Vitamin D deficiency is associated with hepatic decompensation and inflammation in patients with liver cirrhosis: A prospective cohort study

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Abstract

Background

Vitamin D is required to maintain the integrity of the intestinal barrier and inhibits inflammatory signaling pathways.

Objective

Vitamin D deficiency might be involved in cirrhosis-associated systemic inflammation and risk of hepatic decompensation in patients with liver cirrhosis.

Methods

Outpatients of the Hepatology Unit of the University Hospital Frankfurt with advanced liver fibrosis and cirrhosis were prospectively enrolled. 25-hydroxyvitamin D (25(OH)D₃) serum concentrations were quantified and associated with markers of systemic inflammation / intestinal bacterial translocation and hepatic decompensation.

Results

A total of 338 patients with advanced liver fibrosis or cirrhosis were included. Of those, 51 patients (15%) were hospitalized due to hepatic decompensation during follow-up. Overall, 72 patients (21%) had severe vitamin D deficiency. However, patients receiving vitamin D supplements had significantly higher 25(OH)D₃ serum levels compared to patients without supplements (37 ng/mL vs. 16 ng/ml, P<0.0001). Uni- and multivariate analyses revealed an independent association of severe vitamin D deficiency with the risk of hepatic decompensation during follow-up (multivariate P = 0.012; OR = 3.25, 95% CI = 1.30–8.2), together with MELD score, low hemoglobin concentration, low coffee consumption, and presence of diabetes. Of note, serum levels of C-reactive protein, IL-6 and soluble CD14 were significantly higher in patients with versus without severe vitamin D deficiency, and serum levels...
of soluble CD14 levels declined in patients with *de novo* supplementation of vitamin D (median 2.15 vs. 1.87 ng/mL, *P* = 0.002).

**Conclusions**

In this prospective cohort study, baseline vitamin D levels were inversely associated with liver-cirrhosis related systemic inflammation and the risk of hepatic decompensation.

**Introduction**

Vitamin D is a key hormone in the regulation of bone metabolism [1]. However, vitamin D receptor (VDR) signaling has been shown to impact on the expression of more than 9000 genes, and accumulating evidence suggests that these genomic effects of calcitriol, the bioactive form of vitamin D, execute important non-classical (in contrast to bone metabolism) functions of vitamin D such as regulation of immune responses or cell proliferation [2]. For example, vitamin D serves as an anti-inflammatory mediator by inhibiting the differentiation of Th17 cells in favor of regulatory T cells [3]. Furthermore, it was shown that supplementation with the vitamin D precursor cholecalciferol results in a decrease of C-reactive protein (CRP), IL-6 and TNF-α serum levels in hemodialysis patients [4]. A significant reduction of systemic inflammation and consecutive resolution of inflammation has also been observed in an interventional study with high-dose cholecalciferol in patients with lung tuberculosis [5].

Additional studies have suggested a role of VDR signaling in maintaining the integrity of the intestinal barrier and intestinal bacterial homeostasis. For example, a large prospective study has shown that baseline vitamin D deficiency is associated with an increased risk of inflammatory bowel disease during follow-up [6]. Mechanistically, this might be explained by direct effects of VDR signaling on tight junctions and integrity of intestinal epithelial cells [7,8]. Furthermore, polymorphisms in the VDR were identified by a genome-wide association study to be associated with distinct composition of the gut microbiota [9].

Both, systemic inflammation and dysfunction of the intestinal barrier are key drivers of the progression of chronic liver disease. Since vitamin D deficiency is particular frequent in patients with liver disease such as viral hepatitis, or alcoholic hepatitis [10–14], we aimed to further explore the relationship between vitamin D serum levels, systemic inflammation and hepatic decompensation in a prospective cohort study of patients with liver cirrhosis.

**Patients and methods**

**Study population**

Since July 2016, consecutive patients presenting to the outpatient liver clinic of the University Hospital Frankfurt, Germany, with advanced liver fibrosis or cirrhosis were included in a prospective cohort study. Inclusion criteria were age above 18 years, diagnosed advanced fibrosis (Metavir  \( \geq F2 \)) or cirrhosis of different etiologies, and written informed consent to participate in the study. Exclusion criteria were age below 18 years, pregnancy or breastfeeding, presence of hepatocellular carcinoma (HCC) beyond Milan criteria, presence of infection with human immunodeficiency virus (HIV), or therapy with immunosuppressive agents. The patients were followed up every three months and when admitted to hospital with hepatic decompensation. At each follow-up time point, clinical and laboratory variables including 25-hydroxyvitamin D concentration were recorded and serum samples were stored for further analyses. Vitamin D
supplementation was initiated in a number of patients according to the responsible physicians’ discretion.

Liver fibrosis was assessed by shear-wave elastography using a Hitachi HI VISION Ascendus system (pSWE (ARFI); thresholds F3 = >9.5 kPa, F4 = >12.5 kPa) or a Siemens Acuson S2000™ system (pSWE (ARFI) Virtual Touch Quantification (VTQ); thresholds F3 = >1.55 m/s, F4 = >1.8 m/s). In addition, liver fibrosis was assessed by the FibroTest™. Acute decompensation of liver cirrhosis was defined as presence of one of the following criteria: new onset / progression of hepatic encephalopathy graded by West-Haven criteria [15], gastrointestinal hemorrhage, bacterial infection, or ascites grade II-III (graded according to Moore et al.[16]).

The study was approved by the ethics committee of the University- Hospital Frankfurt prior to the study. A written informed consent was obtained from the patients prior to enrollment in the study.

Quantification of 25-hydroxyvitamin D [25(OH)D₃] serum levels
25-hydroxyvitamin (25(OH)D₃) levels were quantified by radioimmunoassay as previously described [17]. 25(OH)D₃ levels above >30 ng/ml were considered as optimal, whereas 25 (OH)D₃ levels between 10–30 ng/ml and <10 ng/ml were considered as deficiency and severe deficiency, respectively.

Quantification of IL-6, I-FABP, and soluble CD14 serum levels
Serum concentrations of IL-6, I-FABP, and soluble CD14 were quantified by ELISA as described previously [18].

Statistical analyses
Statistical analyses were performed using BiAS, Version 11.06, and Graphpad PRISM5. Group differences were assessed by means of χ² contingency tables or Wilcoxon-Mann-Whitney-U-tests, as appropriate. P values < 0.05 were considered to be statistically significant. Associations of outcomes with continuous or dichotomic variables were assessed in linear and logistic regression models, respectively. After univariate analyses, multivariate analyses were performed for significant associations. Multivariate models were obtained by backward selection, using a P value >0.15 for removal from the model.

Results
Patient characteristics
A total of 338 patients with advanced liver fibrosis or cirrhosis of different etiologies were recruited for the present study according to the above defined inclusion criteria. Baseline characteristics of included patients are shown in Table 1. During a median follow-up time of 3–12 months, 51 out of 338 patients (15%) were hospitalized due to hepatic decompensation, including 23 episodes of acute ascites, 16 episodes of acute hepatic encephalopathy, 16 infections, 16 cases of renal failure, and 6 cases of upper GI bleeding. Of patients who were hospitalized with hepatic decompensation, 36 and 44 had a previous history of ascites and overall hepatic decompensation, respectively, whereas 105 and 130 patients without hospitalization at follow-up had a previous history of ascites and overall hepatic decompensation, respectively. Sixteen patients (5%) died during follow-up.
The median 25(OH)D serum concentration of the entire cohort was 23 ng/mL. Of note, 118 patients (35%) out of the entire cohort (n = 338) received vitamin D supplements (1000 IU cholecalciferol daily in 56 patients, 20000 IU cholecalciferol once weekly in 62 patients). The median 25(OH)D serum concentration was significantly higher in patients receiving vitamin D supplements compared to patients who were not supplemented (37 ng/mL vs. 16 ng/ml, P < 0.0001). Of the entire cohort, 132 patients (39%) had optimal 25(OH)D serum levels >30 ng/ml, whereas 72 patients (21%) had severe vitamin D deficiency (25(OH)D serum concentration <10 ng/ml). Only 3 out of 72 patients (4%) with severe vitamin D deficiency received vitamin D supplements (more details in Table 2).

Seasonal variations of 25(OH)D serum levels are shown in S1 Table. Of note, seasonal variations of 25(OH)D serum were extensive in patients not receiving vitamin D supplements, whereas vitamin D supplementation strongly attenuated seasonal fluctuations of 25(OH)D serum levels.

Table 1. Baseline characteristics of included patients.

|                        | No Hospitalization due to decompensation at follow-up | Hospitalization at follow-up due to decompensation |
|------------------------|--------------------------------------------------------|---------------------------------------------------|
| Age (years); [SD]      | 59.40 [12.09]                                          | 61.45 [10.99]                                      |
| Coffee (cups/day); [SD]| 1.65 [1.65]                                             | 0.47 [0.92]                                       |
| Diabetes (presence); N [%] | 63 [22]                                                 | 21 [41]                                           |
| BMI (kg/m²); [SD]      | 27.10 [4.95]                                           | 26.20 [5.81]                                      |
| MELD Score; [SD]       | 9.68 [3.83]                                            | 13.76 [4.39]                                      |
| Creatinin (mg/dl); [SD]| 0.86 [0.29]                                             | 1.14 [0.83]                                       |
| Albumin (g/dl); [SD]   | 4.12 [0.62]                                             | 3.25 [0.59]                                       |
| Bilirubin (mg/dl); [SD]| 1.33 [1.45]                                             | 2.27 [1.68]                                       |
| ALT (U/L); [SD]        | 37.59 [43.70]                                           | 34.62 [24.60]                                     |
| yGTP (U/L); [SD]       | 111.3 [144.82]                                          | 205.66 [296.35]                                   |
| Leukocyte (/nl); [SD]  | 6.03 [2.23]                                             | 5.66 [2.74]                                       |
| Hb (mg/dl); [SD]       | 13.42 [1.91]                                            | 11.15 [2.31]                                      |
| Platelets (/nl); [SD]  | 141.05 [71.21]                                          | 122.96 [78.65]                                    |
| 25(OH)D₃ (ng/ml); [SD] | 27.95 [17.81]                                           | 21.24 [18.75]                                     |
| IL-6 (pg/mL); [SD]     | 3.61 [4.93]                                             | 1.52 [34.03]                                      |
| I-FABP (pg/mL);[SD]    | 1155.5 [928.16]                                         | 1973.2 [2050.9]                                   |
| sCD14 (ng/mL); [SD]    | 2.15 [0.66]                                             | 2.58 [0.59]                                       |
| Ascites at baseline, N [%] | 26 [9]                                                 | 27 [52]                                           |
| Hepatic encephalopathy at baseline, N [%] | 1 [0.35] | 2 [4] |
| History of ascites, N [%] | 105 [37] | 36 [71] |
| History of hepatic decompensation, N [%] | 13 [45] | 44 [86] |

Liver cirrhosis etiology of entire cohort n, (%)

| Etiology                      | Number (Percentage) |
|-------------------------------|---------------------|
| HCV                           | 117 (35)            |
| HBV                           | 53 (16)             |
| Alcoholic                     | 103 (30)            |
| NASH                          | 33 (10)             |
| Other                         | 32 (11)             |

ALT, alanine aminotransferase; BMI, body mass index; range; γGT, γ-glutamyl transferase; Hb, hemoglobin; I-FABP, intestinal fatty acid binding protein; MELD, model of end-stage liver disease.

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25(OH)D₃ serum levels

The median 25(OH)D₃ serum concentration of the entire cohort was 23 ng/mL. Of note, 118 patients (35%) out of the entire cohort (n = 338) received vitamin D supplements (1000 IU cholecalciferol daily in 56 patients, 20000 IU cholecalciferol once weekly in 62 patients). The median 25(OH)D₃ serum concentration was significantly higher in patients receiving vitamin D supplements compared to patients who were not supplemented (37 ng/mL vs. 16 ng/mL, P<0.0001). Of the entire cohort, 132 patients (39%) had optimal 25(OH)D₃ serum levels >30 ng/ml, whereas 72 patients (21%) had severe vitamin D deficiency (25(OH)D₃ serum concentration <10 ng/ml). Only 3 out of 72 patients (4%) with severe vitamin D deficiency received vitamin D supplements (more details in Table 2).

Seasonal variations of 25(OH)D₃ serum levels are shown in S1 Table. Of note, seasonal variations of 25(OH)D₃ serum were extensive in patients not receiving vitamin D supplements, whereas vitamin D supplementation strongly attenuated seasonal fluctuations of 25(OH)D₃ serum levels.
Next, multivariate linear regression analyses were performed to explore association with vitamin D serum levels in patients with advanced liver fibrosis or cirrhosis. The analyses were conducted separately for the entire cohort as well as for the subgroup of patients with and without vitamin D substitution. As shown in Table 3, waist circumference, smoking, and history of ascites were independently associated with lower 25(OH)D₃ serum levels, whereas no significant association between 25(OH)D₃ serum levels and MELD score, coffee or alcohol consumption were observed in the entire cohort. These results were largely comparable in the subgroups of patients with or without vitamin D substitution (Table 3).

Baseline vitamin D deficiency is associated with hepatic decompensation at follow-up

Uni- and multivariate analyses revealed an independent association of severe vitamin D deficiency with the risk of hepatic decompensation during follow-up (multivariate P = 0.012; OR = 3.25, 95% CI = 1.30–8.2), together with MELD score, low hemoglobin concentration, low coffee consumption, and presence of diabetes (Table 4). The association between severe vitamin D deficiency and the risk of hepatic decompensation during follow-up remained significant in the subgroup analysis of patients without vitamin D substitution, but not subgroup analysis of patient with vitamin D substitution (Table 4). Baseline 25(OH)D₃ serum concentration was also associated with hepatic decompensation during follow-up when assessed as a continuous variable (P = 0.002), or when other cut-offs for vitamin D deficiency were applied (P = 0.01 and P = 0.008 for 25(OH)D₃ serum concentration <20 ng/mL and <30ng/mL, respectively). Area under the receiver operating characteristic curve (AUROC) revealed a 25(OH)D₃ serum concentration of 8.5 ng/mL as the optimal cutoff to predict the risk of hepatic decompensation during follow-up (Fig 1). Furthermore, there was a trend for a protective association between vitamin D supplementation and hepatic decompensation (P = 0.1). Finally, severe vitamin D deficiency was associated with mortality during follow-up (P = 0.04), but not with the incidence of hepatocellular carcinoma (P = 0.6).

Table 2. 25(OH)D3 serum levels in patients with advanced liver fibrosis/cirrhosis.

| 25(OH)D₃ serum levels (ng/mL) | Overall (N = 338) | Patients on vitamin D supplements (N = 118) | Patients without vitamin D supplements (N = 220) |
|-------------------------------|------------------|----------------------------------------|---------------------------------------------|
| 25(OH)D₃ >30 ng/ml, N [%]    | 132 [39]         | 84 [71]                                | 48 [22]                                    |
| 25(OH)D₃ 30–20 ng/ml, N [%]  | 61 [18]          | 24 [20]                                | 37 [17]                                    |
| 25(OH)D₃ 20–10 ng/ml, N [%]  | 73 [22]          | 7 [6]                                  | 66 [30]                                    |
| 25(OH)D₃ <10 ng/ml, N [%]    | 72 [21]          | 3 [3]                                  | 69 [31]                                    |

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Vitamin D deficiency is associated with markers of systemic inflammation and bacterial translocation

Due to the anti-inflammatory and barrier-strengthening properties of VDR signaling, cirrhosis-associated systemic inflammation and dysfunction of intestinal barriers might be promoted by vitamin D deficiency. Indeed, patients with versus without severe vitamin D deficiency (25(OH)D$_3$ serum concentration) had significantly higher serum concentrations of CRP (0.85 mg/dL (SD = 1.3) versus 0.43 mg/dL (SD = 0.7), P = 0.007). Therefore, we assessed possible associations between 25(OH)D$_3$ serum concentration and IL-6, I-FABP, and soluble CD14, as additional surrogate markers of systemic inflammation, intestinal barrier dysfunction, and bacterial translocation, respectively. We performed this analyses in a subgroup of patients for which follow-up serum samples were available and in whom 25(OH)D$_3$ serum concentrations remained stable at low levels from baseline to follow-up (n = 39, median 25(OH)D$_3$...
concentration at baseline = 12 ng/mL and 10 ng/mL at follow-up) or in whom *de novo* supplementation of vitamin D was initiated at baseline (n = 55, median 25(OH)D₃ concentration at baseline = 9.8 ng/mL and 31 ng/mL at follow-up; P < 0.0001). Baseline serum levels of IL-6 and soluble CD14, but not of I-FABP, were significantly higher in patients with severe vitamin D deficiency at baseline compared to patients without severe vitamin D deficiency (Fig 2). During follow-up, soluble CD14 levels declined in comparison to baseline in patients with *de novo* supplementation of vitamin D (median 2.15 ng/mL vs. 1.87 ng/mL, P = 0.002), whereas no change was observed in patients with stably low vitamin D serum levels (median 1.97 ng/mL vs. 2.02 ng/mL, n.s.). However, no significant changes between baseline and follow-up were observed for IL-6 serum levels.

**Discussion**

The first main finding of our study is that severe vitamin D deficiency is frequent in patients with decompensated liver cirrhosis and is associated with the risk of hospitalization due to

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Table 4. Logistic regression analyses of hepatic decompensation in patients with liver cirrhosis.

|                      | Univariate analysis |          | Multivariate analysis |          |
|----------------------|---------------------|----------|-----------------------|----------|
|                      | P-value             | OR (95% CI) | P-value               | OR (95% CI) |
| **Entire Cohort**    |                     |          |                       |          |
| Male gender          | 0.92                | 0.97 (0.51–1.83) |                       |          |
| Age                  | 0.4                 | 1.01 (0.98–1.04) |                       |          |
| Coffee, cups per day | 0.000003            | 0.36 (0.23–0.55) | 0.0002                | 0.33 (0.18–0.59) |
| Presence of diabetes | 0.004               | 2.64 (1.37–5.10) | 0.001                 | 4.62 (1.86–11.55) |
| MELD score           | <0.00001            | 1.22 (1.14–1.32) | 0.0004                | 1.20 (1.08–1.32) |
| Leukocytes / nl      | 0.2                 | 0.91 (0.79–1.06) |                       |          |
| Hemoglobin (g/dL)    | <0.00001            | 0.62 (0.53–0.73) | 0.0004                | 0.71 (0.59–0.86) |
| 25(OH)D₃ <10ng/mL    | 0.01                | 2.44 (1.22–4.76) | 0.01                  | 3.25 (1.30–8.20) |
| Presence/history of ascites | 0.00001 | 4.7 (2.36–9.65) |                       |          |

**Subgroup of patients with vitamin D supplementation**

|                      |          |          |                       |          |
| Male gender          | 0.7      | 0.78 (0.23–2.61) |                       |          |
| Age                  | 0.3      | 0.92 (0.97–1.02) |                       |          |
| Coffee, cups per day | 0.02     | 0.11 (0.02–0.75) | 0.04                  | 0.11 (0.01–0.92) |
| Presence of diabetes | 0.3      | 1.90 (0.51–7.03) |                       |          |
| MELD score           | 0.0008   | 1.24 (1.09–1.41) | 0.05                  | 1.16 (1.00–1.35) |
| Leukocytes / nl      | 0.2      | 0.58 (0.59–1.12) |                       |          |
| Hemoglobin (g/dL)    | 0.003    | 0.58 (0.41–0.83) |                       |          |
| 25(OH)D₃ <10ng/mL    | 0.9      | 0.41 (0.01–9.88) |                       |          |
| Presence/history of ascites | 0.01 | 13.5 (1.65–111) |                       |          |

**Subgroup of patients without vitamin D supplementation**

|                      |          |          |                       |          |
| Age                  | 0.1      | 1.02 (0.97–1.08) |                       |          |
| Coffee, cups per day | 0.0001   | 0.41 (0.14–0.82) | 0.003                 | 0.36 (0.19–0.71) |
| Presence of diabetes | 0.006    | 2.92 (1.35–6.32) | 0.006                 | 4.72 (1.56–14.3) |
| MELD score           | 0.00001  | 1.21 (1.11–1.33) | 0.007                 | 1.18 (1.04–1.34) |
| Leukocytes / nl      | 0.5      | 0.95 (0.80–1.12) |                       |          |
| Hemoglobin (g/dL)    | <0.00001 | 0.63 (0.52–0.75) | 0.002                 | 0.70 (0.56–0.88) |
| 25(OH)D₃ <10ng/mL    | 0.02     | 2.43 (1.14–5.00) | 0.04                  | 3.03 (1.06–9.01) |
| Presence/history of ascites | 0.003 | 4.29 (1.94–9.44) |                       |          |

MELD, model of end-stage liver disease.

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hepatic decompensation and death. Furthermore, our study shows that vitamin D supplementation is effective in patients with advanced liver disease and can achieve serum concentrations of 25(OH)D₃ in a healthy range. Finally, our study reveals an association between low 25(OH)D₃ serum levels and liver cirrhosis-associated systemic inflammation, which may provide a functional basis of the relationship between vitamin D deficiency and hepatic decompensation.

Vitamin D deficiency is a frequent finding in healthy world-wide populations [19]. However, the proportion of patients with liver disease suffering from severe vitamin D deficiency is significantly higher compared to healthy controls [17]. An important finding of previous research of our and other groups was that liver-disease associated vitamin D deficiency in non-cirrhotic patients appears to be a result of the underlying liver disease per se, namely infections with hepatotropic viruses or alcoholic and non-alcoholic fatty liver disease, whereas
the degree of liver fibrosis has little impact on 25(OH)D₃ serum levels [10, 12–14,17,20]. This suggests a role of inflammation in the development of vitamin D deficiency, and indeed expression of genes regulating vitamin D metabolism is partially regulated by inflammatory cytokines [3]. In the present study we show that in patients with advanced liver fibrosis or cirrhosis, vitamin D deficiency poorly correlates with the degree of fibrosis / cirrhosis or the MELD score as well. In contrast, there is a strong association between 25(OH)D₃ serum levels and hepatic decompensation, waist circumference and -interestingly-smoking. There is a clinically established role of vitamin D in maintaining bone health and, importantly, muscular integrity and prevention of frailty [21]. Hence, the high risk of vitamin D deficiency in patients with liver cirrhosis should not be neglected, in particular in a pre-transplant setting where optimal bone density is important due to the risk of post-transplant glucocorticoid therapy and due to the detrimental effect of frailty on post-transplant outcome. Our study firmly shows that adequate 25(OH)D₃ serum levels can be achieved in patients with advanced liver disease by cholecalciferol supplementation.

Limitations of our study are a not directly assessed the vitamin D substitution compliance, however the profound increase in 25(OH)D₃ serum levels suggest high adherence. Furthermore possible antibiotic intake was not reliably reported for the entire cohort in this study. Thus a possible effect of concomitant antibiotic therapy on the risk of decompensation cannot be assessed.

Possible beneficial effects of vitamin D signaling on liver disease itself are more controversial due to the lack of appropriate controlled interventional studies. Our study cannot provide sufficient evidence for a causal relationship between vitamin D deficiency and systemic inflammation in patients with liver cirrhosis. The decrease of soluble CD14 levels in patients with adequate response to de novo supplementation of vitamin D may be a hint for such a causal relationship, and previous interventional studies e.g. in patients with hemodialysis or with lung tuberculosis have convincingly shown that vitamin D supplementation can suppress pro-inflammatory cytokine secretion [4,5]. Furthermore, animal models, observational studies and interventional studies have shown that vitamin D deficiency promotes the development of inflammatory bowel disease by disrupting the integrity of the intestinal barrier [6,7,22], and VDR signaling appears to be crucial for the development of the intestinal microbiome [9]. Finally, vitamin D suppresses liver fibrosis progression by a genomic feed-back mechanism suppressing the fibrotic response of hepatic stellate cells [23]. Together with the established benefit on bone and muscle health, these data may further support vitamin D supplementation in patients with liver cirrhosis and severe vitamin D deficiency.

In conclusion, our study reveals a possibly functional relevant association between severe vitamin D deficiency, systemic inflammation and risk of hepatic decompensation in patients with advanced liver fibrosis / cirrhosis.

Supporting information

S1 Table. Vitamin D serum levels by seasonal variations.

(DOCX)
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References

1. Holick MF. The vitamin D deficiency pandemic: Approaches for diagnosis, treatment and prevention. Rev Endocr Metab Disord 2017; 18:153–165. https://doi.org/10.1007/s11154-017-9424-1 PMID: 28516265

2. Ramagopalan SV, Heger A, Berlanga AJ, Maugeri NJ, Lincoln MR, Burrell A, et al. A ChiP-seq defined genome-wide map of vitamin D receptor binding: Associations with disease and evolution. Genome Research 2010; 20:1352–60. https://doi.org/10.1101/gr.107920.110 PMID: 20736230

3. Mora JR, Iwata M, von Andrian UH. Vitamin effects on the immune system: vitamins A and D take centre stage. Nat Rev Immunol 2008; 8:685–98. https://doi.org/10.1038/nri2378 PMID: 19172691

4. Buchanans S, Barberato SH, Stinghen AE, et al. Impact of cholecalciferol treatment on biomarkers of inflammation and myocardial structure in hemodialysis patients without hyperparathyroidism. J Ren Nutr 2012; 22:284–91. https://doi.org/10.1053/j.jrn.2011.07.001 PMID: 21906203

5. Coussens AK, Wilkinson RJ, Hanifa Y, Nikolayevsky V, Elkington PT, Islam K, et al. Vitamin D accelerates resolution of inflammatory responses during tuberculosis treatment. Proc Natl Acad Sci U S A 2012; 109:15449–54. https://doi.org/10.1073/pnas.1200072109 PMID: 22949664

6. Ananthakrishnan AN, Khalili H, Higuchi LM, Bao Y, Korzenik JR, Giovannucci EL, et. al. Intestinal epithelial vitamin D receptor signaling inhibits experimental colitis. J Clin Invest 2013; 123:3983–96. https://doi.org/10.1172/JCI65842 PMID: 23945234

7. Kong J, Zhang Z, Musch MW, Ning G, Sun J, Hart J, et. al. Novel role of the vitamin D receptor in maintaining the integrity of the intestinal mucosal barrier. Am J Physiol Gastrointest Liver Physiol 2008; 294:G208–16. https://doi.org/10.1152/ajpgi.00398.2007 PMID: 17962355

8. Wang J, Thingholm LB, Skiccevicciene J, Rausch P, Kummens M, Hov JR, et al. Genome-wide association studies reveal a novel role of the vitamin D receptor in the gut microbiota. Nat Genet 2016; 48:1396–1406. https://doi.org/10.1038/ng.3695 PMID: 27732756

9. Farnik H, Bojunga J, Berger A, Allwinn R, Waidmann O, Kronenberg 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. https://doi.org/10.1002/hep.26486 PMID: 23703797

10. Lange CM, Bibert S, Dufour JF, Cellera C, Cerny A, Heim MH, et al. Comparative genetic analyses point to HCP5 as susceptibility locus for HCV-associated hepatocellular carcinoma. J Hepatol 2013; 59:504–9. https://doi.org/10.1016/j.jhep.2013.04.032 PMID: 23665287

11. 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. https://doi.org/10.1016/j.jhep.2013.03.024 PMID: 23557869

12. Pett S, Camma C, Scasszone C, Tripodo C, Di Marco V, Bono A, et al. Low vitamin D serum level is related to severe fibrosis and low responsiveness to interferon-based therapy in genotype 1 chronic hepatitis C. Hepatology 2010; 51:1156–67. https://doi.org/10.1002/hep.23489 PMID: 20162613
14. Stokes CS, Volmer DA, Grünhage F, Lammert F. Vitamin D in chronic liver disease. Liver Int 2013; 33:338–52. https://doi.org/10.1111/liv.12106 PMID: 23402606

15. Blei AT, Cordoba J. Practice Parameters Committee of the American College of G. Hepatic Encephalopathy. Am J Gastroenterol 2001; 96:1968–76. https://doi.org/10.1111/j.1572-0241.2001.03964.x PMID: 11467622

16. Moore KP, Wong F, Gines P, Bernardi M, Ochs A, Salerno F, et al. The management of ascites in cirrhosis: report on the consensus conference of the International Ascites Club. Hepatology 2003; 38:258–66. https://doi.org/10.1053/jhep.2003.50315 PMID: 12830009

17. Lange CM, Bojunga J, Ramos-Lopez E, von Wagner M, Hassler A, Vermehren J, et al. Vitamin D deficiency and a CYP27B1-1260 promoter polymorphism are associated with chronic hepatitis C and poor response to interferon-alfa based therapy. J Hepatol 2011; 54:887–93. https://doi.org/10.1016/j.jhep.2010.08.036 PMID: 21145801

18. Villa E, Camma C, Marietta M, Luongo M, Critelli R, Colopi S, et al. Enoxaparin prevents portal vein thrombosis and liver decompensation in patients with advanced cirrhosis. Gastroenterology 2012; 143:1253–60 e1-4. https://doi.org/10.1053/j.gastro.2012.07.018 PMID: 22819864

19. Rosen CJ. Clinical practice. Vitamin D insufficiency. N Engl J Med 2011; 364:248–54. https://doi.org/10.1056/NEJMcp1009570 PMID: 21247315

20. 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. https://doi.org/10.1016/j.jhep.2011.01.041 PMID: 21334402

21. Bischoff-Ferrari H, Staehelin HB, Walter P. Vitamin D effects on bone and muscle. Int J Vitam Nutr Res 2011; 81:264–72. https://doi.org/10.1024/0300-9831/a000072 PMID: 22237776

22. Raftery T, Martineau AR, Greiller CL, Ghosh S, McNamara D, Bennett K, et al. Effects of vitamin D supplementation on intestinal permeability, cathelicidin and disease markers in Crohn’s disease: Results from a randomised double-blind placebo-controlled study. United European Gastroenterol J 2015; 3:294–302. https://doi.org/10.1177/2050640615572176 PMID: 26137304

23. Ding N, Yu RT, Subramaniam N, Sherman MH, Wilson C, Rao R, et al. A vitamin D receptor/SMAD genomic circuit gates hepatic fibrotic response. Cell 2013; 153:601–13. https://doi.org/10.1016/j.cell.2013.03.028 PMID: 23622244