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ORIGINAL ARTICLE

# Disturbances of parathyroid hormone–vitamin D axis in non-cholestatic chronic liver disease: a cross-sectional study

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**Abstract**
*Purpose* Liver has an important role in metabolism of vitamin D. This study aimed to evaluate the patterns of vitamin D–parathyroid hormone (PTH) disturbance and correlate it in patients with non-cholestatic chronic liver disease (CLD).
*Methods* A total of 40 healthy controls and 90 consecutive patients with evidence of non-cholestatic CLD due to hepatitis C ($n = 28$), hepatitis B ($n = 26$), autoimmune hepatitis ($n = 19$), and cryptogenic causes ($n = 17$) were enrolled. Cirrhosis was evident in 51 patients. Serum concentrations of 25-hydroxy vitamin D, PTH, calcium, phosphate, and liver enzymes were measured. Child–Pugh classification was determined in cirrhotic patients.
*Results* Vitamin D deficiency (<50 nmol/l) was found in 46 (51.1%) patients and vitamin D insufficiency (50–80 nmol/l) in 15 (16.7%) patients. Secondary hyperparathyroidism (serum PTH > 6.8 pmol/l) was present in 6 (6.7%) patients. The prevalence of vitamin D deficiency was significantly higher in cirrhotic versus noncirrhotic patients (76.5 vs. 17.9%; $P < 0.001$), whereas there was no significant difference in serum calcium, phosphate, and PTH levels. Child–Pugh class B and C patients had significantly lower vitamin D level compared with class A patients ($P < 0.001$), whereas there was no significant difference in serum calcium, phosphate, and PTH levels. No significant correlation was seen between vitamin D and PTH, calcium or phosphate levels. Lower serum level of vitamin D was associated with coagulopathy, hyperbilirubinemia, hypoalbuminemia, anemia, and thrombocytopenia.
*Conclusions* Vitamin D inadequacy and the severity of liver dysfunction move in parallel in patients with non-cholestatic CLD. Vitamin D assessment and replacement should be considered in the management of patients with non-cholestatic CLD.

**Keywords** Vitamin D · Liver · Cirrhosis · Parathyroid hormone · Child–Pugh score · MELD

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## Introduction

Liver plays an important role in vitamin D and bone metabolism. Vitamin D is hydroxylated by liver to 25-hydroxy vitamin D, the main circulating form, and then is converted into the active form 1, 25-dihydroxyvitamin D in kidney [1, 2]. Given that liver is involved in bile salt production, absorption of vitamin D, and 25-hydroxylation of vitamin D, it might be expected that vitamin D deficiency would be common in patients with chronic liver disease (CLD) [2].

Although in advanced stages of CLD, from any cause, bone mass loss is frequently (20–60%) evident [3, 4], the clinical relevance of vitamin D–parathyroid hormone (PTH) disturbances in hepatic osteodystrophy is still unclear. The intestinal absorption of cholecalciferol (vitamin D3) and 25-hydroxycholecalciferol is affected only in the presence of severe cholestasis. Experimental studies

have demonstrated that hepatic 25-hydroxylation of vitamin D3 is not impaired in cirrhotic rats, however, there is no evidence in humans [2].

Previous studies investigating the correlation between vitamin D, serum PTH level and severity of hepatic dysfunction have shown conflicting results. A study demonstrated that about two-third of patients with end stage liver disease and more than 90% of patients who are candidate for liver transplantation do have low vitamin D levels without osteomalacia [5]. There are some other studies, however, which have shown conflicting results [6–8].

It is notable that activities such as regulation of synthesis of metalloproteinase and their inhibitors, activation of fibroblasts, and collagen synthesis are also considered as properties of vitamin D [9–11]. These evidences bring this hypothesis in mind that vitamin D can have a role in progression of hepatic damage and CLD. Considering that there are limited studies about vitamin D–PTH status in patients with non-cholestatic CLD, in this study we aimed to evaluate the patterns of vitamin D–PTH disturbance and correlate it in a sample of Iranian patients with non-cholestatic CLD.

## Patients and methods

### Patients

Ninety consecutive patients with confirmed diagnosis of non-cholestatic CLD were enrolled from the patients referred to the outpatient clinic of hepatology department or those admitted at gastroenterology ward of Imam Hospital, Tehran, Iran. Our patients consisted of 50 men and 40 women, with a mean age of 42.3 ± 12.2 (SD) years. A control group of 40 participants was enrolled from the healthy participants who regularly visited our general clinic or their volunteer concomitants. The causes of CLD were viral hepatitis C ($n = 28$), viral hepatitis B ($n = 26$), autoimmune hepatitis ($n = 19$), and cryptogenic ($n = 17$). The diagnosis of CLD was based on consistent clinical findings, serologic markers of hepatitis B and C, hepatitis B virus DNA, and hepatitis C virus RNA measurements by polymerase chain reaction method, auto antibodies (antinuclear antibody, anti-smooth muscle antibody), biochemical features (including iron studies, ceruloplasmin, and urinary copper), endoscopic and imaging (including abdominal ultrasonography) evidence, and histological examinations (liver biopsy examination). Cirrhosis was evident in 51 patients. The diagnosis of cirrhosis was established by liver biopsy or definitive clinical or biochemical evidence of hepatocellular failure and/or portal hypertension. Liver biopsy was performed for patients who did not have contraindication and samples were studied for fibrosis and inflammation. Our sample was categorized into two groups of cirrhotic ($n = 51$) and noncirrhotic ($n = 39$) patients. The severity of cirrhosis was graded according to the degree of ascites, the plasma concentrations of bilirubin and albumin, the prothrombin time, and the degree of encephalopathy, using the Child–Pugh score [12], and patients were grouped into three categories: class A (well-compensated disease, scores 5–6; $n = 5$), class B (significant functional compromise, scores 7–9; $n = 16$), or class C (decompensated disease, scores 10–15; $n = 20$). The Model for End-Stage Liver Disease (MELD) score was also calculated [13]. None of the patients were under treatment with vitamin D or calcium supplements, bisphosphonates, calcitonin, hormone replacement therapy, corticosteroids, or antiviral drugs. Serum vitamin D concentration was categorized [14] as deficient when it was less than 50 nmol/l (severe deficiency, <12.5 nmol/l; moderate deficiency, 12.5–24 nmol/l; mild deficiency, 25–50 nmol/l), insufficient when it was 50–79 nmol/l, and sufficient when it exceeded 80 nmol/l.

### Laboratory analysis

Venous blood samples were obtained after an overnight 10–12 h of fasting. Each blood sample was divided into three portions: serum, plasma (using Na-citrate for prothrombin time) and blood EDTA for cell blood count. The samples were kept frozen at −70°C for the assay of vitamin D and intact PTH. The tests were performed using commercially available kits according to the manufacturers' instructions. 25-hydroxy vitamin D was measured with $^{125}$I radioimmunoassay kit (DiaSorin, Stillwater, MN, USA), and the laboratory reference range was 31–107 nmol/l. Intact PTH was measured by 2-site chemiluminescent enzyme-labeled immunoassay for the 1–84 amino acid chain on the Immunolite 2000 auto-analyzer (Diagnostics Products Corporation, Los Angeles, CA, USA). The laboratory reference range was 1.3–6.8 pmol/l.

For diagnosis of hepatitis B and C, antibodies to hepatitis C virus, hepatitis B surface antigen, hepatitis B surface antibody, hepatitis B core antibody, hepatitis B e antigen, and hepatitis B e antibody were measured using commercially available ELISA kits (DRG Diagnostics GmbH, Germany). Serum calcium (reference range: 8.6–10.3 mg/dl) and phosphate (reference range: 2.6–4.5 mg/dl) were measured by colorimetry using the Kavoshyar enzyme kit (Tehran, Iran). Prothrombin time (PT, reference: <12 s) was studied with BIO-TP kit (BIOLABO SA, Maizy, France). Serum albumin (reference range: 3.5–5.5 g/dl), total bilirubin (reference range: <1.2 mg/dl), alanine transaminases (ALT, reference range: ≤31 IU/l for females, and ≤41 IU/l for males), aspartate transaminases (AST, reference range: ≤31 IU/l for females, and ≤37 IU/l

for males), alkaline phosphatase (ALP, reference range: 64–306 IU/l for females, and 80–306 IU/l for males) were studied using Parsazmun commercial kits (Karaj, Iran). Serum ALT and AST were measured by the IFCC (International Federation of Clinical Chemistry and Laboratory Medicine) method (ALT intra-assay coefficient of variation [CV] = 3.7%, AST intra-assay CV = 2.5%). Serum ALP was measured using the DGKC (Deutsche Gesellschaft für Klinische Chemie) method (Intra-assay CV = 1.5%). Assays were performed with Robert Riele KG/photometer 5010 biochemical automated analyzer (Berlin, Germany). Hemoglobin and full blood count were determined by routine laboratory techniques. The serum calcium level was corrected for albumin concentration. The international normalized ratio (INR) for prothrombin time was calculated. Abdominal ultrasonography (Hitachi EUB 405 apparatus equipped with a convex 3.5 MHz probe) for evaluation of liver, spleen and ascites was performed in all patients by an experienced radiologist.

### Statistical analysis

Data are analyzed using SPSS software (version 16.0; SPSS Inc., Chicago, USA). Variables are expressed as percentage or mean ± standard deviation (SD). Patients with and without cirrhosis were compared using Chi-square analysis for categorical variables and independent sample *t* test for continuous variables. Comparison of variables between categories of vitamin D was performed using analysis of variance (ANOVA). Pearson correlation coefficients were calculated between vitamin-D, Child–Pugh score and other variables. $P$ value $< 0.05$ was considered significant.

## Results

### Characteristics of participants

Table 1 summarizes the demographic characteristics of the study participants. The age of the patients ranged from 16 to 74 years. There was no significant difference between cirrhotic and noncirrhotic patients with respect to sex, age and cause of CLD. Also, there was no significant difference in age and sex between healthy controls and patients. The main causative factor for cirrhosis was viral hepatitis C (31.4%), whereas in the noncirrhotic group viral hepatitis B (33.3%) and C (30.8%) were more prevalent. Biochemical characteristics of the studied participants are presented in Table 2. As expected, cirrhotic patients had significantly higher mean INR values, increased concentrations of serum bilirubin, and lower serum albumin, hemoglobin, and platelet count. No differences were seen between cirrhotic and noncirrhotic patients with respect to creatinine and urea concentrations. Serum ALT and AST were the only variables with significant difference between healthy individuals and noncirrhotic patients.

### Vitamin D status

Inadequate vitamin D, defined as a serum vitamin D level lower than 80 nmol/l, was present in 61 (67.8%) patients. Vitamin D deficiency (<50 nmol/l) was seen in 46 (51.1%), and insufficiency (50–79 nmol/l) was seen in 15 (16.7%) patients with non-cholestatic CLD (Table 3). Twenty-two (56.41%) noncirrhotic versus 7 (13.7%) cirrhotic patients showed a normal (>80 nmol/l) serum vitamin D concentration ($P < 0.001$). When cirrhotic patients were classified according to Child–Pugh classification, there was a consistent trend toward lower vitamin D levels with increasing severity of cirrhosis ($P < 0.001$) (Table 3). The Child–Pugh score ($r = -0.524, P < 0.001$) and MELD score ($r = -0.507, P < 0.001$) significantly showed correlation to serum vitamin D concentration in cirrhotic patients (Table 4). The mean serum concentration of vitamin D was significantly lower in patients with cirrhosis compared with noncirrhotic patients (Table 2), whereas there was no significant difference in serum level of calcium, phosphate, and PTH. Serum concentration of vitamin D was significantly lower in cirrhotic patients with Child–Pugh class-C compared with class-B or class-A groups, whereas there was no significant difference in

**Table 1** Demographic characteristics of the studied participants

| Parameter | Healthy controls ($n = 40$) | Noncirrhotic patients ($n = 39$) | Cirrhotic patients ($n = 51$) |
|---|---|---|---|
| Age (years) | 40.98 ± 9.29 | 43.52 ± 13.77 | 41.26 ± 12.27 |
| Sex (M/F) | 24/16 | 22/17 | 28/23 |
| Cause of CLD (*n*, %) | | | |
| Hepatitis B | – | 13 (33.3) | 13 (25.5) |
| Hepatitis C | – | 12 (30.8) | 16 (31.4) |
| Cryptogenic | – | 8 (20.5) | 9 (17.6) |
| Autoimmune | – | 6 (15.4) | 13 (25.5) |

No significant association was found between groups with respect to age, sex and cause of CLD

*CLD* chronic liver disease

**Table 2** Biochemical characteristics of the studied participants

| Parameter | Healthy controls ($n = 40$) | Noncirrhotic patients ($n = 39$) | Cirrhotic patients ($n = 51$) |
|---|---|---|---|
| PTH (pmol/dl) | 20.26 ± 9.09 | 20.13 ± 11.08 | 24.36 ± 14.23 |
| Vitamin D (nmol/l)* | 95.28 ± 29.41 | 81.37 ± 30.44 | 40.721 ± 22.43 |
| Ca (mg/dl) | 9.02 ± 0.53 | 8.84 ± 0.68 | 8.21 ± 0.55 |
| P (mg/dl) | 3.04 ± 0.47 | 3.03 ± 0.51 | 3.12 ± 0.63 |
| Albumin (g/dl)* | 4.41 ± 0.48 | 4.21 ± 0.54 | 3.07 ± 0.52 |
| INR* | 1.05 ± 0.08 | 1.11 ± 0.11 | 1.54 ± 0.41 |
| PLT count* | 210,983 ± 68,941 | 216,102 ± 70,612 | 85,823 ± 36,895 |
| Hb (g/l)* | 14.53 ± 1.69 | 14.17 ± 1.50 | 10.74 ± 2.22 |
| Bil (mg/dl)* | 0.83 ± 0.58 | 1.16 ± 0.83 | 3.15 ± 3.52 |
| ASL (U/l)*,† | 27.87 ± 20.85 | 51.05 ± 37.94 | 103.76 ± 67.62 |
| ALT (U/l)† | 32.44 ± 23.71 | 63.71 ± 53.99 | 71.10 ± 72.80 |
| ALP (U/l) | 185.39 ± 98.77 | 195.46 ± 110.05 | 230.82 ± 296.60 |
| Cr (mg/dl) | 0.89 ± 0.03 | 0.95 ± 0.15 | 0.81 ± 0.93 |
| Urea (mg/dl) | 30.9 ± 6.53 | 31.6 ± 6.88 | 31.6 ± 9.06 |
| MELD score | – | – | 14.73 ± 5.20 |

Data are expressed as mean ± SD

*CLD* chronic liver disease, *MELD* Model for End-Stage Liver Disease, *PTH* parathyroid hormone, *Ca* calcium, *P* phosphate, *INR* international normalized ratio, *PLT* platelet count, *Hb* hemoglobin, *Bil* bilirubin, *AST* aspartate transaminases, *ALT* alanine transaminases, *ALP* alkaline phosphatase, *Cr* creatinine

* $P < 0.001$ when comparing cirrhotic and noncirrhotic patients

† $P < 0.001$ when comparing healthy controls and noncirrhotic patients

serum levels of calcium, phosphate, and PTH. None of the cirrhotic patients had a desirable level of serum vitamin D. There were no differences in serum vitamin D levels between men and women.

## Parathyroid hormone status

There was no difference in serum PTH concentrations neither between cirrhotic and noncirrhotic patients (Table 2), nor between the Child–Pugh classifications (25.40 ± 16.28, 24.70 ± 14.99 and 18.97 ± 9.81, for Child–Pugh groups A, B and C, respectively; $P = 0.251$). Two patients in each of the cirrhotic and noncirrhotic groups had PTH levels less than the lower level of reference interval (<1.3 pmol/l). The percentage of patients with increased PTH levels (>6.8 pmol/l) was not significantly different between the groups of patients (5.7 and 8.3% in cirrhotic and noncirrhotic patients, respectively; $P = 0.247$). There were also no significant differences in serum level of albumin, calcium and phosphate among patients with increased or suppressed PTH levels in comparison to those with normal serum PTH concentrations (data not shown). There were no differences in serum PTH levels between men and women.

## Relationship between serum 25-hydroxy vitamin D level and markers of liver disease, parathyroid hormone, calcium and phosphate

Patients with vitamin D deficiency (<50 nmol/l) had significantly higher values of INR and bilirubin, and lower levels of serum albumin, hemoglobin, and platelet count in comparison to patients with vitamin D insufficiency (50–80 nmol/l) or normal (>80 nmol/l) levels. In contrast, the mean values of serum PTH, ALT, ALP, calcium, and phosphate showed no differences among groups with the lowest to the highest vitamin D levels (Table 3).

In univariate analysis in patients with non-cholestatic CLD (Table 4), significant ($P < 0.001$) positive correlations were found between serum level of vitamin D and platelet count, hemoglobin, or serum albumin. Also, there were significant ($P < 0.01$) negative correlations between vitamin D concentration and INR or serum bilirubin. No significant correlation was seen between vitamin D and serum level of PTH, calcium, phosphate, ALT, AST, ALP, urea, or creatinine (Table 4). Likewise, there was no correlation between serum PTH levels and any of the earlier mentioned variables.

**Table 3** Characteristics of the studied patients with non-cholestatic CLD by 25-hydroxy vitamin D status ($n = 90$)

| Variables | Vitamin D (nmol/l) | | | |
|---|---|---|---|---|
| | <25 | 25–49 | 50–79 | ≥80 |
| *n* (%) | 23 (25.6) | 23 (25.6) | 15 (16.7) | 29 (32.2) |
| Vitamin D (*n* mol/l)* | 17.67 ± 3.48 | 38.09 ± 7.76 | 64.75 ± 10.27 | 103.78 ± 16.90 |
| PTH (pmol/dl) | 18.97 ± 9.81 | 21.04 ± 9.18 | 24.70 ± 14.99 | 25.41 ± 16.28 |
| Ca (mg/dl) | 8.99 ± 0.39 | 8.95 ± 0.77 | 8.85 ± 0.57 | 8.94 ± 0.52 |
| P (mg/dl) | 2.98 ± 0.61 | 3.08 ± 0.58 | 3.15 ± 0.65 | 3.13 ± 0.55 |
| Cirrhotic patients, *n* (%)* | 23 (45.1) | 16 (31.4) | 5 (9.8) | 7 (13.6) |
| Child–Pugh classification (*n*, %)[a,]* | | | | |
| Child A | 5 (22.7) | 5 (22.7) | 5 (22.7) | 7 (31.8) |
| Child B | 6 (60.0) | 4 (40.0) | 0 (0) | 0 (0) |
| Child C | 12 (63.2) | 7 (36.8) | 0 (0) | 0 (0) |
| MELD score[a,]* | 17.70 ± 5.57 | 13.62 ± 3.34 | 10.71 ± 2.77 | 10.20 ± 2.43 |
| Albumin (g/dl)* | 2.87 ± 0.47 | 3.43 ± 0.75 | 4.13 ± 0.78 | 4.21 ± 0.48 |
| INR* | 1.72 ± 0.47 | 1.39 ± 0.27 | 1.13 ± 0.12 | 1.15 ± 0.18 |
| PLT count* | 74,130 ± 32,169 | 137,652 ± 94,800 | 164,400 ± 63,359 | 188,551 ± 79,999 |
| Hb (g/l)* | 10.04 ± 1.88 | 11.87 ± 2.83 | 13.32 ± 2.17 | 13.80 ± 1.62 |
| Bil (mg/dl)* | 4.40 ± 4.01 | 1.89 ± 1.06 | 1.46 ± 0.82 | 1.26 ± 1.01 |
| AST (U/l) | 89.39 ± 60.00 | 89.43 ± 75.24 | 76.14 ± 45.11 | 64.13 ± 61.03 |
| ALT (U/l) | 55.83 ± 34.44 | 69.26 ± 59.81 | 77.87 ± 49.04 | 84.17 ± 73.35 |
| ALP (U/l) | 269.83 ± 89.22 | 278.78 ± 133.75 | 246.87 ± 89.97 | 269.24 ± 112.77 |
| Cr (mg/dl) | 0.96 ± 0.21 | 0.95 ± 0.18 | 0.93 ± 0.12 | 0.97 ± 0.17 |
| Urea (mg/dl) | 35.17 ± 9.60 | 29.83 ± 6.97 | 29.80 ± 6.71 | 31.28 ± 7.94 |

Data are expressed as mean ± SD, unless otherwise is stated

*CLD* chronic liver disease, *MELD* Model for End-Stage Liver Disease, *PTH* parathyroid hormone, *Ca* calcium, *P* phosphate, *INR* international normalized ratio, *PLT* platelet count, *Hb* hemoglobin, *Bil* bilirubin, *AST* aspartate transaminases, *ALT* alanine transaminases, *ALP* alkaline phosphatase, *Cr* creatinine

[a] Calculated in cirrhotic patients only

* $P < 0.001$; *P* values are derived from chi square analysis or analysis of variances (ANOVA) among the four groups

## Discussion

In this study, we evaluated the association between parameters of calcium–phosphate metabolism (vitamin D, PTH, calcium and phosphate) and the parameters that are clinically valuable in cirrhotic and noncirrhotic patients with non-cholestatic CLD (ALT, AST, ALP, bilirubin, albumin, INR, Child–Pugh score and MELD score). We demonstrated that the majority of non-cholestatic CLD patients (67.8%) had inadequate serum vitamin D concentrations. The prevalence of vitamin D inadequacy (<80 nmol/l) was 86% in cirrhotic and 56% in noncirrhotic patients. The prevalence of vitamin D deficiency (<50 nmol/l) varied from 17.9% in noncirrhotic patients to 76.5% in cirrhotic patients, but secondary hyperparathyroidism was relatively uncommon and occurred in only 7% of those with vitamin D deficiency. Although serum vitamin D levels were significantly low in cirrhotic versus noncirrhotic patients (and in Child–Pugh class C vs. class A and B), there was no significant difference in serum PTH, calcium, and phosphate between cirrhotic and noncirrhotic groups. In some studies serum vitamin D levels were reduced in patients with advanced non-cholestatic liver dysfunction [15–17], whereas there are studies which do not support this finding [8, 18]. This difference may be partially due to different methods and definitions used in these studies.

We showed that, in CLD, the degree of vitamin D deficiency has correlation to the severity and progression of liver disease according to the Child–Pugh classification and MELD score. This finding may point to the specific impairment of vitamin D metabolism in a cirrhotic liver. Previous studies have shown inconsistent results about the correlation between serum vitamin D level and the severity of liver dysfunction. Our results are in line [3, 19] with some studies, and in contradiction to some other studies [16, 20]. Our study also showed a significant correlation between low serum vitamin D level and markers of liver function insufficiency including coagulopathy, hypoalbuminemia, hyperbilirubinemia, and thrombocytopenia, in

**Table 4** Correlation coefficients between serum 25-hydroxy vitamin D and characteristics of patients with noncholestatic CLD

| Variables | Child–Pugh score† | Vitamin D†† |
|---|---|---|
| Vitamin D (nmol/l) | −0.524*** | |
| PTH (pmol/dl) | −0.153 | 0.197 |
| Age (year) | 0.461 | −0.293 |
| Ca (mg/dl) | −0.334 | 0.407 |
| P (mg/dl) | −0.541 | 0.115 |
| Albumin (g/dl) | −0.429*** | 0.485*** |
| INR | 0.372*** | −0.454*** |
| PLT count | −0.271*** | 0.444*** |
| Hb (g/l) | −0.246*** | 0.469*** |
| Bil (mg/dl) | 0.536*** | −0.334** |
| Urea (mg/dl) | −0.136 | −0.141 |
| Cr (mg/dl) | 0.042 | 0.047 |
| AST (U/l) | 0.107 | −0.041 |
| ALT (U/l) | −0.284 | 0.246 |
| ALP (U/l) | 0.538 | −0.051 |
| MELD score | 0.813*** | −0.507*** |

*CLD* chronic liver disease, *PTH* parathyroid hormone, *Ca* calcium, *P* phosphate, *INR* international normalized ratio, *PLT* platelet count, *Hb* hemoglobin, *Bil* bilirubin, *AST* aspartate transaminases, *ALT* alanine transaminases, *ALP* alkaline phosphatase, *Cr* creatinine, *MELD* Model for End-Stage Liver Disease

** $P < 0.01$, *** $P < 0.001$

† Correlation coefficients are calculated in cirrhotic patients ($n = 51$)

†† Correlation coefficients are calculated in all patients ($n = 90$)

agreement with other studies [21–23]. Fisher et al. [23] showed that serum vitamin D levels less than 25 nmol/l would be a reliable predictor of higher INR and serum bilirubin as well as lower serum albumin and platelet count.

In our study, we did not find any significant association between serum calcium level and the severity of liver dysfunction. Serum calcium was not different between cirrhotic and noncirrhotic patients. This finding is not in line with the study by Duarte et al. [8], in patients with chronic viral liver disease, which showed a lower serum level of calcium in cirrhotic versus noncirrhotic patients. However, similar to our findings, serum PTH was similar in patients with and without cirrhosis. In our study, serum levels of calcium and phosphate were normal in many patients with vitamin D deficiency. This can be explained by reabsorption of minerals from bones. So, osteopenia and osteomalacia could be expected in these patients.

In the present study, the severity of CLD was not associated with the serum level of PTH. This finding is similar to the observations of other studies [15, 20]. In our series, 61 patients with CLD had vitamin D levels less than 80 nmol/l, but only in 6 (9.8%) patients the serum PTH level was increased (>6.8 pmol/l). The cause of normal to low PTH levels in presence of vitamin D insufficiency and severe deficiency, observed in our study and other studies [24], is unclear. Possible explanations may be certain vitamin D-receptor gene polymorphisms which can induce suppression of PTH secretion [25]. Understanding the pathophysiologic mechanisms which contribute to the vitamin D–PTH paradox in CLD requires further studies.

It should be noted that vitamin D insufficiency is not only a causative factor for bone diseases in the general population but also a risk factor for a wide range of chronic inflammatory and autoimmune diseases (inflammatory bowel disease, rheumatoid arthritis, psoriasis, multiple sclerosis and diabetes mellitus), cancers (colon, prostate and breast), and metabolic disorders (metabolic syndrome and hypertension) [19, 26]. Vitamin D can influence hepatic injury, fibrosis, and tissue remodeling by different mechanisms [27]. Therefore, determination and treatment of vitamin D deficiency may represent an important therapeutic target in the follow-up of CLD patients. Vitamin D deficiency may present with bone pain, proximal muscle weakness, and bone fracture, but many patients are asymptomatic. After liver transplantation and corticosteroid therapy many patients will be symptomatic [28]. Our results, demonstrating the high rate of vitamin D deficiency in CLD patients, could possibly suggest that screening and treatment of vitamin D deficiency should be considered in the management of patients with CLD.

This study has some limitations. The cross-sectional nature of the study precludes cause and effect interpretations. Furthermore, it was fitting if we had data of steatorrhea and malabsorption in our patients. Although we found a strong association between serum vitamin D concentration and liver injury, other factors that contribute to vitamin D deficiency such as reduced exposure to sunlight, malnutrition, and drug effects must be kept in mind. One could speculate that in an individual CLD patient, inadequacy in vitamin D status can be caused by different pathogenic factors. Nonetheless, our study, within an appropriate sample of patients with CLD, provided useful additional evidence in a challenging field of hepatology with gap of sufficient knowledge.

In conclusion, this study showed that vitamin D inadequacy and the severity of the liver dysfunction move in parallel in patients with non-cholestatic CLD. Vitamin D inadequacy is very common in these patients, though secondary hyperparathyroidism is rather rare. Vitamin D assessment and replacement should be considered in management of patients with non-cholestatic CLD. Intervals for biochemical examination can be regulated due to severity of liver dysfunction (Child–Pugh groups or MELD score).

**Conflict of interest** None.

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