



Effect of vitamin D supplementation on chronic liver disease: systematic literature review

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ABSTRACT

Introduction: It is long known that vitamin D deficiency was common in patients with liver disease, but little is known on the therapeutic effects of vitamin D, especially in patients with chronic liver disease. In this study, we aimed to systematically review the literatures and study the evidences in which the effects of vitamin D supplementation had been investigated on the severity of chronic liver disease or liver cirrhosis.

Methods: A systematic literature search was performed by using the following key terms "vitamin D supplementation" and "chronic liver disease" in the PubMed, Scopus and Google scholar to find relevant articles. After collecting the eligible documents, data were extracted and described based on the purpose of this review.

Result: Of total 196 articles found, only 7 relevant documents with 518 studied patients were included. The results of this study showed that the levels of 25(OH) D were considerably lower in patients with chronic liver disease. Findings showed that vitamin D supplementation can rise up the mean serum level of 25(OH) D in patients with severe vitamin D deficiency, especially patients with liver cirrhosis.

Conclusion: The results of this review showed that vitamin D deficiency is associated with the severity of liver disease and may have prognostic value in the assessment of liver disease. Also, it was shown that vitamin D supplementation may be helpful for the treatment of liver disease at least in certain groups of patients.

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Introduction

Vitamin D is a fat-soluble sterol that is synthesized in the liver and has various functions in the body (1). In addition to its role in bone health, vitamin D plays a role in the balance of immune system and dealing with viruses and bacterial agents as well as the pathogenesis of autoimmune diseases (2,3). Recent studies have shown that vitamin D may have role in the progression of chronic liver disease (4,5). Due to the severity of liver dam-

age and impaired synthesis of certain proteins, patients with vitamin D deficiency are at greater risk of chronic liver disease (6,7). It appears that hepatitis C virus (HCV) inhibits the synthesis of 25 (OH) D by altering the fat metabolism; moreover, it prevents the production of pre-vitamin D (8). On the other hand, vitamin D deficiency is associated with the severity of liver disease and fibrosis in chronic hepatitis C (CHC) (9,10).

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It has been shown that the change in the metabolism of 25 (OH) D is associated with stiffness of the liver in chronic liver disease, and vitamin D plays a role in the onset of fibrosis (11). It has also been shown that low levels of vitamin D receptor (VDR) are the most important factor influencing fibrosis (12). Findings have also suggested that VDR polymorphisms may be associated with the development of cirrhosis (13). In addition, in patients with CHC, vitamin D deficiency was associated with reduced viral response to treatment with pegylated-interferon (PEG-IFN) / ribavirin (RBV) (14). In some studies, the addition of vitamin D to the treatment regimen of PEG/RBV has resulted in increased therapeutic response in CHC (15). The results of some studies show that vitamin D inhibits replication of the HCV virus, which represents the antiviral effect of this vitamin; moreover, it has synergistic antiviral effect with interferon (16).

It seems that 1, 25 (OH) D has anti fibrosis effect that is mainly mediated by bone marrow stem cells. It is shown that 1, 25 (OH) D can increase VDR and inhibits proliferation of stellate cell and also induce the expression of cyclin D1 (inhibitor of metalloproteinase and collagen) (17). In addition, vitamin D has the ability to reduce the production of smooth muscle actin and collagen and thus can inhibit the progression of liver cirrhosis induced by thioacetamide (18). All of these evidences suggest that vitamin D is an anti-fibrosis agent. Available evidences suggest that the addition of vitamin D to a normal diet may improve the prognosis of patients with chronic hepatitis (19). According to the U.S. National Institutes of Health for clinical trials (<https://clinicaltrials.gov/>), many trials are under study to evaluate the effects of vitamin D supplementation on different disorders, particularly in cirrhotic patients. In this survey, we aim to systematically review the evidences in which the effects of vitamin D or vitamin D supplementation had been investigated on the severity of chronic liver disease or liver cirrhosis.

Methods

Search methods

We conducted a systematic literature search to evaluate the effects of vitamin D supplementation on the severity of chronic liver disease in patients with liver cirrhosis. For this purpose, we independently searched PubMed, Scopus, and Google scholar for “vitamin D supplementation” and “liver cirrhosis” in the title, abstract and keywords of documents. To perform literature search in PubMed, following search strategy (((vitamin D supplementation OR vitamin D supplement OR vitamin D therapy OR vitamin D OR cholecalciferol))

AND (chronic liver disease OR chronic hepatitis OR cirrhosis OR liver cirrhosis OR fibrosis OR liver fibrosis)) AND (severity OR intensity) was used with customized search wherein the records were limited to those articles with English language. To find relevant articles in the Scopus, we used a similar search method. For this purpose, vitamin D supplementation was searched in the Scopus and liver cirrhosis was searched within the results. Afterwards, we limited the records to those articles published in English language. Google scholar was also searched for the described key terms. In addition to the described electronic data-bases, we conducted a manual search of the reference lists to minimize the risk of data loss, and also to include other potentially eligible documents.

Study selection and inclusion/exclusion criteria

We did not define time limitation for the collection of articles during literature selection. Hence, all relevant documents to the main purpose of this survey wherein the effects of vitamin D therapy or vitamin D supplementation had been studied on the severity of liver cirrhosis were included. Articles with nearly all types of study design including controlled clinical trial, observational, cross-sectionals, comparative, prospective cohorts, evaluation and multicenter studies were included in this study to collect all available data on the issue. Moreover, conference abstracts or presentations, book sections, letters, review articles and meta-analysis were excluded from further assessment. However, the search was limited to only those articles with English language to avoid any misconceptions during data analysis. Documents with subject and/or language irrelevancy were excluded in the first step of article selection. Likewise, duplicated documents as well as articles with inadequate data were excluded from further evaluation.

Data extraction

All available information including author's name, publication date, country of study, and studied sample size in each study were extracted. Based on the main purpose of this study, other necessary information including target population, age and sex ratio of studied population, type of study design, methods of assessment, and the key findings of each study were extracted and described. According to inclusion/exclusion criteria, eligible articles among the collected documents were identified and data were extracted by two investigators independently. To avoid potential errors and probable miscalculation during data processing, any likely disagreements between the investigators were resolved in each step prior to

further data processing. All processes including methods of literature search, selection of article, and data processing and qualitative analysis were performed according to the protocol recommended in PRISMA checklist 2009 (20).

Measured variables

Various methods including standard biochemical examinations, serological analysis, liver biopsy or imaging, isotope-dilution liquid chromatography–tandem mass spectrometry, immunonephelometry, and chemiluminescent microparticle immunoassay had been used for clinical evaluation of the studied patients in the selected literatures. The variables of interest that were extracted and compared included the levels of vitamin D2 and D3, liver function, and liver enzymes. Other variables that had been evaluated in the included literatures were serum levels of albumin, bilirubin, aminotransferases, alkaline phosphatase and gamma-glutamyl transferase.

Results

Literature search results

Nearly 194 documents were collected by search in PubMed, Scopus, and Google scholar. Of these articles, 131 potentially relevant articles were in PubMed, 51 were in Scopus and 12 were in Google scholar. Two other potentially relevant articles were also found through reference list screening at final assessment of included documents. Of all collected literatures, 75 articles were disqualified in the first step after reviewing the title and abstract due to subject irrelevancy. Thirty two additional documents were also excluded from collected document pool by limiting the results to studies conducted on human. In addition, 28 documents were excluded due to language irrelevancy. Other 21 articles were further excluded due to data inadequacy. Likewise, 19 review articles were excluded from additional assessment. Finally, full text of 21 articles were collected and used for data collection. After reviewing the full text of eligible documents, only 7 relevant articles that fully met the defined inclusion/exclusion criteria and contained data in which the effects of vitamin D supplementation had been evaluated on the severity of chronic liver disease were included and used for data processing. The step by step process of literature search and selection is illustrated in Figure 1.

General characteristics of the included articles

The total number of patients studied for the effect of vitamin D or vitamin D supplementation on the severity of chronic liver disease was 518. The number of studied patients varied from 17

in retrospective study to 158 in a prospective cohort study among the included documents. All patients had various kinds of chronic liver disease, particularly liver cirrhosis before vitamin D therapy. The studied populations were both male and female patients with confirmed chronic liver disease or liver cirrhosis, and of these patients, 270 were male and 187 were female; moreover, the sex of 61 patients had not been reported in some articles. The age of patients varied from 25 to 84 among the included documents. The most old and recent articles that were included in this survey had been published in 2010 and 2015, respectively. Documents that were used for data extraction and qualitative evaluation included 1 retrospective, 2 prospective cohorts, 2 cross-sectional, 1 case-control and 1 pilot study. General information of articles included in this survey is demonstrated in Table 1 in their chronological order of published time.

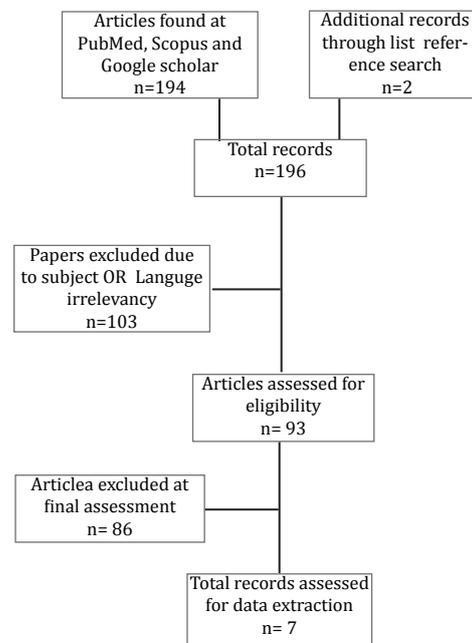


Figure 1. Flowchart of the literature search and strategy for the selection of relevant document.

Study findings

As expected, the results of this survey showed that patients with liver cirrhosis had considerably lower 25(OH) D3 levels compared to healthy individuals without complications. Qualitative assessment of the results described in the included documents showed that there is correlation between vitamin D level and the degree of liver disease. Findings suggested that vitamin D supplementation can result in up to 141.1% increase in the mean serum level of 25(OH) D in patients with severe vitamin D deficiency. Also, it was shown that only a single dose of oral D3 supplementation (300 000 IU) could increase

Table 1. General information of the included literatures.

NO	Author Reference	Year	Country	Study design *	Mean age	Sex (M/F)	Patients number
1	Finkelmeier (21)	2015	Germany	PCS	57.17	-	44
2	Ladero (22)	2013	Spain	CSS	54.3	60/48	108
3	Atsukawa (23)	2013	Japan	PiS	70	14/16	30
4	Malham (24)	2012	Denmark	CSS	-	25/7	32
5	Corey (25)	2012	USA	CCS	49.5	89/40	129
6	Malham (26)	2011	Denmark	RS	-	-	17
7	Rode (27)	2010	Australia	PCS	-	82/76	158

*PCS: Prospective cohort study, CCS: Case-control study, PiS: Pilot study, CSS: Cross-sectional study, RS: Retrospective study.

Table 2. Main findings of included literatures.

NO	Author Reference	Types of the disease	Methods and variables *	Mean follow-up	Main findings
1	Finkelmeier (21)	Cirrhosis	Laboratory parameters, Vitamin D level	1.5 years	Vitamin D is an independent prognostic parameter of cirrhosis.
2	Ladero (22)	Chronic hepatitis	Vitamin D level, fibrosis stage, biochemical tests	3 months	Vitamin D supplementation is related neither to biochemical variables nor with the fibrosis stage.
3	Atsukawa (23)	Chronic hepatitis	Laboratory parameters, Vitamin D level	1 month	Vitamin D supplementation significantly decreased the relapse rate in chronic Hepatitis.
4	Malham (24)	Alcoholic liver cirrhosis	Vitamin D level, liver biopsy and imaging, IdLC-TMS, immunonephelometry	3 months	Vitamin D therapy was effective for the treatment of patients with liver cirrhosis.
5	Corey (25)	Advanced fibrosis	Vitamin D2 and D3 level	45 months	Vitamin D supplementation may be associated with improved outcomes in chronic liver disease.
6	Malham (26)	Cirrhosis	Vitamin D level, liver biopsy and imaging, IdLC-TMS, immunonephelometry	-	Vitamin D deficiency in cirrhosis should be treated with higher doses of vitamin D.
7	Rode (27)	Chronic liver disease	Serum albumin, bilirubin, ALT, AST, ALP and GGT	4 months	Vitamin D deficiency correlates with liver disease severity.

*ALP: Alkaline phosphatase, ALT: Alanine transaminase, AST: Aspartate aminotransferase, GGT: Gamma-glutamyl transferase, IdLC-TMS: Isotope-dilution liquid chromatography-tandem mass spectrometry.

25(OH) D plasma levels to standard values in all of the patients with liver cirrhosis. Findings also showed that serum levels of 25(OH) D3 decrease with the progress of liver disease, especially liver cirrhosis. Although the results showed that vitamin D supplementation may alter biochemical indices of the liver, but there were no significant association between the plasma levels of 25(OH) D and biochemical liver tests, as well as with fibrosis stage in some studies. Similarly, the results of some studies demonstrated that vitamin D levels did not differ in patients who were under treatment with vitamin D and those who did not receive supplementation. Although the results were contradictory, but the results of studies demonstrated that vitamin D supplementation may be beneficial for the treatment of chronic liver disease at least at early stages of liver disease. Main findings of included documents as well as methods and variables are summarized in Table 2.

Discussion

Chronic liver diseases refer to liver pathologies including chronic hepatitis, and cirrhosis of the liver. These diseases are slowly progressive pathologies that may last over several months, and can cause several complications in the liver including hepatic encephalopathy, and hepatocellular carcinoma. Previously, it has been shown that chronic liver diseases may arise from vitamin D deficiency as a result of disorders in the vitamin D absorption, decreased synthesis or inadequate dietary vitamin D intake from foods or other supplements. Malabsorption may sometimes be attributable to the hypertension in the portal vein system caused by the liver disease. Findings suggested that there is association between lower vitamin D levels with the incidence of chronic liver disease (28). Also, it is demonstrated that patients with vitamin D deficiency are at greater risk of liver disease and fibrosis. In addition, the progression of fibrosis and hepatic inflammation is rather rapid in these patients. On the other hand, it is suggested that adequate levels of vitamin D can decrease the incidence of fibrosis in patients with CHC (29). Despite correlation between vitamin D deficiency and occurrence or progression of liver dysfunction, the evidences still do not support the effectiveness of vitamin D supplementation for the treatment of liver disease, especially liver cirrhosis in clinical practice, and further studies is suggested to evaluate the effects of vitamin D therapy in chronic liver disease (30).

Recent researches suggested that nutritional support, especially adequate intake of vitamin D supplementation may be helpful for patients with various forms of chronic liver disease (31,32).

The results of present review also indicated that the relapse rate was significantly decreased in patients with CHC who were under treatment with alfacalcidol supplementation as a source of vitamin D (23). Moreover, findings have shown that vitamin D supplementation can considerably improve depressive symptoms in female patients with chronic liver disease (33,34). Although the results were promising, but there were some studies that did not support such findings and showed that vitamin D supplementation may normalize the level of 25(OH)D in all patients with various types of chronic liver disease, but biochemical markers of liver necroinflammation may not be affected immediately (22,26). Since, the oldest articles included in this review had been published in 2010; therefore, it is clear that vitamin D therapy is a recent issue for the treatment of chronic liver disease, and enough researches had not been conducted regarding the efficacy of vitamin D supplementation in the treatment or lowering the progression of chronic liver disease (35).

Although the findings as well as the results of this review are suggestive for the possible role of vitamin D therapy for the management of liver disease at least for certain groups of patients, but so far the exact role and possible efficacy of vitamin D supplementation has not been investigated in clinical trials. According to the U.S. National Institutes of Health for clinical trials, some trials on the role of vitamin D therapy in patients with chronic liver disease are in progress. The major limitations of this review include lack of enough documents so that most of data extracted from studies were only a small part of the trials wherein the effects of vitamin D supplementation had been investigated on the severity of chronic liver disease in a limited number of populations. Therefore, the exact role and also assessing the effectiveness of vitamin D supplementation on the severity of chronic liver disease requires further investigations.

Conclusion

The results of studies show that vitamin D supplementation may be beneficial for the management of liver disease at least in certain groups of patients. Also, it was shown that vitamin D deficiency is associated with the severity of liver disease and can be considered as an independent prognostic parameter in liver disease, indicating that 25(OH)D3 levels decrease with the progress of liver cirrhosis while vitamin D therapy may or may not improve the progression of disease.

Conflict of Interest

The authors declare no conflict of interest.

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