Clinics and Research in Hepatology and Gastroenterology (2019) 43, 51—57

Available online at
ScienceDirect
www.sciencedirect.com

Elsevier Masson France
EM|consulte
www.em-consulte.com/en

ORIGINAL ARTICLE

Role of vitamin D deficiency as a risk factor for infections in cirrhotic patients

Haidi K. Ramadan[a], **Nahed A. Makhlouf**[a,*], **Amal A. Mahmoud**[b], **Mohamed Abd Elrhman**[b], **Muhammad Abbas El-Masry**[c]

[a] *Tropical Medicine and Gastroenterology Department, Faculty of Medicine, Assiut University, Assiut 71515, Egypt*
[b] *Clinical Pathology Department, Faculty of Medicine, Assiut University, Assiut 71515, Egypt*
[c] *Internal Medicine Department, Division of Gastroenterology, Faculty of Medicine, Assiut University, Assiut 71515, Egypt*

Available online 11 October 2018

KEYWORDS
Infection;
Liver cirrhosis;
Vitamin D;
Disease severity;
Predictor

Summary
Background: Vitamin D plays a role in innate and acquired immunity. The risk for bacterial infections is increased in cirrhotic patients due to low levels of vitamin D. This study aimed to determine serum 25-(OH) vitamin D levels among cirrhotic patients in the presence and absence of infections and correlate this level with liver disease severity.
Methods: This cross-sectional analytic study recruited 87 hospitalised cirrhotic patients who were divided into the following groups: group with evidence of infection (45 cases) and group without infection (42 cases). Urine analysis, ascetic fluid study and chest X-rays were performed to find the site of infection. Serum 25-(OH) vitamin D was also measured.
Results: Vitamin D levels were lower in the cirrhotic with infection group than in the cirrhotic without infection group (17.3 ± 2.5 vs. 41.1 ± 3.1, respectively) (P-value < 0.001). Approximately 71.4% cirrhotic patients without infection had sufficient vitamin D levels, while 60% of cirrhotic patients with infection had insufficient vitamin D levels, and 28.9% had vitamin D deficiency (P-value < 0.001). Spontaneous bacterial peritonitis was the most common infection (62.2%). The cutoff point of vitamin D levels for cirrhotic patients with infection was 21 ng/mL.
Conclusion: Vitamin D deficiency was found to be an independent predictor of infection in cirrhotic patients suggesting that vitamin D supplementation may be useful in these patients. No significant correlations were found between the vitamin D level and the Child—Pugh class and MELD score among the infected group and non-infected group.

* Corresponding author.
E-mail addresses: Heidi_ramadan@yahoo.com (H.K. Ramadan), nahedmak@yahoo.com (N.A. Makhlouf), Amal11068@yahoo.com (A.A. Mahmoud), m_z_abokrisha@yahoo.com (M. Abd Elrhman), masaeed2@yahoo.com (M.A. El-Masry).

https://doi.org/10.1016/j.clinre.2018.09.001
2210-7401/

25-OH vitamin D	twenty-five hydroxy vitamin D
MELD	Model for End Stage Liver Disease
SBP	spontaneous bacterial peritonitis
CBC	complete blood count
ELISA	enzyme-linked immunosorbent assay

Introduction

Vitamin D plays a role in the metabolism of calcium and has an effect on bone mineralisation. Rickets in children and osteomalacia in adults are both consequences of vitamin D deficiency [1]. Vitamin D also participates in innate and acquired immunity; it increases innate immunity and modifies lymphocyte activation, leading to a change towards the T2 helper response [2,3].

Low twenty-five hydroxy vitamin D (25-OH vitamin D) levels were associated with an increased risk of bacterial infection in intensive care units [4]. Studies in children reported an association between vitamin D deficiency and the risk of viral diseases [5].

Disturbed vitamin D metabolism in liver cirrhosis was first reported in the late '1970s and was attributed to defective 25-(OH) vitamin D hydroxylation of the precursor of vitamin D caused by impaired liver function [6—8]. Moreover, vitamin D deficiency was associated with increased bacterial infections in patients with liver cirrhosis [9].

The relation between vitamin D deficiency and mortality in cirrhotic patients could be related to bacterial infections [9]. Low vitamin D levels were associated with liver insufficiency and infections; thus, vitamin D can be used to assess prognosis in patients with cirrhosis [9,10].

Few studies have focused on the role of vitamin D as a predictive factor for infections among cirrhotic patients in our locality.

The aim of the work: to determine the serum 25(OH) vitamin D level among cirrhotic patients in the presence and absence of infections and correlate it with the risk of infections.

Patients and methods

This cross-sectional analytic study was conducted in the Tropical Medicine and Gastroenterology Department, Al Rajhi Liver Hospital, Assiut, Egypt. The inclusion criteria were as follows: admitted patients with liver cirrhosis during 6 months from August 2017 to January 2018. Patients were divided into 2 groups. Group I comprised patients with cirrhosis with infection at any site, and group II comprised patients with cirrhosis with no evidence of infection.

The diagnosis of infection was based on clinical data with laboratory and radiological findings.

The exclusion criteria were as follows: patients with cholestatic liver disease, patients receiving antibiotics to treat their infection prior hospital admission and patients refusing to participate in the study.

All included patients were subjected to history taking; physical examination; laboratory assessment, including complete blood count, liver function, serum urea and creatinine, and chemical analysis of ascitic fluid (if the patient has ascites). In addition, urine analysis and chest X-rays were performed. The Child—Pugh score and Model for End Stage Liver Disease (MELD) score were used to assess liver disease severity.

The diagnosis of spontaneous bacterial peritonitis (SBP) was made based on the presence of ≥ 250 polymorphonuclear (PMN) cells/m^3 in ascitic fluid with or without a positive ascitic fluid bacterial culture with no secondary peritonitis [11]. Serum 25-(OH) vitamin D was measured for both groups.

Laboratory methods

1. Eight millilitres blood was withdrawn by venepuncture and distributed into three tubes, with 2 mL in an EDTA tube for CBC, 2 mL for prothrombin time and concentration, and 4 mL in a plastic tube that was allowed to clot for serum separation. Non-haemolyzed serum was separated by centrifugation, and part was used for the determination of creatinine and liver functions; another part was stored in aliquots at $-20\,^{\circ}C$ to measure vitamin D levels.

2. Ascitic fluid samples were obtained by paracentesis performed under complete aseptic conditions.

Laboratory tests

The level 25-hydroxy vitamin D in the serum was measured by the competitive enzyme-linked immunosorbent assay (ELISA) technique using a CALBIOTECH kit (A life science company, Catalogue No.: VD220B, San Diego-based company established in 1998, USA). The vitamin D level was defined as sufficient if between 30—100 ng/mL, insufficient between 10—30 ng/mL and deficient if < 10 ng/mL.

The institutional review board statement

This study was approved by the Faculty of Medicine Ethics and Scientific Research Committees (ID: 17300136. Clinical trial, No.: NCT03391245). All patients provided written consent. The data were confidential. All procedures performed in this study were in accordance with the ethical standards of the institution and/or national research committee and with the 1964 Helsinki Declaration and its later amendments.

Statistical analysis

Statistical Package for the Social Sciences (SPSS, version 20; SPSS Inc., Chicago, IL, USA) software was used for statistical analysis. The means $\pm$ standard deviation/error or frequencies were used. Chi^2 tests were applied for comparison between proportions. Continuous variables were tested for a normal distribution using the Shapiro—Wilk test and Q-Q Plots. The data were nonparametric.

The Mann—Whitney U test was applied for comparisons of continuous variables between the 2 groups. Spearman's correlation analysis was performed for assessment of correlations between the vitamin D level and both the Child—Pugh class and MELD scores among the infected and non-infected

Table 1 Demographic characteristics and disease severity of the study groups.

Variable	Cirrhotic with infection $n=45$	Cirrhotic without infection $n=42$	*P*-value
Age (yr)[a]	59.7 ± 11.7	59.3 ± 10.2	0.881
Gender			0.681
Male	27 (60%)	27 (64.3%)	
Female	18 (40%)	15 (35.7%)	
Child-Pugh class			0.202
A	0 (0%)	1 (2.4%)	
B	11 (24.4%)	16 (38.1%)	
C	34 (75.6%)	25 (59.5%)	
MELD score[a]	20.67 ± 6.9	18.6 ± 5.4	0.085
Ascites	40 (88.9%)	34 (81%)	0.299

Data are expressed as numbers and percentages. *n*: number.
[a] Data are expressed as the mean ± standard deviation (SD).

Table 2 Laboratory data of the study groups.

Variable	Cirrhotic with infection $n=45$	Cirrhotic without infection $n=42$	*P*-value
WBCS ($\times 1000/mm^3$)	9.2 ± 5.6	6.8 ± 0.8	0.020[b]
RBCS	3.6 ± 0.9	3.5 ± 0.5	0.276
Hb (g/dL)	10.3 ± 0.4	9.8 ± 0.3	0.313
PLT ($\times 1000/mm^3$)	105.7 ± 11.7	118.8 ± 9.5	0.390
Urea (mmol/L)	15.7 ± 1. 8	11.7 ± 1.1	0.102
Baseline creatinine (umol/L)	151.4 ± 20.1	111.4 ± 8.5	0.042[b]
Total bilirubin (umol/L)	78.5 ± 11.3	70.4 ± 17.3	0.690
Total protein g/L	63.8 ± 1.9	66.4 ± 1.5	0.301
Albumin g/L	23.3 ± 0.9	24.4 ± 1.1	0.419
AST (U/L)	95.1 ± 11.4	67.6 ± 10.1	0.076
ALT (U/L)	54.7 ± 8.4	63.5 ± 27.4	0.753
Prothrombin time	21.0 ± 0 .7	19.0 ± 0.5	0.026[b]
Number of cases with diagnostic paracentesis[a]	32/40(80%)	27/34(79.4%)	0.949
Polymorph in ascitic fluid	3031.3 ± 917.2	57.1 ± 9.7	0.003[b]
Protein in ascitic fluid	10.9 ± 1.7	14.0 ± 2.0	0.244
Albumin in ascitic fluid	5.2 ± 1.2	6.6 ± 0.9	0.343

Hb: haemoglobin; WBC: white blood cell count; PLT: platelet count; AST: aspartate aminotransferase; ALT: alanine aminotransferase; data are expressed as the mean ± SE; *n*: number.
[a] Data are expressed as the number and percentage.
[b] Significant.

groups. Univariate and multivariate regression were applied for detection of the risk factors for infection. *P*-values < 0.05 were considered significant. The receiver operator characteristic (ROC) curve was used to determine the optimum vitamin D level cutoff points for infected cirrhotic patients.

Results

The present study included 87 cases with liver cirrhosis. The aetiology of liver cirrhosis was HCV in 74 cases (85.1%), HBV in 6 cases (6.9%), Budd—Chiari syndrome in 3 cases (3.4%), and others in 4 cases (4.4%) (including autoimmune disease, cryptogenic, combined HBV and HCV, and Wilson's disease). Patients were divided into 2 groups. Group 1 included 45 cirrhotic patients with infection, and group 2 included 42 cirrhotic patients with no infection.

Patients were age and sex matched. The majority of cases in both groups were either Child—Pugh class C or B. The MELD scores were not significantly different between the two groups ($P=0.085$) (Table 1).

Regarding the common sites of infection among the cirrhotic group with infection, SBP was the most common in 28 patients (62.2%), followed by respiratory tract infection in 10 patients (22.2%), skin and soft tissue infection (cellulitis) in 4 patients (8.8%) and urinary tract infection in 3 patients (6.6%).

Laboratory data of the study groups

The WBC count, baseline creatinine, prothrombin time, and polymorph count in ascitic fluid were significantly different between the two groups. These measures were elevated

Table 3 Vitamin D level and status in the study groups.

Variable	Cirrhotic with infection $n=45$	Cirrhotic without infection $n=42$	*P*-value
Vitamin D level (ng/mL)	17.3 ± 2.5	41.1 ± 3.1	< 0.001[b]
Vitamin D status[a]			< 0.001[b]
Sufficient	5 (11.1%)	30 (71.4%)	
Insufficient	27 (60%)	12 (28.6%)	
Deficient	13 (28.9%)	0 (0%)	

Data are expressed as the mean ± standard error (SE); *n*: number.
[a] Data are expressed as the number and percentage.
[b] Significant; sufficient: reference range (30—100 ng/mL). Insufficient: reference range (10—30 ng/mL). Deficient: reference range < 10 ng/mL.

Table 4 Independent predictors of infection among cirrhotic patients using multivariate regression analysis.

Variable	EXP (B)	*P*-value	95% CI for EXP (B)
WBCS ($\times 1000/mm^3$)	1.1	0.131	0.966—1.303
Baseline creatinine (umol/L)	1.0	0.200	0.977—1. 015
Prothrombin time (min)	1.2	0.069	0.988—1.387
Vitamin D level (ng/mL)	0.93	0.000[a]	0.894—0.959

[a] Significant.

in the cirrhotic with infection group ($P=0.020$, $P=0.042$, $P=0.026$, $P=0.003$, respectively). The remaining laboratory data showed no differences between the groups ($P>0.05$) (Table 2).

Vitamin D levels and status in the study groups

The mean vitamin D level was lower in the cirrhotic with infection group than in the cirrhotic without infection group (17.3 ± 2.5 and 41.1 ± 3.1, respectively) (*P*-value < 0.001). Approximately 71.4% of cirrhotic patients without infection had sufficient levels of vitamin D. However, 27 (60%) cirrhotic patients with infection had insufficient levels of vitamin D, and 13 (28.9%) had a vitamin D deficiency (*P*-value < 0.001) (Table 3). Among the infected group, the mean levels of vitamin D were lower in Child—Pugh class C ($n=34$) than in Child—Pugh class B ($n=11$) (11.9 ± 0.9 vs. 19.1 ± 3.2) (*P*-value = 0.037).

Among the cirrhotic without infection group, there was no significant difference between the Child—Pugh class and mean vitamin D level (*P*-value = 0.256).

Using Spearman's correlation analysis, no significant correlations were found between the vitamin D level and the Child—Pugh class and MELD score among the infected group and non-infected group ($P=0.987$, $r=0.003$; $P=0.112$, $r=0.240$; $P=0.05$, $r=0.305$; $P=0.221$, $r=0.193$, respectively).

According to multivariate regression analysis, a low vitamin D level was an independent predictor of infection among cirrhotic patients (Table 4).

ROC curve analysis of vitamin D levels

Using a ROC curve, the optimal vitamin D level cutoff point for cirrhotic patients with infection was 21 ng/mL with a sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and overall accuracy of 84.44%, 88.10%, 88.4%, 84.1%, and 86.2%, respectively (area under the curve: 0.861) (Fig. 1).

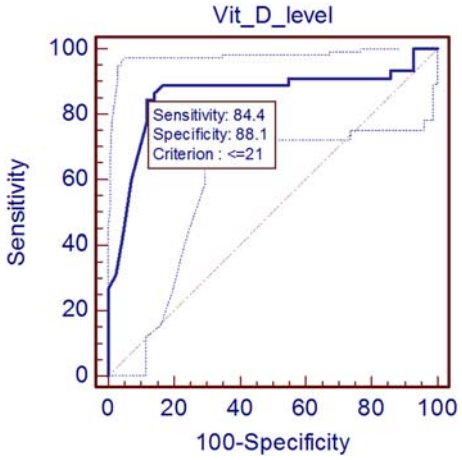

Figure 1 Receiver operating characteristic (ROC) curves of vitamin D levels in detecting infection among cirrhotic patients.

Discussion

In Egypt, the highest prevalence of vitamin D insufficiency was found in the elderly population (77.2%) and in pregnant females (72%), while the lowest prevalence was found in children (11.5%) [12—14].

Vitamin D deficiency has a higher prevalence in chronic liver disease (CLD) cases than in the general population, with a range between 64% and 92% [15]. This high prevalence occurs regardless of the aetiology of CLD [16]. In the

current study, 27 (60%) cirrhotic with infection cases had insufficient levels of vitamin D, and 13 (28.9%) had vitamin D deficiency (P-value < 0.001). In contrast, vitamin D levels were insufficient in only 12 patients (28.6%) among those without infection.

El Tayeb et al. examined 59 healthy Egyptian men (age range: 40—59 years), and found 13.6% and 23.7% having insufficient and deficient vitamin D status, respectively [17].

A low level of vitamin D in CLD patients is caused by several mechanisms, such as malnutrition, low sunlight exposure, low intestinal absorption of vitamin D caused by intestinal oedema complicating portal hypertension, or cholestasis-induced bile salt disruption. In addition, low levels of vitamin D-binding proteins (DBPs) and albumin, which transfer vitamin D to the liver and kidney for subsequent activation, could be a contributing factor. Moreover, hydroxylation of vitamin D by the liver is impaired, leading to low production of the active form of vitamin D, while the catabolism of the vitamin remains high [18].

Macrophages, dendritic cells, and lymphocyte T and B cells release CYP27B1 enzymes, which change 25-(OH) vitamin D to calcitriol. Calcitriol then binds to receptors in innate immune cell nuclei, particularly in antigen-presenting cells, acting as a transcription factor for the antimicrobial peptides cathelicidin and beta defensins. This process leads to an acceleration of 3 actions, phagocytic, chemotactic, and antimicrobial effects [19,20].

Therefore, vitamin D contributes to immune regulation with a protective effect against infections. Vitamin D deficiency worsens as liver disease stages become more advanced. In the current study, the mean level of vitamin D was lower in infected patients with Child—Pugh class C than in those with Child—Pugh class B (P-value = 0.037). This finding was similar to the results of Fisher et al. who reported more vitamin D deficiency in cirrhotic patients with Child—Pugh grade C than in those with Child—Pugh grade A [21].

Infection in cirrhotic patients mostly represents a particular prognostic stage of cirrhosis, which affects survival regardless of liver disease severity. Additionally, infected patients have a higher risk of mortality even if they survive an acute episode of infection [22]. Gentile et al. concluded that infection in hospitalised cirrhotic patients had an impact on survival over a median follow-up of one year irrespective of liver disease stage with 30% mortality [23].

Moreover, in a recent prospective multicentre study, the thirty-day mortality in cirrhotic patients with infection was 25%. SBP in 36% of patients and pneumonia in 31% were associated with the highest mortality rates, followed by primary blood stream infection (29%) [24].

In the current study, SBP was the most common infection among cirrhotic patients (62.2%). Respiratory tract infection was the second most common (22.2%), followed by skin and soft tissue infection and urinary tract infection as the least common. Low vitamin D levels could be a risk factor for SBP; this group of patients requires vitamin D supplementation, which could also be used as a prophylactic therapy. Trepo et al. reported a tendency towards an increased incidence of SBP (15.7 vs. 6.9%, P = 0.056) in cirrhotic patients with (n = 142) and without (n = 112) a severe vitamin D deficiency [25].

The antimicrobial peptide cathelicidin (LL-37) is involved in protecting the epithelial barrier against infection and is secreted by immune cells in blood circulation. Vitamin D intracellular signalling activates cathelicidin via the vitamin D receptor (VDR) [26].

Zhang et al. evaluated the role of the vitamin D/LL-37 pathway in the pathogenesis and treatment of SBP and reported that vitamin D supplementation enhances peritoneal macrophage VDR and LL-37 expression levels to prevent SBP in decompensated cirrhosis [27]. However, in a recent study, urinary tract infections were the most common, followed by lower respiratory tract infections, SBP and sepsis; thus, the authors concluded that vitamin D deficiency was one of the possible predictive factors for infections in liver cirrhosis [28].

In multivariate regression analysis, vitamin D deficiency was an independent predictor of infection in cirrhotic patients in the current study (P-value < 0.001). In the present study, the optimum vitamin D cutoff level in cirrhotic patients with infection was 21 ng/mL with a sensitivity and specificity of 84.44% and 88.10%, respectively. However, Anty et al. studied 88 subjects and found that cirrhotic patients with marked vitamin D deficiencies (< 10 ng/mL) had more bacterial infections than did those with vitamin D levels $\geq$ 10 ng/mL (54% versus 29%, P = 0.02) [9].

The Institute of Medicine (IOM) of the National Academies in the United States considers a vitamin D level of 20 ng/ml adequate [29]. In contrast, the Endocrine Society (Maryland, USA) considers 30 ng/mL vitamin D (i.e., 75 nmol/L) adequate. However, optimal levels were defined as 40—60 ng/mL (i.e., 100—150 nmol/L) [30]. Nonetheless, there is still no definition of the optimal levels of vitamin D for patients with CLDs [31].

In a prospective study conducted on 101 patients with liver cirrhosis, compared with the control group, the treatment group showed a trend towards greater survival (69% vs. 64%) and longer survival (155 days vs. 141 days), however, it was non-significant. Thus, vitamin D supplementation in patients with liver cirrhosis was significantly associated with survival over 6 months [32].

The efficacy of vitamin D supplementation in liver cirrhosis in decreasing infection risk with the determination of the optimal dose, route of administration and duration must be further validated in large prospective studies and randomised trials.

Although a previous study investigated this association between vitamin D and infection in liver cirrhosis, our study took more advanced stages of liver cirrhosis into account. Our study also included a cirrhotic group with infection and another group without infection as a control group. Both groups were age and sex matched, as well as matched with regard to the severity of liver cirrhosis.

However, our study has some limitations. First, this is a single centre study. Second, no culture was used to determine the specific organisms causing the infections. However, culture testing takes time, and patients usually receive empirical antibiotics on admission before culture results are obtained. Third, we did not assess the effect of vitamin D administration in these cases.

Conclusion

Vitamin D deficiency was found to be an independent predictor of infection in cirrhotic patients suggesting that Vitamin D supplementation may be useful in these patients. No significant correlations were found between the vitamin D level and the Child—Pugh class and MELD score among the infected group and non-infected group.

Author contributions

Makhlouf NA and Ramadan HK were responsible for the idea and the design of the study; Makhlouf NA designed the sheet for collection of the data and analysed and interpreted the data; Ramadan HK collected the data; Mahmoud AA and Abd Elrhman MZ performed all the laboratory work related to the research and contributed to the writing of the laboratory methods used in the study. Makhlouf NA, Ramadan HK, and El-Masry MA performed the research and wrote the paper. Makhlouf NA, Ramadan HK, Mahmoud AA, Abd Elrhman MZ, and El-Masry MA revised the manuscript for final submission.

Fund

This research received no specific grant from any funding agency. Funding for this research was covered by the authors.

The institutional review board statement

This study was approved by the Faculty of Medicine Ethics and Scientific Research Committees. ID:17300136.

The informed consent statement

Informed consent was obtained from all the patients.

Disclosure of interest

The authors declare that they have no competing interest.

References

[1] Holick MF. Vitamin D deficiency. N Engl J Med 2007;357:266—81.
[2] Baeke F, Takiishi T, Korf H, et al. Vitamin D modulator of the immune system. Curr Opin Pharmacol 2010;10:482—96.
[3] Bikle DD. Vitamin D regulation of immune function. Vitam Horm 2011;86:1—21.
[4] Moromizato T, Litonjua AA, Braun AB, et al. Association of low serum 25-hydroxyvitamin D levels and sepsis in the critically III. Crit Care Med 2014;42:97—107.
[5] Yamshchikov AV, Desai NS, Blumberg HM, et al. Vitamin D for treatment and prevention of infectious diseases: a systematic review of randomized controlled trials. Endocr Pract 2009;15:438—49.
[6] Hepner GW, Roginsky M, Moo HF. Abnormal vitamin D metabolism in patients with cirrhosis. Am J Dig Dis 1976;21:527—32.
[7] Jung RT, Davie M, Hunter JO, et al. Abnormal vitamin D metabolism in cirrhosis. Gut 1978;19:290—3.
[8] Long RG, Skinner RK, Wills MR, et al. Serum-25-hydroxyvitamin-D in untreated parenchymal and cholestatic liver disease. Lancet 1976;2:650—2.
[9] Anty R, Tonohouan M, Ferrari-Panaia P, et al. Low levels of 25-hydroxy vitamin D are independently associated with the risk of bacterial infection in cirrhotic patients. Clin Transl Gastroenterol 2014;4:e56.
[10] Stokes CS, Krawczyk M, Reichel C, et al. Vitamin D deficiency is associated with mortality in patients with advanced liver cirrhosis. Eur J Clin Invest 2014;44:176—83.
[11] Rimola A, Gracía-Tsao G, Navasa M, et al. Diagnosis, treatment and prophylaxis of spontaneous bacterial peritonitis: a consensus document. International Ascites Club. J Hepatol 2000;32:142—53.
[12] El Rifai NM, Abdel Moety GA, Gaafar HM, et al. Vitamin D deficiency in Egyptian mothers and their neonates and possible related factors. J Matern Fetal Neonatal Med 2014;27:1064—8.
[13] Abu Shady MM, Youssef MM, Salah El-Din EM, et al. Predictors of serum 25-hydroxyvitamin D concentrations among a sample of Egyptian school children. Sci World J 2016;2016:8175768, http://dx.doi.org/10.1155/2016/8175768.
[14] Hwalla N, Al Dhaheri AS, Radwan H, et al. The prevalence of micronutrient deficiencies and inadequacies in the Middle East and approaches to interventions. Nutrients 2017;9, http://dx.doi.org/10.3390/nu9030229 [pii: E229].
[15] Arteh J, Narra S, Nair S. Prevalence of vitamin D deficiency in chronic liver disease. Dig Dis Sci. 2010; 55:2624-2628.
[16] Malham M, Jorgensen SP, Ott P, et al. Vitamin D deficiency in cirrhosis relates to liver dysfunction rather than etiology. World J Gastroenterol 2011;17:922—5.
[17] El Tayeb IM, El-Saghier EOA, Cheta S, et al. Assessment of vitamin D status among senior executive managers in large scale industries in the 10th of Ramadan city, Egypt. IOSR J Dent Med Sci 2013;12:77—83.
[18] Stokes CS, Volmer DA, Grunhage F, et al. Vitamin D in chronic liver disease. Liver Int 2013;3:338—52.
[19] Gombart AF. The vitamin D-antimicrobial peptide pathway and its role in protection against infection. Future Microbiol 2009;4:1151—65.
[20] Lin R. Crosstalk between vitamin D metabolism, VDR signalling, and innate immunity. BioMed Res Int 2016;2016:5 pages, http://dx.doi.org/10.1155/2016/1375858 [Article ID 1375858].
[21] Heuman DM, Mihas AA, Habib A, et al. MELD-XI: a rational approach to ''sickest first'' Liver transplantation in cirrhotic patients requiring anticoagulant therapy. Liver Transpl 2007;13:30—7.
[22] Dionigi E, Garcovich M, Borzio M, et al. Bacterial infections change natural history of cirrhosis irrespective of liver disease severity. Am J Gastroenterol 2017;112:588—96.
[23] Gentile I, Buonomo AR, Scotto R, et al. Infections worsen prognosis of patients with cirrhosis irrespective of the liver disease stage. Eur J Intern Med 2017;46:e45—7.
[24] Bartoletti M, Giannella M, Lewis R, et al. A prospective multicentre study of the epidemiology and outcomes of bloodstream infection in cirrhotic patients. Clin Microbiol Infect 2018;24:546.e1—8.
[25] Trepo E, Ouziel R, Pradat P, et al. Marked 25-hydroxyvitamin D deficiency is associated with poor prognosis in patients with alcoholic liver disease. J Hepatol 2013;59:344—50.
[26] Liu PT, Stenger S, Li H, et al. Toll-like receptor triggering of a vitamin D mediated human antimicrobial response. Science 2006;311:1770—3.
[27] Zhang C, Zhao L, Ding Y, et al. Enhanced LL-37 expression following vitamin D supplementation in patients with cirrhosis and spontaneous bacterial peritonitis. Liver Int 2016;36:68.

[28] Buonomo AR, Zappulo E, Scotto R, et al. Vitamin D deficiency is a risk factor for infections in patients affected by HCV-related liver cirrhosis. Int J Infect Dis 2017;63: 23.
[29] Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D. Calcium: the national academies collection: reports funded by National Institutes of Health. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Dietary reference intakes for calcium and vitamin D. Washington (DC): National Academies Press (US) National Academy of Sciences; 2011.
[30] Holick MF, Binkley NC, Bischoff-Ferrari HA, et al. Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2011;96:1911—30.
[31] Konstantakis C, Tselekouni P, Kalafateli M, et al. Vitamin D deficiency in patients with liver cirrhosis. Ann Gastroenterol 2016;29:297—306.
[32] Jha AK, Jha SK, Kumar A, et al. Effect of replenishment of vitamin D on survival in patients with decompensated liver cirrhosis: a prospective study. World J Gastrointest Pathophysiol 2017;8:133—41.