Original Article

Association between Vitamin D Deficiency and the Severity of Chronic Liver Disease and Liver Cirrhosis: Systematic Literature Review

Hosein Ali Abbasi[1], Homan Mosannen Mozaffari[2], Abbas Esmaeilzadeh[2], Ali Bahari[3], Kambiz Akhavan Rezayat[2], Omid Ghanaei[2], Azita Ganji[2], Ali Mokhtarifar[2], Ladan Goshayeshi[2]

[1] Fellow of Gastroenterology and Hepatology, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[2] Associate Professor, Gastroenterology and Hepatology Research Center, Facuilty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
[3] Assistant Professor, Gastroenterology and Hepatology Research Center, Faculty of Medicine, Mashhad University of Medical Sciences, Mashhad, Iran

ABSTRACT

Background:
Vitamin D deficiency is believed to cause variety of abnormalities such as liver stiffness and fibrosis. It is also shown that vitamin D deficiency may result in chronic liver disease or liver cirrhosis. In this study, we aimed to systematically review the literature wherein the relationship between vitamin D deficiency and the severity of chronic liver disease or liver cirrhosis had been investigated.

Materials and Methods:
PubMed, Scopus, and Google scholar were searched using the following search method *(((vitamin D deficiency OR vitamin D insufficiency OR insufficient vitamin D)) AND (chronic liver disease OR chronic hepatitis OR cirrhosis OR liver cirrhosis)) AND (severity OR intensity)* to evaluate the role of vitamin D deficiency or vitamin D inadequacy in the occurrence and severity of chronic liver disease. Articles were collected and the data were extracted.

Results:
Totally, 641 articles were found through searching the databases and reference list scanning. Of the collected documents, only 19 articles with 4895 studied patients were included and analyzed. The results of this study showed that almost 80% of patients with chronic liver disease had severe vitamin D deficiency.

Conclusion:
Vitamin D deficiency is associated with the occurrence of chronic liver disease. The severity of liver cirrhosis is also associated with the level of 25(OH)D in progressive liver disease.

Keywords: Chronic hepatitis, Liver disease, Vitamin D, Vitamin D deficiency

please cite this paper as:
Abbasi HA, Mosanan mozaffari H, Esmaeilzadeh A, Bahari A, Akhavan Rezayat K, Ghanaei O, Ganji A, Mokhtarifar A, Goshayeshi L. Association between Vitamin D Deficiency and the Severity of Chronic Liver Disease and Liver Cirrhosis: Systematic Literature Review. *Govaresh* 2016;21: 64-71.

Corresponding author:
Ladan Goshayeshi, MD
Accociate Professor of Gastroenterology and Hepatology, Facultyof Medicine, Mashhad University of Medical Sciences, Mashhad, Iran
Tel: + 98 511 8012753
Fax: + 98 511 8932481
E-mail: goshayeshil@mums.ac.ir
Received: 27 Jan. 2016
Edited: 16 Mar. 2016
Accepted: 17 Mar. 2016

INTRODUCTION

Vitamin D or cholecalciferol is one of the necessary fat-soluble vitamins that plays an important role in bone growth through regulating the balance between calcium and phosphorus. Recently, a significant amount of information has been found regarding the physiological as well as pathophysiological role of vitamin D(1). The positive effects of activation and regulation of both the innate and adaptive immunity by vitamin D and also its role in autoimmune disorders and cancers

have been presented in several studies(2). Vitamin D is converted into its active form (1, 25-dihydroxy-vitamin D3) in the liver(3,4). The production of active vitamin D metabolites, therefore, may be negatively affected in individuals with chronic liver disease(5). 1, 25 vitamin D3 seems to have a modulatory role in the immune system, mainly by regulating the function of T cells(6). Furthermore, most cells involved in the function of the immune system express the vitamin D receptor (VDR)(7). Increasing information show that vitamin D provides better immunity by protecting the host from pathogens and the deleterious effects of prolonged inflammatory responses(8). Vitamin D can regulate the bone metabolism by increasing the absorption of phosphorus and calcium from the intestine and reducing their excretion from the kidney(9). Also, plant and animal sources are some source of vitamin intake. Most of the vitamin D is produced in the body through exposure to sunlight(10). Vitamin D and calcium, especially when used in combination increase the strength and coordination of the muscles in elderly. Also, it is shown that vitamin D can help to prevent the diseases such as rickets in children, osteomalacia in adults, and osteoporosis in the elderly. Daily need for this vitamin for adults is 10 micrograms or up to 2,000 units per day(11-13).

Vitamin D deficiency can be usually associated with some symptoms such as general weakness, bone pain, bowel problems, and boredom(14,15). In some people including pregnant women, children under five years old, and people over 65 years who are not exposed enough to sunlight, and in some gastrointestinal, liver and kidney diseases the risk of vitamin D deficiency is high. Although subclinical vitamin D deficiency is a common medical issue, it is shown that chronic vitamin D deficiency may typically be associated with osteomalacia, cancer, cardiovascular disease, and stress. Vitamin D deficiency can cause variety of abnormalities including osteoporosis, especially in older age(11,16). Evidence also suggests that vitamin D is an anti-fibrotic agent, and changes in its metabolism are associated with liver stiffness and fibrosis(17). Some studies show that vitamin D alone or synergistically with interferon can suppress the proliferation of the HCV virus(18). It has also been shown to increase the risk of hepatocellular carcinoma in Chronic Hepatitis C(19). Some studies indicate that low levels of vitamin D were associated with a higher level of HBV-DNA in patients with chronic hepatitis B infection. Similarly, it is suggested that vitamin D deficiency may be a possible risk factor for wide spectrum of illnesses such as musculoskeletal complications, autoimmune and cardiovascular diseases, malignancies,and dementia as well as increased rate of mortality(20). On the other hand, it is suggested that vitamin D supplementation enhances the response to interferon based regimen in chronic hepatitis C(21).

Since the metabolism of vitamin D is performed in the liver and kidney, it is possible that people with liver disease be more susceptible to vitamin D deficiency. In this study, we aimed to systematically review all available articles that reported the relationship between vitamin D deficiency and the severity of chronic liver disease or liver cirrhosis.

MATERIALS AND METHODS

Search methods

By using "*vitamin D deficiency*" and "*chronic liver disease*" as key terms, we performed a systematic literature search in the PubMed, Scopus, and Google scholar to evaluate the role of vitamin D deficiency or vitamin D insufficiency in the incidence, progression, and severity of chronic liver disease or liver cirrhosis. For this purpose, following search method *(((vitamin D deficiency OR vitamin D insufficiency OR insufficient vitamin D)) AND (chronic liver disease OR chronic hepatitis OR cirrhosis OR liver cirrhosis)) AND (severity OR intensity)* was used to find potentially appropriate articles in the PubMed and Google scholar. We used a similar search method to find other eligible documents in the Scopus. For this purpose, "*vitamin D deficiency OR insufficient vitamin D*" was searched and then the "*chronic liver disease OR liver cirrhosis*" were searched within the results. Afterwards, the records were limited to only those articles published in English language. Likewise, the reference lists of relevant articles were also searched to collect other potentially eligible documents. All the procedures including literature search and data synthesis were performed by two independent authors. The literature search was completed on January 2016.

Eligibility criteria

We did not define time limitation during literature search to collect all qualified related documents.

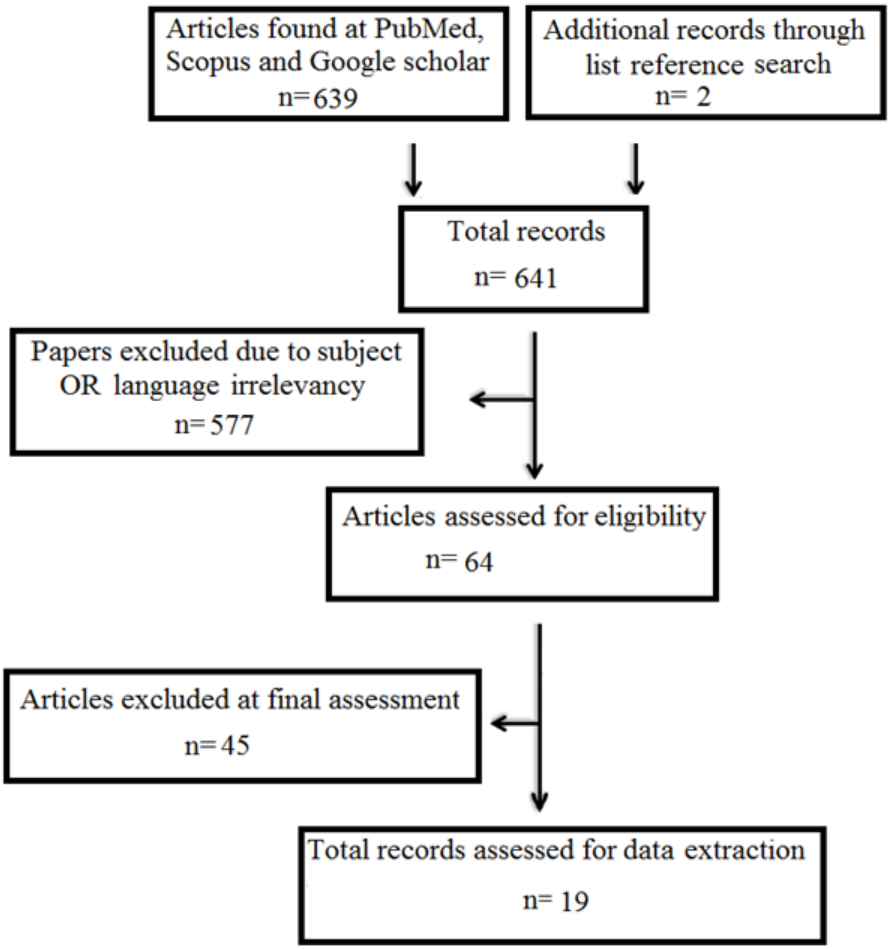

Fig.1: Flowchart of the literature search and strategy for the selection of relevant document.

Thus, all documents relevant to the purpose of this study in which the relationship between vitamin D deficiency and the severity of chronic liver disease had been investigated were collected and used in this survey. To include all registered records on the subject, articles with all types of medical design were included. However, conference proceedings, letters, editorials, and review articles were crossed out from additional assessment. Moreover, the search was limited to articles with English language that had only been conducted on human. Likewise, duplicated documents as well as articles with inaccessible data were disqualified from additional assessment.

Data synthesis

Necessary information including the name of authors, date of publication, type of study design, country of the study, demographic data of studied populations, and total number of patients were collected. Other essential data including methods of assessment, studied variables, and the key findings of studies were extracted and compared on the basis of the study purpose. All procedures including literature search, and data processing were performed according to recommendations described in PRISMA checklist 2009(22). According to the described checklist for data analysis, all procedures are recommended to be performed by at least two researchers, and to avoid probable miscalculations, any probable discrepancies between the investigators were resolved before additional data processing.

Studied variables

Different methods had been used in the selected

Table 1: General information of the included literature.

N	First author	Year	Country	Study design*	Sex ratio Male/female	Number of participants
1	Costa Silva M(23)	2015	Brazil	CSS	96/67	163
2	Bril F(24)	2015	USA	CS	203/36	239
3	Gerova DI(25)	2014	Bulgaria	PiS	161/135	296
4	Guzmán-Fulgencio M(26)	2014	Spain	CSS	130/44	174
5	Savic Z (27)	2014	Serbia	CSS	30/-	30
6	Corey RL (28)	**2014**	USA	PCS	-	190
7	Finkelmeier F (29)	2014	Germany	PCS	161/39	200
8	White DL(30)	2013	USA	CSS	289/-	289
9	Trépo E(31)	2013	Belgium	CSS	455/70	525
10	El-Maouche D(32)	2013	USA	PCS	73/43	116
11	Putz-Bankuti C(33)	2012	Austria	CSS	51/24	75
12	Chatrath H(34)	2012	USA	PCS	41/109	150
13	Terrier B(35)	2011	France	PCS	146/43	189
14	Pincikova T(36)	2011	Denmark	CSS	429/467	896
15	Malham M(37)	2011	Denmark	RCS	-	89
16	Pincikova T(38)	2011	Sweden	CSS	468/430	898
17	Arteh J(5)	2010	USA	CSS	-	118
18	Rode A(39)	2010	Australia	PCS	-	158
19	Fisher L(40)	2007	Australia	CSS	63/37	100
RCS: Retrospective case series, CS: Comparative study, CSS: Cross-sectional study, PiS: Pilot study, PCS: Prospective cohort study.					Male: 2796 Female: 1544	Total: 4895

documents to investigate the relationship between vitamin D deficiency and the severity of liver cirrhosis. These methods included high performance liquid chromatography (HPLC), liquid chromatography/tandem-mass spectrometric detection, enzyme immunoassay, FibroSURE-Acti Test, chemiluminescent or electrochemiluminiscence microparticle immunoassay, polymerase chain reaction (PCR), and magnetic resonance spectroscopy. The studied variables that were reflected the occurrence or severity of liver cirrhosis included serum total immunoglobulin G (IgG) levels, 25(OH) D level, biochemical factors, and level of parathyroid hormone. In addition, clinical and inflammatory markers, degree of liver dysfunction, bone metabolic activity and bone mass, alanine aminotransferase (ALT), aspartate aminotransferase (AST), fasting blood sugar (FBS), and inflammatory activity grade were also other variables that had been evaluated in some included studies.

RESULT

Literature search results

Totally, 639 articles were found through the data bases search, of which 66 articles were in the PubMed, 570 in the Scopus, and 3 additional documents in Google Scholar. In addition, two other potentially appropriate documents were found through manual reference list search of the collected literature. By reviewing the abstracts, and titles in the first step, 477 documents including 452 irrelevant articles and 25 articles with language irrelevancy were excluded. Additional 37 articles were further excluded due to duplication. Moreover, 108 documents including 87 articles with inappropriate data and 21 review articles were excluded from further evaluation. Finally, full texts of 19 articles in which the relationship between vitamin D deficiency and the severity of chronic liver disease had been investigated and fully met the eligibility criteria were fully reviewed and used for data extraction. The procedures of literature search

Table 2: General information of the included literature.

N	First author	Methods*	Variables®	Findings
1	Costa Silva M(23)	Immunoassay	25OHD	Hypovitaminosis D was prevalent in cirrhosis and it was associated with adiposity.
2	Bril F(24)	MRS, LB	Vitamin D status	Plasma vitamin D levels are not associated with the severity of non-alcoholic steatohepatitis.
3	Gerova DI(25)	LC-TMS	25OHD	Almost all HCV-infected patients are vitamin D-deficient.
4	Guzmán-Fulgencio M(26)	Immunoassay	25(OH)D, IAG	Plasma 25(OH)D deficiency was associated with liver disease severity in HIV/HCV co-infected patients.
5	Savic Z(27)	Immunoassay	Vitamin D status, bone metabolic activity and bone mass	Vitamin D deficiency is present in patients with alcoholic liver cirrhosis.
6	Corey RL(28)	Biochemical tests	25(OH)D, PTH, calcium, and BMD	Low vitamin D levels and bone disease are common among patients with end-stage liver disease.
7	Finkelmeier F(29)	Radioimmunoassay	25(OH)D, biochemical factors	25(OH)D3 deficiency is associated with advanced stages of hepatocellular carcinoma.
8	White DL(30)	Fibro SURE-Acti Test	25(OH)D, IAG	Vitamin D levels are associated with risk of hepatitis C-related liver disease.
9	Trépo E(31)	Immunoassay, biochemical test	25(OH)D,ALT, AST, FBS	Low 25(OH)D levels are associated with increased liver damage and mortality in alcoholic liver disease.
10	El-Maouche D(32)	Immuno-chemilumi-nometric assay	25(OH)D, BMD	Vitamin D deficiency was not related to bone mineral density or liver disease severity.
11	Putz-Bankuti C(33)	Biochemical test	25(OH)D, DLD	There was significant association of 25(OH)D with the degree of liver dysfunction.
12	Chatrath H(34)	Biochemical test	25(OH)D, muscle cramp	Muscle cramps are associated with diminished quality of life in patients with cirrhosis.
13	Terrier B(35)	radio-immunoassay	25(OH)D	Low serum 25(OH)D3 levels correlate with severe liver fibrosis in HIV-HCV co-infected patients.
14	Pincikova T(36)	HPLC	25(OH)D, HbA1c	Vitamin D status is associated with HbA(1c) and diabetes in children with cystic fibrosis.
15	Malham M(37)	LC-TMS	25(OH)D	Serum vitamin D levels decreased with increasing liver disease severity.
16	Pincikova T(38)	Radioimmunoassay, HPLC	25(OH)D, IgG levels	Increasing vitamin D intake may positively modulate inflammation in Cystic fibrosis.
17	Arteh J(5)	Biochemical test	Vitamin D status	Vitamin D deficiency is universal (about 92%) among patients with chronic liver disease.
18	Rode A(39)	Biochemical test	Vitamin D level	Patients with chronic liver disease are at very high risk of vitamin D deficiency regardless of etiology or severity.
19	Fisher L(40)	Radioimmunoassay	25(OH)D, PTH	Vitamin D inadequacy is common in chronic liver disease and correlates with disease severity.

* LC-TMS: liquid chromatography/tandem-mass spectrometry, HPLC: High performance liquid chromatography, MRS: Magnetic resonance spectroscopy, LB: Liver biopsy. ® 25OHD: 25-hydroxyvitamin-D, IAG: Inflammatory activity grade, BMD: Bone mineral density, PTH: Parathyroid hormone, IgG: Immunoglobulin G, DLD: Degree of liver dysfunction, ALT: Alanine transaminase, AST: Aspartate aminotransferase, FBS: Fasting blood sugar

and article selection is summarized in figure 1.

Literature characteristics

The total number of participants in the collected literature in which the association between insufficient vitamin D and the severity of chronic liver disease had been investigated was 4895 patients. They included 2796 male and 1544 female patients with age ranged from 1 to 70 years. The number of studied participants varied from 30 to 898, both in cross-sectional studies among the included documents. The sex of 555 patients had not been reported. The oldest and recent articles that were included in this survey had been published in 2007 and 2015, respectively. Among the studied documents used for data extraction, there were 10 cross-sectional, 6 prospective, one retrospective case series, one pilot, and one comparative studies. (table 1)

The results of this study showed that nearly all of patients with advanced liver disease had 25(OH) D deficiency. Of all studied patients, only in one

study with overall 116 participants, vitamin D deficiency did not have correlations with the bone mineral density as well as liver disease severity. Also, the results revealed that vitamin D deficiency was a valuable and independent predictor for the occurrence of chronic liver disease. A significant correlation was also suggested between low 25(OH) D level with the degree of liver dysfunction. Findings were also suggestive of association between low 25(OH)D levels with increased liver damage as well as increased rate of mortality in patients with alcoholic liver disease. Findings showed that there was an association between plasma levels of vitamin D and degree of HCV-related hepatic fibrosis. In addition, the results of some studies showed that racial differences might also be associated with vitamin D levels and the degree of hepatic fibrosis. They showed that black populations were at highest risk of vitamin D deficiency, and therefore at higher risk of developing liver fibrosis(5,30, 32). Unlike adult populations, it was also shown that vitamin D deficiency was associated with diabetes mellitus in children with cystic fibrosis(36). The methods of assessment, studied variables and main findings of included articles are demonstrated in table 2.

DISCUSSION

Vitamin D after synthesis in the skin or receiving through the meal is metabolized to the active metabolite calcitriol in the liver and kidney. Since a part of vitamin D is metabolized in the liver, some studies suggested that vitamin D deficiency might be associated with certain liver diseases. Cirrhosis of the liver is one of the top ten causes of death worldwide. Despite the increased risk of bone loss and its association with hepatic osteodystrophy as a cause of cirrhosis, the clinical significance of Parathyroid hormone (PTH)-vitamin D remained unclear in patients with hepatic disorders. Studies have also shown that regardless of the cause, a high prevalence of vitamin D deficiency can be observed in patients with liver diseases (25,33,41). Some studies suggested that racial difference might also affect the relationship between vitamin D levels and degree of HCV-related hepatic fibrosis as well as the incidence of liver cirrhosis. They showed that black populations had a reduced level of vitamin D compared with white patients(30).

Recently, due to the activation of vitamin D in the liver and the high prevalence of vitamin deficiency in liver disease, studies have focused on the role of vitamin D in liver disease. Studies have shown that decreased levels of vitamin D to less than 20 ng/mL are commonly observed in 64% to 92% of patients with chronic liver diseases and the reduced vitamin D level is associated with the type and progression of liver disease(26,33,35). Therefore, findings show that severe vitamin D deficiency is strongly associated with the incidence and prevalence of liver cirrhosis(5). It is also shown that vitamin D inadequacy is more common among young children with cystic fibrosis(42). Similarly, findings of a study indicated that vitamin D insufficiency can be considered as a strong and independent predictor for the incidence and progression of advanced fibrosis, especially in HCV-infected patients(43). Also, findings show that severe 25(OH)D deficiency can be associated with higher serum levels of AST, increased liver damage, and mortality, especially in patients with alcoholic liver disease(31). Vitamin D deficiency is also shown to be associated with adiposity and systemic inflammation or liver dysfunction(23).

In this review, we aimed to investigate the association between vitamin D levels with liver disease, particularly liver cirrhosis. The results showed that almost 80% of studied patients with chronic liver disease were vitamin D deficient. Also, the results of included literature showed that vitamin D level was also associated with the severity of HCV/ HBV chronic hepatitis and liver cirrhosis.

CONCLUSION

The results of this study showed that prolong vitamin D deficiency could lead to chronic liver disease. Also, it was shown that low levels of vitamin D were associated with the incidence and progression of chronic liver disease. The severity of liver cirrhosis also correlated with the plasma level of 25(OH)D in advanced liver disease.

ACKNOWLEDGMENT

The results of this study showed that prolong vitamin D deficiency could lead to chronic liver disease. Also, it was shown that low levels of vitamin

D were associated with the incidence and progression of chronic liver disease. The severity of liver cirrhosis also correlated with the plasma level of 25(OH)D in advanced liver disease.

CONFLICT OF INTERESTS

Authors have declared that no conflicting interests exist.

REFERENCES

1. Watkins RR, Lemonovich TL, Salata RA. An update on the association of vitamin D deficiency with common infectious diseases. *Can J Physiol Pharmacol* 2015;93:363-8.
2. Iruzubieta P, Teran A, Crespo J, Fabrega E. Vitamin D deficiency in chronic liver disease. *World J Hepatol* 2014;6:901-15.
3. DeLuca HF. Overview of general physiologic features and functions of vitamin D. Am J Clin Nutr 2004;80:1689S-96S.
4. Dusso AS, Brown AJ, Slatopolsky E. Vitamin D. *Am J Physiol Renal Physiol* 2005;289:F8-28.
5. Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. *Dig Dis Sci* 2010;55:2624-8.
6. Müller K, Bendtzen K. 1,25-Dihydroxyvitamin D3 as a natural regulator of human immune functions. *J Investig Dermatol Symp Proc* 1996;1:68-71.
7. Hewison M. Vitamin D and the intracrinology of innate immunity. *Mol Cell Endocrinol* 2010;321:103-11.
8. Trochoutsou AI, Kloukina V, Samitas K, Xanthou G. Vitamin-D in the Immune System: Genomic and Non-Genomic Actions. *Mini Rev Med Chem* 2015;15:953-63.
9. DeLuca HF. The vitamin D system in the regulation of calcium and phosphorus metabolism. *Nutr Rev* 1979;37:161-93.
10. Glerup H, Mikkelsen K, Poulsen L, Hass E, Overbeck S, Thomsen J, et al. Commonly recommended daily intake of vitamin D is not sufficient if sunlight exposure is limited. *J Intern Med* 2000;247:260-8.
11. Holick MF. High prevalence of vitamin D inadequacy and implications for health. *Mayo Clin Proc* 2006;81:353-73.
12. Calvo MS, Whiting SJ, Barton CN. Vitamin D intake: a global perspective of current status. *J Nutr* 2005;135:310-6.
13. Norman AW. From vitamin D to hormone D: fundamentals of the vitamin D endocrine system essential for good health. *Am J Clin Nutr* 2008;88:491S-9S.
14. Eriksen EF, Glerup H. Vitamin D deficiency and aging: implications for general health and osteoporosis. *Biogerontology* 2002;3:73-7.
15. Holick MF. Vitamin D deficiency. *N Engl J Med* 2007; 357:266-81.
16. Nair S. Vitamin d deficiency and liver disease. *Gastroenterol Hepatol (N Y)* 2010;6:491-3.
17. Grunhage F, Hochrath K, Krawczyk M, Hoblinger A, Obermayer-Pietsch B, Geisel J, et al. Common genetic variation in vitamin D metabolism is associated with liver stiffness. *Hepatology* 2012;56:1883-91.
18. Villar LM, Del Campo JA, Ranchal I, Lampe E, Romero-Gomez M. Association between vitamin D and hepatitis C virus infection: a meta-analysis. *World J Gastroenterol* 2013;19:5917.
19. Lange CM, Miki D, Ochi H, Nischalke HD, Bojunga J, Bibert S, et al. Genetic analyses reveal a role for vitamin D insufficiency in HCV-associated hepatocellular carcinoma development. *PLoS One* 2013;8:e64053.
20. Pludowski P, Holick MF, Pilz S, Wagner CL, Hollis BW, Grant WB, et al. Vitamin D effects on musculoskeletal health, immunity, autoimmunity, cardiovascular disease, cancer, fertility, pregnancy, dementia and mortality-a review of recent evidence. *Autoimmun Rev* 2013;12:976-89.
21. Farnik H, Bojunga J, Berger A, Allwinn R, Waidmann O, Kronenberger B, et al. Low vitamin D serum concentration is associated with high levels of hepatitis B virus replication in chronically infected patients. *Hepatology* 2013;58:1270-6.
22. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Annals Intern Med* 2009;151:W-65-W-94.
23. Costa Silva M, Erotides Silva T, de Alentar ML, Honorio Coelho MS, Wildner LM, Bazzo ML, et al. Factors associated with 25-hydroxyvitamin D levels in patients with liver cirrhosis. *Ann Hepatol* 2015;14:99-107.
24. Bril F, Maximos M, Portillo-Sanchez P, Biernacki D, Lomonaco R, Subbarayan S, et al. Relationship

of vitamin D with insulin resistance and disease severity in non-alcoholic steatohepatitis. *J Hepatol* 2015;62:405-11.

25. Gerova DI, Galunska BT, Ivanova, II, Kotzev IA, Tchervenkov TG, Balev SP, et al. Prevalence of vitamin D deficiency and insufficiency in Bulgarian patients with chronic hepatitis C viral infection. *Scand J Clin Lab Invest* 2014;74:665-72.
26. Guzman-Fulgencio M, Garcia-Alvarez M, Berenguer J, Jimenez-Sousa MA, Cosin J, Pineda-Tenor D, et al. Vitamin D deficiency is associated with severity of liver disease in HIV/HCV coinfected patients. *J Infect* 2014;68:176-84.
27. Savic Z, Damjanov D, Curic N, Kovacev-Zavisic B, Hadnadjev L, Novakovic-Paro J, et al. Vitamin D status, bone metabolism and bone mass in patients with alcoholic liver cirrhosis. *Bratisl Lek Listy* 2014;115:573-8.
28. Corey RL, Whitaker MD, Crowell MD, Keddis MT, Aqel B, Balan V, et al. Vitamin D deficiency, parathyroid hormone levels, and bone disease among patients with end-stage liver disease and normal serum creatinine awaiting liver transplantation. *Clin Transplant* 2014;28:579-84.
29. Finkelmeier F, Kronenberger B, Koberle V, Bojunga J, Zeuzem S, Trojan J, et al. Severe 25-hydroxyvitamin D deficiency identifies a poor prognosis in patients with hepatocellular carcinoma - a prospective cohort study. *Aliment Pharmacol Ther* 2014;39:1204-12.
30. White DL, Tavakoli-Tabasi S, Kanwal F, Ramsey DJ, Hashmi A, Kuzniarek J, et al. The association between serological and dietary vitamin D levels and hepatitis C-related liver disease risk differs in African American and white males. *Aliment Pharmacol Ther* 2013;38:28-37.
31. Trepo E, Ouziel R, Pradat P, Momozawa Y, Quertinmont E, Gervy C, et al. Marked 25-hydroxyvitamin D deficiency is associated with poor prognosis in patients with alcoholic liver disease. *J Hepatol* 2013;59:344-50.
32. El-Maouche D, Mehta SH, Sutcliffe CG, Higgins Y, Torbenson MS, Moore RD, et al. Vitamin D deficiency and its relation to bone mineral density and liver fibrosis in HIV-HCV coinfection. *Antivir Ther* 2013;18:237-42.
33. Putz-Bankuti C, Pilz S, Stojakovic T, Scharnagl H, Pieber TR, Trauner M, et al. Association of 25-hydroxyvitamin D levels with liver dysfunction and mortality in chronic liver disease. *Liver Int* 2012;32:845-51.
34. Chatrath H, Liangpunsakul S, Ghabril M, Otte J, Chalasani N, Vuppalanchi R. Prevalence and morbidity associated with muscle cramps in patients with cirrhosis. *Am J Med* 2012;125:1019-25.
35. Terrier B, Carrat F, Geri G, Pol S, Piroth L, Halfon P, et al. Low 25-OH vitamin D serum levels correlate with severe fibrosis in HIV-HCV co-infected patients with chronic hepatitis. *J Hepatol* 2011;55:756-61.
36. Pincikova T, Nilsson K, Moen IE, Karpati F, Fluge G, Hollsing A, et al. Inverse relation between vitamin D and serum total immunoglobulin G in the Scandinavian Cystic Fibrosis Nutritional Study. *Eur J Clin Nutr* 2011;65:102-9.
37. Malham M, Jorgensen SP, Ott P, Agnholt J, Vilstrup H, Borre M, et al. Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than aetiology. *World J Gastroenterol* 2011;17:922-5.
38. Pincikova T, Nilsson K, Moen IE, Fluge G, Hollsing A, Knudsen PK, et al. Vitamin D deficiency as a risk factor for cystic fibrosis-related diabetes in the Scandinavian Cystic Fibrosis Nutritional Study. *Diabetologia* 2011;54:3007-15.
39. Rode A, Fourlanos S, Nicoll A. Oral vitamin D replacement is effective in chronic liver disease. *Gastroenterol Clin Biol* 2010;34:618-20.
40. Fisher L, Fisher A. Vitamin D and parathyroid hormone in outpatients with noncholestatic chronic liver disease. *Clin Gastroenterol Hepatol* 2007;5:513-20.
41. Stokes CS, Volmer DA, Grunhage F, Lammert F. Vitamin D in chronic liver disease. *Liver Int* 2013;33:338-52.
42. Simoneau T, Bazzaz O, Sawicki GS, Gordon C. Vitamin D status in children with cystic fibrosis. Associations with inflammation and bacterial colonization. *Ann Am Thorac Soc* 2014;11:205-10.
43. Avihingsanon A, Jitmitraparp S, Tangkijvanich P, Ramautarsing RA, Apornpong T, Jirajariyavej S, et al. Advanced liver fibrosis by transient elastography, fibrosis 4, and alanine aminotransferase/platelet ratio index among Asian hepatitis C with and without human immunodeficiency virus infection: role of vitamin D levels. *J Gastroenterol Hepatol* 2014;29:1706-14.