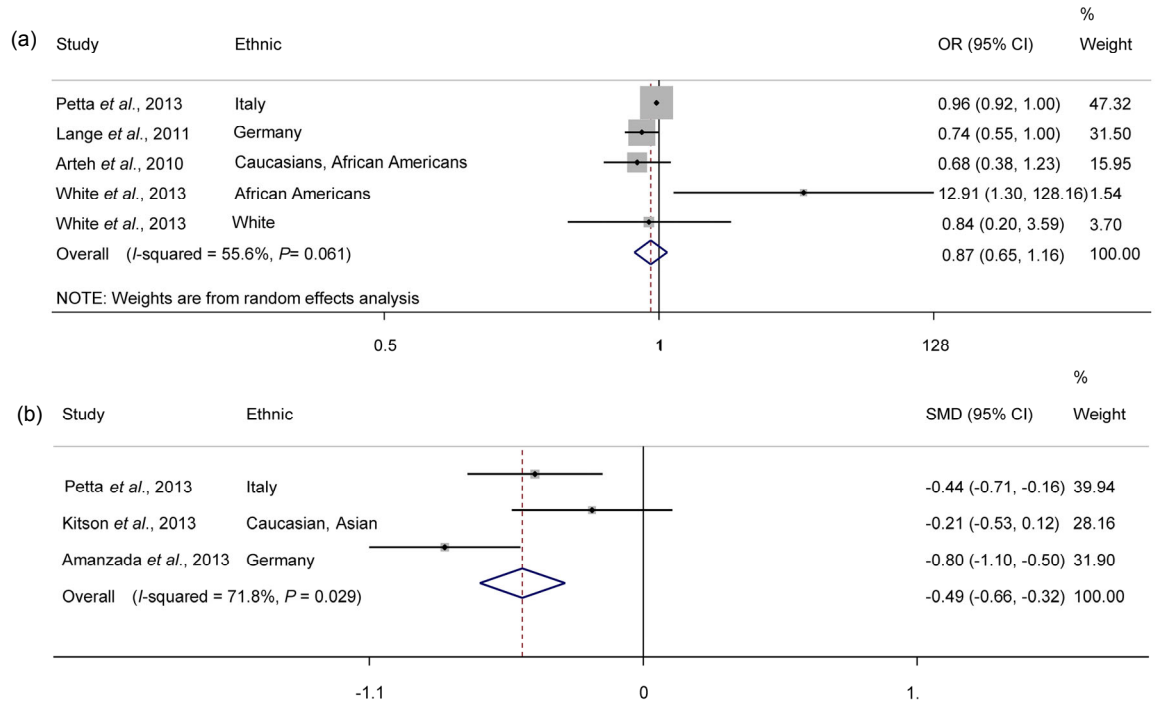

Fig. 2 Forest plot of serum vitamin D status and severity of liver fibrosis
(a) Pooled OR; (b) Pooled mean

3.4 Stratifying analysis

Stratifying by geographic region, the pooled ORs of studies were 1.33 (95% CI, 0.35 to 5.08; P=0.052; I^2=66.2%) for studies conducted in the United States, and 0.88 (95% CI, 0.694 to 1.116; P=0.096; I^2=64.0%) for studies conducted in Europe. There was no statistically significant heterogeneity among the studies (United States, P=0.052 and P=0.096). Stratifying by ethnic background, the pooled ORs of studies were 0.902 (95% CI, 0.762 to 1.068; P=0.246; I^2=28.8%) for those with a European ethnic origin (Table 2). We did not do subgroup analysis about the mean data extracted studies because only three studies were included in our research (Amanzada *et al*., 2013; Kitson *et al*., 2013; Petta *et al*., 2013).

Table 2 Association between serum vitamin D status and severity of liver fibrosis stratified according to geographic region and ethnic background

Factor	RR	95% CI	Heterogeneity	
			P	I^2 (%)
Geographic region				
United States	1.33	0.35–5.08	0.052	66.2
Europe	0.88	0.694–1.116	0.096	64.0
Ethnic background				
European	0.902	0.762–1.068	0.246	28.8

RR: relative risk; CI: confidence interval

3.5 Sensitivity analysis and publication bias

We performed sensitivity analysis by omitting one study at a time and calculating the pooled OR for the remainder of the studies. The result showed that the study of White *et al*. (2013) influenced the pooled OR. After excluding this single study, the heterogeneity was significantly reduced (P=0.246; I^2=28.8%; 95% CI, 0.762 to 1.068). The Egger's test showed no evidence of publication bias for OR (P=0.902) or mean (P=0.888) data extracted studies.

4 Discussion

Vitamin D deficiency is a global problem. There are 20% to 100% of people suffering from this problem when referring to serum vitamin D concentrations <20 ng/ml (Holick *et al*., 2011). Low vitamin D status associated with advanced fibrosis in chronic hepatitis C patients (Arteh *et al*., 2010; Geier, 2011) has been reported. The reasons why vitamin D deficiency occurs in chronic hepatitis C patients are far from conclusive. A possible reason of this finding should consider the multiple interconnections among vitamin D, the immune response, and inflammatory status (Baeke *et al*., 2010; Hewison, 2010).

The current meta-analysis summarizes the results of group studies, including six studies and a total of 8321 participants. The findings from the mean data extracted studies indicated that serum vitamin D status is inversely associated with the severity of liver fibrosis, but the results from the OR data extracted studies showed that there was no significant association between serum vitamin D status and the severity of liver fibrosis. When the analysis was stratified according to geographic region and ethnic background, the results were unchanged. However, after excluding the study of White *et al*. (2013), the heterogeneity was significantly reduced.

White *et al*. (2013) found that serum levels of vitamin D (>50 ng/ml) have a higher risk of advanced fibrosis (F3/F4–F4) in African American males. Corey *et al*. (2012) found that African Americans whose liver fibrosis clinically progressed over a 4-year period had higher baseline vitamin D levels compared with African Americans whose fibrosis had not progressed (32.7 ng/ml vs. 25.2 ng/ml; P=0.08). These different results may be due to the different vitamin D measurements, study design, or skin tone. It has been reported that very few foods naturally contain vitamin D and the major cause of vitamin D deficiency is due to the inadequate exposure to sunlight (Holick *et al*., 2007; Holick and Chen, 2008). People with a naturally dark skin tone have natural sun protection and require three to five times longer exposure to make the same amount of vitamin D as a person with a white skin tone (Clemens *et al*., 1982; Hintzpeter *et al*., 2008).

The findings from this meta-analysis need to be confirmed in large randomized clinical trials. Some suggestions should be considered in further studies. First, most of the studies included were conducted in America and Europe. Even more studies should be conducted in other populations such as South-African and Asian, considering the underlying disease-effect unconformity across different geographical locations.

Second, more accurate questionnaires or other accurate methods assessing serum vitamin D status could provide better results for estimating the association.

Several limitations of this study should be addressed. First, meta-analyses are considered hypothesis-generating. The quality and usefulness of any meta-analysis are dependent on the quality and comparability of data from the component studies (Hennekens and Demets, 2009). Inadequate or inaccurate data may bias the results. And unknown confounding cannot be excluded as a potential explanation for the observed findings. Second, the related data on serum vitamin D concentration were measured by different methods. This may possibly lead to less accurate estimates of risk. Meanwhile, only six studies were available for this study, some of the subgroup analyses were difficult to perform. Third, although there was a lack of any indication of major publication bias in the formal evaluation we used, potential publication bias is impossible to completely exclude because some studies with null results tend not to be published. Finally, There was significant heterogeneity for mean data extracted studies (I^2=71.8%) in the pooled analysis. This may be due to the different serum vitamin D concentration detection, different ethnic backgrounds included, different fibrosis assessing models, or other confounding factors which have not been considered.

In summary, although data from the mean data extracted studies suggest that lower serum vitamin D is a risk factor for severity of liver fibrosis, there is no conclusive evidence on this association because of inconsistencies between OR data extracted studies and mean data extracted studies. Prospective studies focusing on more detailed results, including more accurate vitamin D measurement technology, and taking a broad range of confounders into account are required to clarify this relationship.

Compliance with ethics guidelines

Yue-qiu LUO, Xiao-xing WU, Zong-xin LING, Yi-wen CHENG, Li YUAN, and Charlie XIANG declare that they have no conflict of interest.

This article does not contain any studies with human or animal subjects performed by any of the authors.

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中文概要：

本文题目：慢性丙型肝炎患者的血清维生素 D 与严重肝纤维化相关性研究：系统性的荟萃分析

Association between serum vitamin D and severity of liver fibrosis in chronic hepatitis C patients: a systematic meta-analysis

研究目的：利用 meta 分析方法来探索慢性丙型肝炎患者低血清维生素 D 水平与严重肝纤维化相关性。

创新要点：丙型病毒性肝炎病人的低血清维生素 D 水平与严重肝纤维化并不一定有相关性。

研究方法：结合已发表的临床研究数据，采用荟萃分析方法，定量分析低血清维生素 D 水平与慢性丙型肝炎患者严重肝纤维化相关性（图 2；表 2）。

重要结论：此荟萃分析对于认识丙型肝炎病人低血清维生素 D 水平与肝纤维化严重程度的相关性有重要意义，对未来相关临床研究具有指导意义。

关键词组：维生素 D；纤维化；丙型病毒性肝炎；荟萃分析