Original Article

High Prevalent Hypovitaminosis D Is Associated with Dysregulation of Calcium-parathyroid Hormone-vitamin D Axis in Patients with Chronic Liver Diseases

Krishnasamy Narayanasamy[#*1], Rajendran Karthick[#*2] and A. Koodal Raj[2]

[1]*Department of Hepatology, Madras Medical College, Chennai, Tamil Nadu, India;* [2]*Multidisciplinary Research Unit (MRU), Madras Medical College, Chennai, Tamil Nadu, India*

Abstract

Background and Aims: Although hypovitaminosis D is common among patients with chronic liver disease (CLD), the data are inconsistent on its prevalence and its relationship with CLD. This study aimed to estimate the prevalence of hypovitaminosis D among patients with CLD and to determine the relationship between hypovitaminosis D and severity of liver dysfunction, and calcium (Ca), phosphate (PO4) and parathyroid hormone (PTH) levels in CLD. ***Methods:*** The study included 236 CLD patients attending the Department of Hepatology, Rajiv Gandhi Government General Hospital (Chennai, India). Serum levels of 25-hydroxyvitamin D (25 (OH)D), PTH, Ca, and PO4 were estimated. Severity of liver dysfunction was graded using the Child–Turcotte–Pugh (CTP) score. ***Results:*** The first report from our population showed that 162 of 236 (68.6%) CLD patients had hypovitaminosis D (25(OH)D levels of <30 ng/mL), with higher frequency (124/162) 76.5% among CTP B, C patients. Significant negative correlation ($r = -0.288$, $p = 0.0001$) between 25(OH)D and CTP scores was noted in hypovitaminosis D conditions. Level of 25(OH)D was correlated negatively with PTH ($r = -0.537$, $p = 0.0001$), positively with Ca ($r = 0.657$, $p = 0.0001$), and positively with PO4 ($r = 0.477$, $p = 0.0001$) in sufficient vitamin D conditions. ***Conclusions:*** Hypovitaminosis D is associated with higher CTP scores and is strongly associated with dysregulation of the Ca-PTH-vitamin D axis in CLD. Timely measurement of vitamin D levels is essential, along with levels of PTH, Ca and PO4, to manage CLD patients.

Citation of this article: Narayanasamy K, Karthick R, Raj AK. High prevalent hypovitaminosis D is associated with dysregulation of calcium-parathyroid hormone-vitamin D axis in patients with chronic liver diseases. J Clin Transl Hepatol 2019;7(1):1–6. doi: 10.14218/JCTH.2018.00018.

Keywords: Hypovitaminosis D; Chronic liver disease; Liver dysfunction; Hypocalcemia; Vitamin D.

Abbreviations: 25(OH)D, 25–hydroxyvitamin D; Ca, calcium; CLD, chronic liver disease; CTP, Child–Turcotte–Pugh; PO4, phosphate; PTH, parathyroid hormone.

Received: 7 March 2018; Revised: 22 September 2018; Accepted: 24 September 2018

[#]These two authors contributed equally to this study.

[*]**Correspondence to:** Krishnasamy Narayanasamy, Department of Hepatology, Madras Medical College, Chennai, Tamil Nadu 600003, India. Tel: +91-9841170145, E-mail: drkns_1963@yahoo.com; Rajendran Karthick, Multidisciplinary Research Unit (MRU), Madras Medical College, Chennai, Tamil Nadu 600003, India. Tel: +91-9790787578, E-mail: rkarthickphd@gmail.com

Introduction

Healthy liver function is important in the metabolism of the secosteroid hormone, vitamin D. Biologically inactive vitamin D from the skin and diet is first hydroxylated into 25-hydroxyvitamin D (25(OH)D) in the liver. The active metabolite $1,25(OH)_2D$ is formed in the kidney by second hydroxylation of 25(OH)D. The amount of circulating levels of 25(OH)D is mainly used to determine the status of vitamin D in the human body.[1]

Hypovitaminosis D is very common in the general population, and chronic liver disease (CLD) patients are at very high risk.[2] Hence, association between CLD and vitamin D status has been intensively investigated.[3–6] Previous studies have reported inconsistent data for prevalence rates with respect to serum concentrations of 25(OH)D and its relationship with the severity of liver disease. Some studies have suggested that 25(OH)D levels decrease with progression of liver disease;[7–9] others, however, did not find a difference between cirrhotic and noncirrhotic patients[10] or between various Child-Pugh groups,[11] and still others demonstrated it as not predictive of the progression of CLD in hepatitis C.[12]

The pleiotropic hormone of vitamin D is very essential for many physiologic processes, especially the regulation of calcium (Ca) and bone metabolism. The Ca-parathyroid hormone (PTH)-vitamin D axis is believed to play a crucial role in many diseases,[13–15] including CLDs. However, very few studies have investigated the shift of this axis in CLD. Thus, the primary objective of our study was to estimate the prevalence of hypovitaminosis D in patients with CLD. The secondary objective of our study was to determine the relationships between hypovitaminosis D and the severity of liver dysfunction, and levels of Ca, phosphate (PO4) and PTH in CLDs.

Methods

Study subjects and design

We conducted a prospective cross-sectional study of 236 CLD subjects referred to the Outpatient Unit of the Department of Hepatology at Rajiv Gandhi Government General Hospital (Chennai, India) between July 2016 and June 2017. Subjects under 18 years of age and those suffering from cholestatic liver diseases (primary biliary cirrhosis, primary sclerosing cholangitis, etc.), parathyroid disease, chronic kidney disease and fluid resuscitation, those who were pregnant or breast-feeding, and those taking vitamin D supplementation, Ca supplementation or any other drug known to affect vitamin D or Ca metabolism were excluded from the present study. The

study was approved by the Institute Ethics Committee of Madras Medical College. All subjects gave their informed consent to participate in the study.

Sample size determination

The sample size of 227 was determined based on the following assumptions (http://www.openepi.com): 1) 92% is the previous prevalence reported,[7] 2) 5% absolute precision, 3) 95% confidence interval, and 4) 2 design effect.

Data collection

Venous blood was collected from the subjects in the morning after an overnight fast. The levels of serum 25(OH)D, ionized Ca, inorganic PO4 and intact PTH were determined, in addition to routine testing for levels of urea, creatinine, hemoglobin, aspartate aminotransferase, alanine aminotransferase, total alkaline phosphatase, albumin, bilirubin, protein, prothrombin time and international normalized ratio. Levels of 25(OH)D, Ca, PO4 and PTH were measured using the Roche Cobas analyzer and the appropriate test kit. Levels of 25(OH)D and PTH were determined by electrochemiluminescence, and levels of Ca and PO4 were measured by photometrically. Patient data, including demographics, diagnosis, and Child–Turcotte–Pugh (CTP) score, were also collected.

Definitions

Vitamin D status was assessed based on the serum concentration of 25(OH)D. Serum level falling between the range of 0–19.9 ng/mL was defined as a vitamin D deficiency, whereas those between the concentration range of 20–29.9 ng/mL and ≥30 ng/mL were defined as insufficiency and sufficiency of the hormone, respectively.[16,17] Levels of 25(OH)D <30 ng/mL were defined as hypovitaminosis D. Secondary hyperparathyroidism was defined as a serum level of PTH of >65 pg/mL, and hypocalcemia was defined as a Ca level of < 9 mg/dL.

Severity of cirrhosis was graded using the CTP score, and patients were grouped into the following three categories: class A for scores 5–6, class B for scores 7–9, and class C for scores 10–15. The diagnosis of cirrhosis was established by liver biopsy or by definitive clinical or biochemical evidence of hepatocellular failure and/or portal hypertension.

Statistical analysis

Continuous variables were expressed as medians, with the first and third interquartile ranges. Categorical variables were reported as percentages. Differences between groups were assessed using the chi-squared test for categorical variables and the Mann-Whitney test and Kruskal-Wallis test for continuous variables with two and three groups, respectively. Coefficients of correlation between variables were calculated using Spearman's analysis. Two-sided p values <0.05 were considered statistically significant. Data were analyzed using SPSS 17 (IBM Corp., Armonk, NY, USA).

Results

Patient characteristics

A total of 236 eligible CLD patients were included in the study. Table 1 summarizes the baseline characteristics of patients, including the etiologic, biochemical and hematologic data, stratified by vitamin D status. A predominance of male gender (74.2%) compared to female gender (25.8%) was observed in the study group. The median age of the patients was 48 (42–54) years, with a median CTP score of 8 (6–10). The main causative factor for CLD was viral hepatitis (38.1%); other etiologies comprised alcoholic (31.4%), cryptogenic (12.7%), autoimmune (11.0%) and metabolic (6.8%) liver disease.

Vitamin D status among CLD patients

Of the 236 patients studied, 87 (36.9%) were deficient (0–19.9 ng/mL), 75 (31.8%) were insufficient (20–29.9 ng/mL) and 74 (31.4%) were sufficient (≥30 ng/mL) for levels of 25(OH)D. Hypovitaminosis D was seen in 162 out of 236 patients (68.6%). The lowest and highest observed levels of serum 25(OH)D were 3 ng/mL and 70 ng/mL, respectively. Chennai is located at 13°N, and the majority of the population receive ample sunlight throughout the year. The patient recruitment and study was also carried out for all seasons of the year. Hence, there was no seasonal variability in 25(OH)D levels in our study. The prevalence of vitamin D deficiency, insufficiency and sufficiency among CLD was 36.6%, 32.0% and 31.4%, respectively in men, and 37.7%, 31.1% and 31.1%, respectively in women. There was slight difference in median serum 25(OH)D levels between the sexes (23.3 (14.9–35.5) ng/mL in men vs. 22.0 (13.3–33.7) ng/mL in women).

The severity of CLD classified according to Child–Pugh classification scores showed significant association with the serum concentration of 25(OH)D by the Kruskal–Wallis test (Table 1). When CLD patients were classified according to their CTP score, there was a steady decreasing tendency for levels of 25(OH)D with increasing severity of cirrhosis (p = 0.006). The median serum concentration of 25(OH)D was significantly lower in patients with higher CTP score (CTP A: 27.9, CTP B: 24.2, CTP C: 20.2). The percentages of subjects with hypovitaminosis D (<30 ng/mL) were as follows: 54.3% of Child–Pugh class A, 75.3% of class B, and 74.2% of class C. 25(OH)D deficiency was present in 49.4% of the patients classified according to CTP C scores.

Most of the hematologic characteristics and biochemical parameters of liver function did not differ significantly between the vitamin D deficient, insufficient and sufficient groups. Similarly, the three groups did not significantly differ in age, sex, body mass index, serum protein, creatinine and urea based on vitamin D levels. It may possible that age and body mass index were almost similar between the groups. The vitamin D deficient group had lower mean international normalized ratio values, decreased concentrations of serum bilirubin, increased concentrations of alkaline phosphatase, lower levels of serum alanine aminotransferase and hemoglobin, and increased concentrations of platelets. These differences were not related to vitamin D status and were more pronounced according to severity of the liver diseases. Although, these findings are limited by the possibility that levels may fluctuate over time. Etiology varied significantly in relation to vitamin D status (p = 0.0001).

PTH status

There was significant difference in serum PTH concentrations between the three groups of 25(OH)D status (p = 0.001)

Table 1. Demographic, biochemical and hematologic data in patients with chronic liver disease stratified by serum 25(OH)D levels

Variable	Total Subjects	Sufficient (≥30 ng/mL, *n* = 74)	Insufficient (20-29.9 ng/mL, *n* = 75)	Deficient (0-19.9 ng/mL, *n* = 87)	*p*
Age	48 (42–54)	48 (39.7–55)	46 (42–52)	48.5 (42–55.7)	0.4
Sex					0.986
Male	174 (73.7%)	55 (74.3%)	56 (74.7%)	64 (73.6%)	
Female	62 (26.3%)	19 (25.7%)	19 (25.3%)	23 (26.4%)	
Cause					0.0001
Alcohol	74 (31.4%)	16 (21.6%)	25 (33.3%)	33 (37.9%)	
Viral hepatitis	90 (38.1%)	19 (25.7%)	32 (42.7%)	39 (44.8%)	
Metabolic	26 (11%)	17 (23.0%)	6 (8.0%)	3 (3.4%)	
Autoimmune	16 (6.8%)	5 (6.8%)	6 (8.0%)	5 (5.7%)	
Cryptogenic	30 (12.7%)	17 (23.0%)	6 (8.0%)	7 (8.0%)	
25(OH)D	23.05 (14.52–34.9)	40.9 (35.5–46.7)	23.9 (21.8–26.5)	13.02 (8.5–15.9)	0.0001
Ca	7.6 (6.32–8.4)	8 (7.2–8.5)	7.9 (6.9–9.1)	7.2 (5.72–7.8)	0.0001
PO4	2.8 (2.3–3.4)	3.1 (2.6–3.4)	2.8 (2.5–3.3)	2.45 (1.9–3.2)	0.0001
PTH	21.46 (13.12–30.77)	17.8 (10.9–27.9)	18.0 (12.3–28.3)	25.8 (16.9–36.0)	0.0001
CTP (Levels)	8 (6–10)	7 (6–10)	8 (7–10)	9 (6–12)	0.006
CTP (Grade)					0.0001
CTP A	74 (31.4%)	32 (43.2%)	19 (17.3%)	23 (28.7%)	
CTP B	75 (31.8%)	13 (25.7%)	39 (52.0%)	23 (21.8%)	
CTP C	87 (36.9%)	25 (31.1%)	19 (30.7%)	43 (49.4%)	
Total bilirubin	1.9 (1–3.5)	2.1 (0.9–3.9)	2.2 (1.0–4.0)	1.7 (1.0–2.9)	0.338
Albumin	3.3 (2.7–3.8)	3.4 (2.7–3.9)	3.3 (2.7–3.8)	3.2 (2.8–3.8)	0.907
INR	1.3 (1.1–1.5)	1.3 (1.1–1.6)	1.3 (1.2–1.5)	1.2 (1.1–1.4)	0.149
BMI	22 (18.5–24.6)	21.4 (18.5–24.0)	23.4 (19.6–25.7)	22.4 (18.6–25.3)	0.073
Hemoglobin	10.9 (9.4–12.1)	11.2 (9.7–12.5)	10.8 (9.4–12.5)	10.4 (9.0–11.6)	0.085
Platelet	107000 (78250–170750)	110000 (72000–179250)	102000 (66000–180000)	117500 (80000–183750)	0.696
Urea	20.5 (15–26)	20.5 (15.0–26.0)	21.0 (15.0–27.0)	20.0 (15.0–23.0)	0.499
Creatinine	0.9 (0.8–1.0)	0.80 (0.7–0.9)	0.90 (0.8–1.0)	0.90 (0.8–1.0)	0.504
AST	36.5 (24–68.2)	40.5 (23.7–74.7)	43.0 (23.0–66.0)	32.0 (20.0–64.5)	0.299
ALT	28 (19–44)	26.5 (20.0–43.0)	29.0 (20.0–40.0)	23.0 (17.0–39.5)	0.095
ALP	114.5 (82.2–153.7)	114.5 (84.5–159.5)	103.0 (81.0–123.0)	119.5 (79.7–160.7)	0.159
Protein	7.1 (6.4–7.6)	6.9 (6.3–7.7)	7.2 (6.5–7.6)	7.1 (6.5–7.6)	0.709

Continuous variables presented as median (25^{th}–75^{th} interquartile range). Categorical variables presented as number (percentage).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; Ca, calcium; CTP, Child–Turcotte–Pugh; INR, international normalized ratio; PO4, phosphate; PTH, parathyroid hormone.

(Table 1). Though CLD patients with hypovitaminosis D had a slightly higher median level of PTH compared to CLD patients with normal level of 25(OH)D (Table 2), secondary hyperparathyrodism was observed in only 3 patients (PTH of >65 pg/mL).

Ca and PO4 status

The concentrations of Ca and PO4 showed significant difference between the three groups of 25(OH)D status. CLD patients with deficiency in 25(OH)D had lower median levels of PO4 (p = 0.027) and Ca (p = 0.0001) than the other two groups. Hypocalcemia (defined as Ca of <9 mg/dL) and hypophosphatemia (defined as PO4 of <2.5 mg/dL) was present in 68.6% and 35.8% of patients exhibiting hypovitaminosis D, respectively.

Associations between components of the Ca-PTH-vitamin D axis and CLD severity

Spearman's correlation coefficient analysis showed negative correlation of CTP scores with levels of 25(OH)D (r = −0.288, p = 0.0001) in patients afflicted with hypovitaminosis D. Similarly, levels of Ca correlated negatively with CTP score (r = −0.169, p = 0.032). In contrast, levels of 25(OH)D,

Table 2. Difference of 25(OH)D, Ca, PO4, PTH and CTP score in patients with chronic liver disease between patients with hypovitaminosis D and patients with sufficient vitamin D level

Variable	Sufficient (≥ 30 ng/mL, *n* = 74)	Hypovitaminosis D (0–29.9 ng/mL, *n* = 162)	*p*
25(OH)D	40.75 (35.57–46.36)	18.9 (12.5–23.3)	0.0001
Ca	7.9 (7.05–8.5)	7.3 (6.2–8.2)	0.002
PO4	3.0 (2.6–3.4)	2.6 (2.1–3.3)	0.0001
PTH	18.35 (10.97–27.9)	22.0 (14.9–32.92)	0.002
CTP (Levels)	7 (6–10)	8 (6–10)	0.003
CTP (Grade)			0.008
CTP A	32 (43.2%)	38 (23.5%)	
CTP B	19 (25.7%)	58 (35.8%)	
CTP C	23 (31.1%)	66 (40.7%)	

Continuous variables presented as medians (25^{th}-75^{th} interquartile range). Categorical variables presented as number (percentage).
Abbreviations: Ca, calcium; CTP, Child–Turcotte–Pugh; PO4, phosphate; PTH, parathyroid hormone.

Ca, PTH and PO4 did not show significant correlation with CTP score among patients with sufficient vitamin D (Table 3).

Relationships among components of the Ca-PTH-vitamin D axis

Spearman's correlation coefficient analysis revealed that for patients with sufficient vitamin D, levels of 25(OH)D negatively correlated with PTH levels ($r = -0.537$, $p = 0.0001$), but positively correlated with levels of Ca ($r = 0.657$, $p = 0.0001$) and PO4 ($r = 0.477$, $p = 0.0001$) (Table 3). Whereas, such significant correlations were not observed in CLD patients with hypovitaminosis D, excepting a weak correlation with Ca ($r = 0.188$, $p = 0.0001$).

Discussion

This study demonstrated a high prevalence of hypovitaminosis D (68.6%) in the South Indian CLD population, with vitamin D deficiency observed in 36.9% of the patients. To our knowledge, this is the first study to report the prevalence of vitamin D deficiency and correlation between serum 25(OH)D concentration and PTH, Ca and PO4 levels in this study population.

Our study showed very high prevalence of hypovitaminosis D (124/162; 76.5%), defined as 25(OH)D <30 ng/mL among patients with CTP C and CTP B scores due to severe liver disease. In addition, we also observed that vitamin D deficiency, defined as 25(OH)D <20 ng/mL, was more common among patients with CTP C score (49.4%) than among those with CTP B (21.8%) and CTP A (28.7%). This suggests that hypovitaminosis D was associated with higher disease severity of our CLD patients. Our findings are consistent with previous studies reporting high prevalence of hypovitaminosis D among patients with severe liver disease. Hypovitaminosis D has been reported in different CLDs, especially in relation to viral load or fibrosis stage in chronic hepatitis B,[4] alcoholic,[18] hemochromatosis,[19] nonalcoholic fatty liver disease[20] and in patients awaiting liver transplantation.[21] However, some studies have shown no evidence of low vitamin D levels in cirrhosis,[10,22,23] noncirrhotic viral liver disease,[24] hemochromatosis[25] and nonalcoholic fatty liver disease.[26]

Serum 25(OH)D concentrations were categorized into sufficient, insufficient and deficient groups to evaluate whether there is a statistically significant downward trend associated with increasing severity of CLD in patients. Levels of 25(OH)D showed a stable decreasing trend for increasing severity of CLD classified according to Child–Pugh scores. This may clearly indicate specific impairment of vitamin D metabolism in the liver due to disease severity. Recently, Jia *et al.*[27] also reported observing significantly decreased levels of vitamin D with higher CTP scores in CLD. In contrast to our studies, others have also reported an association of serum 25(OH)D levels with no variation between Child–Pugh scores.[11] An additional method for separating 25(OH)D levels into distinct groups involves sufficient and hypovitaminosis D groups. Such an analysis in our study revealed that hypovitaminosis D was associated with higher CTP scores, whereas the sufficient vitamin D condition in CLD was not significantly associated.

Vitamin D is well known as a key participant in the Ca-PTH axis,[28] which is responsible for maintaining Ca homeostasis; still, how the axis changes during CLD is poorly understood. In the present study, hypocalcemia was found in 85.59% (202/236) of CLD patients, with a prevalence of 69.3% (140/202) in hypovitaminosis D patients. In addition, levels of 25(OH)D in hypovitaminosis D condition weakly correlated with Ca, whereas the high correlation was observed in the sufficient vitamin D condition, suggesting that vitamin D is required to maintain normal blood levels of Ca. A study analyzing hypocalcemia with hypovitaminosis D[29] reported increased bone turnover, fracture risk, as well as shorter survival.

Only three of our patients with hypovitaminosis D showed secondary hyperparathyroidism. This result is similar to a study reported by Klein *et al.*[30] However, the potential causes and mechanisms of the relation are yet to be identified. Our study data indicate that severity of CLD in hypovitaminosis D parallels the reduction in serum Ca changes and is similar to the observations of PO4.

No significant correlations were found between 25(OH)D levels and PO4 or PTH levels. A weak correlation was found between 25(OH)D levels and Ca levels among patients with hypovitaminosis D, whereas high significant correlations were found between 25(OH)D levels and PO4, PTH and Ca levels among CLD patients with sufficient 25(OH)D level. It can be speculated that hypovitaminosis D is the most likely cause of an altered Ca-PTH-vitamin D axis. Such may be responsible for the frequent increased disease severity observed in our

Table 3. Spearman's correlation coefficient analysis between 25(OH)D, CTP, Ca, PO4, and PTH

Variable	Hypovitaminosis D (<30 ng/mL)				Sufficient 25(OH)D level (>30 ng/mL)			
	25(OH)D	CTP	PTH	CA	25(OH)D	CTP	PTH	CA
CTP	−0.288**	–	–	–	0.051	–	–	–
PTH	−0.147	0.146	–	–	−0.537**	0.019	–	–
Ca	0.188*	−0.169*	−0.143	–	0.657**	−0.130	−0.432**	–
PO4	0.142	0.127	−0.092	0.171*	0.477**	−0.136	−0.345**	0.450**

*Correlation is significant at the 0.05 level (2-tailed);
**Correlation is significant at the 0.01 level (2-tailed).
Abbreviations: Ca, calcium; CTP, Child–Turcotte–Pugh; PO4, phosphate; PTH, parathyroid hormone.

CLD patients. This raises the intriguing possibility that an altered Ca-PTH-vitamin D axis plays an important role in prognosis in the CLD population, which should be explored further.

Our study highlighted a significant association of hypovitaminosis D in liver dysfunction, and levels of Ca, PO4 and PTH. Even though our study established these associations, clinical trials are necessary to evaluate whether 25(OH)D supplementation could improve the liver disease and levels of Ca, PO4 and PTH. Our study could not find the cause and effect interpretations due to its cross-sectional nature. Unfortunately, our study also did not investigate bone diseases or other conditions related with 25(OH)D in CLD. Another limitation of the study is that we did not take the lifestyle parameters (i.e. inadequate exposure to the sun, malnutrition) into consideration; hence, we could not explore further the association of interaction between these factors and 25(OH)D levels.

Conclusions

Vitamin D deficiency and hypocalcemia are highly prevalent in the severe CLD population, and hypovitaminosis D is also associated with higher CTP score. CLD patients with hypovitaminosis D often show significant dysregulation of the Ca-PTH-vitamin D axis, and vitamin D deficiency is an independent risk factor for hypocalcemia. Our findings highlight the complex interactions between hypovitaminosis D, hypocalcemia, hypophosphatemia and secondary hyperparathyroidism, which merit further research that should examine whether correction of 25(OH)D deficiency improves outcomes for CLD patients. Our results also suggest that 25(OH)D and Ca levels should be measured as part of the routine tests performed in CLD patients.

Conflict of interest

The authors have no conflict of interests related to this publication.

Author contributions

Conception of the study and overall study supervision (KN), design of the study (KN, RK), data analysis, drafting of the article, and statistical analysis (RK), assay performance and assistance in acquisition of data (AKR).

References

[1] Hollis BW. Assessment of vitamin D nutritional and hormonal status: what to measure and how to do it. Calcif Tissue Int 1996;58:4–5. doi: 10.1007/bf02509538.
[2] Rode A, Fourlanos S, Nicoll A. Oral vitamin D replacement is effective in chronic liver disease. Gastroenterol Clin Biol 2010;34:618–620. doi: 10.1016/j.gcb.2010.07.009.
[3] Rahman AH, Branch AD. Vitamin D for your patients with chronic hepatitis C? J Hepatol 2013;58:184–189. doi: 10.1016/j.jhep.2012.07.026.
[4] Yu R, Sun J, Zheng Z, Chen J, Fan R, Liang X, *et al*. Association between vitamin D level and viral load or fibrosis stage in chronic hepatitis B patients from Southern China. J Gastroenterol Hepatol 2015;30:566–574. doi: 10.1111/jgh.12783.
[5] Efe C, Kav T, Aydin C, Cengiz M, Imga NN, Purnak T, *et al*. Low serum vitamin D levels are associated with severe histological features and poor response to therapy in patients with autoimmune hepatitis. Dig Dis Sci 2014;59:3035–3042. doi: 10.1007/s10620-014-3267-3.
[6] Stokes CS, Krawczyk M, Reichel C, Lammert F, Grünhage F. Vitamin D deficiency is associated with mortality in patients with advanced liver cirrhosis. Eur J Clin Invest 2014;44:176–183. doi: 10.1111/eci.12205.
[7] Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. Dig Dis Sci 2010;55:2624–2628. doi: 10.1007/s10620-009-1069-9.
[8] Heuman DM, Mihas AA, Habib A, Gilles HS, Stravitz RT, Sanyal AJ, *et al*. MELD-XI: a rational approach to "sickest first" liver transplantation in cirrhotic patients requiring anticoagulant therapy. Liver Transpl 2007;13:30–37. doi: 10.1002/lt.20906.
[9] Finkelmeier F, Kronenberger B, Zeuzem S, Piiper A, Waidmann O. Low 25-hydroxyvitamin D levels are associated with infections and mortality in patients with cirrhosis. PLoS One 2015;10:e0132119. doi: 10.1371/journal.pone.0132119.
[10] Duarte MP, Farias ML, Coelho HS, Mendonça LM, Stabnov LM, do Carmo d Oliveira M, *et al*. Calcium-parathyroid hormone-vitamin D axis and metabolic bone disease in chronic viral liver disease. J Gastroenterol Hepatol 2001;16:1022–1027. doi: 10.1046/j.1440-1746.2001.02561.x.
[11] Monegal A, Navasa M, Guañabens N, Peris P, Pons F, Martinez de Osaba MJ, *et al*. Osteoporosis and bone mineral metabolism disorders in cirrhotic patients referred for orthotopic liver transplantation. Calcif Tissue Int 1997;60:148–154. doi: 10.1007/s002239900205.
[12] Corey KE, Zheng H, Mendez-Navarro J, Delgado-Borrego A, Dienstag JL, Chung RT. Serum vitamin D levels are not predictive of the progression of chronic liver disease in hepatitis C patients with advanced fibrosis. PLoS One 2012;7:e27144. doi: 10.1371/journal.pone.0027144.
[13] Bushinsky DA. Dysregulation of the calcium, phosphorus, parathyroid hormone, and vitamin D axis: what are the causes and risks? Am J Kidney Dis 2001;37:1310–1312. doi: 10.1053/ajkd.2001.25519.
[14] Hu J, Luo Z, Zhao X, Chen Q, Chen Z, Qin H, *et al*. Changes in the calcium-parathyroid hormone-vitamin d axis and prognosis for critically ill patients: a prospective observational study. PLoS One 2013;8:e75441. doi: 10.1371/journal.pone.0075441.
[15] Long Kv, Nguyễn LT. Roles of vitamin D in amyotrophic lateral sclerosis: possible genetic and cellular signaling mechanisms. Mol Brain 2013;6:16. doi: 10.1186/1756-6606-6-16.
[16] Dawson-Hughes B, Heaney RP, Holick MF, Lips P, Meunier PJ, Vieth R. Estimates of optimal vitamin D status. Osteoporos Int 2005;16:713–716. doi: 10.1007/s00198-005-1867-7.
[17] Holick MF, Binkley NC, Bischoff-Ferrari HA, Gordon CM, Hanley DA, Heaney RP, *et al*. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911–1930. doi: 10.1210/jc.2011-0385.

[18] García-Valdecasas-Campelo E, González-Reimers E, Santolaria-Fernández F, De la Vega-Prieto MJ, Milena-Abril A, Sánchez-Pérez MJ, *et al*. Serum osteoprotegerin and RANKL levels in chronic alcoholic liver disease. Alcohol Alcohol 2006;41:261–266. doi: 10.1093/alcalc/agl004.
[19] Chow LH, Frei JV, Hodsman AB, Valberg LS. Low serum 25-hydroxyvitamin D in hereditary hemochromatosis: relation to iron status. Gastroenterology 1985;88:865–869. doi: 10.1016/s0016-5085(85)80001-9.
[20] Barchetta I, Angelico F, Del Ben M, Baroni MG, Pozzilli P, Morini S, *et al*. Strong association between non alcoholic fatty liver disease (NAFLD) and low 25(OH) vitamin D levels in an adult population with normal serum liver enzymes. BMC Med 2011;9:85. doi: 10.1186/1741-7015-9-85.
[21] 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;28:579–584. doi: 10.1111/ctr.12351.
[22] Floreani A, Zappala F, Fries W, Naccarato R, Plebani M, D'Angelo A, *et al*. A 3-year pilot study with 1,25-dihydroxyvitamin D, calcium, and calcitonin for severe osteodystrophy in primary biliary cirrhosis. J Clin Gastroenterol 1997;24:239–244. doi: 10.1097/00004836-199706000-00012.
[23] Bouillon R, Auwerx J, Dekeyser L, Fevery J, Lissens W, De Moor P. Serum vitamin D metabolites and their binding protein in patients with liver cirrhosis. J Clin Endocrinol Metab 1984;59:86–89. doi: 10.1210/jcem-59-1-86.
[24] Diamond TH, Stiel D, Lunzer M, McDowall D, Eckstein RP, Posen S. Hepatic osteodystrophy. Static and dynamic bone histomorphometry and serum bone Gla-protein in 80 patients with chronic liver disease. Gastroenterology 1989;96:213–221. doi: 10.1016/0016-5085(89)90783-x.
[25] Guggenbuhl P, Deugnier Y, Boisdet JF, Rolland Y, Perdriger A, Pawlotsky Y, *et al*. Bone mineral density in men with genetic hemochromatosis and HFE gene mutation. Osteoporos Int 2005;16:1809–1814. doi: 10.1007/s00198-005-1934-0.
[26] Anty R, Hastier A, Canivet CM, Patouraux S, Schneck AS, Ferrari-Panaia P, *et al*. Severe vitamin D deficiency is not associated with liver damage in morbidly obese patients. Obes Surg 2016;26:2138–2143. doi: 10.1007/s11695-016-2070-y.
[27] Zhao XY, Li J, Wang JH, Habib S, Wei W, Sun SJ, *et al*. Vitamin D serum level is associated with Child-Pugh score and metabolic enzyme imbalances, but not viral load in chronic hepatitis B patients. Medicine (Baltimore) 2016;95:e3926. doi: 10.1097/MD.0000000000003926.
[28] Nykjaer A, Dragun D, Walther D, Vorum H, Jacobsen C, Herz J, *et al*. An endocytic pathway essential for renal uptake and activation of the steroid 25-(OH) vitamin D3. Cell 1999;96:507–515. doi: 10.1016/s0092-8674(00)80655-8.
[29] Chen JS, Sambrook PN, March L, Cameron ID, Cumming RG, Simpson JM, *et al*. Hypovitaminosis D and parathyroid hormone response in the elderly: effects on bone turnover and mortality. Clin Endocrinol (Oxf) 2008;68:290–298. doi: 10.1111/j.1365-2265.2007.03040.x.
[30] Klein GL, Endres DB, Colonna JD 2nd, Berquist WE, Goldstein LI, Busuttil RW, *et al*. Absence of hyperparathyroidism in severe liver disease. Calcif Tissue Int 1989;44:330–334. doi: 10.1007/bf02556312.