Research Article

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Characteristics of bone disease in cirrhotic patients

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Prevalence and characteristics of bone disease in cirrhotic patients

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Abstract

Background and Aim: Chronic liver disease is a risk factor for osteoporosis, osteopenia and bone fractures. In this study, prevalence and risk factors of osteoporosis and vitamin D deficiency and also their effects on survival were investigated in 218 patients with chronic liver disease.

Materials and Methods: Prevalence of osteoporosis and vitamin D levels was calculated. Risk factors for osteoporosis (gender, age, body mass index, etiology), serum bilirubin, albumin, 25-hydroxy (OH) vitamin D, parathyroid hormone levels, bone mineral density (BMD) with DEXA, bone formation (osteocalcin) and bone resorption (type 1 collagen) levels, Model for End-Stage Liver Disease (MELD) Na and Child-Pugh (CP) score were recorded. The effects of vitamin D levels and BMD on survival were evaluated.

Results: One hundred forty-seven (67.4%) patients were female (mean age, 50.4±11.7). Patients were Child A by 40.8%, Child B by 47.1%, and Child C by 12.1%. Mean MELD Na score was 8.4±2.8. Data of the BMD were established in 218 patients and 25-OH D levels in 122 patients. Mean serum 25-OH D level was 14.26±9.44 ng/mL. Osteoporosis was identified in 42 (19.3%) and osteopenia in 115 (52.8%) patients, according to BMD. Osteocalcin levels and collagen type 1 levels were high in 25.6% and 12.5% of patients, respectively. No statistically difference was found, including gender (p=0.69), age (p=0.38), etiology (p=0.16), BMI (p=0.32), CP score (p=0.42), MELD (0.14), albumin (p=0.11), total bilirubin (p=0.99), Ca (0.67), PTH (0.88), osteocalcin (0.92), collagen type 1(p=0.25) between osteoporotic and non-osteoporotic patients. Patients were followed-up for a median of 30.07±11.83 months after BMD measurement. Fifty-four (24.8%) patients died during the follow-up period, none of them are related to bone fracture. There was no statistically difference on survival between osteoporosis group (32.2±2.3 months) and non-osteoporosis group (37.2±1.7 months; p=0.26) or when patients with 25-OH D_3 ≤10 ng/mL were compared to patients with 25-OH D_3 >20 ng/mL (34.4±2.0 months vs. 39.1±1.6 months, p=0.308).

Conclusion: In conclusion, the prevalence of bone disease was found to be higher in cirrhotic patients. Although osteoporosis and vitamin D deficiency were found to decrease survival, this effect was not statistically significant. We suggest designing multi-institutional and/or multinational studies with larger and more heterogenous patient groups would enable better testing of this phenomenon.

Keywords: chronic liver disease; osteopenia; osteoporosis; survival; 25-OH vitamin D.

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Introduction

Chronic liver disease is a significant cause for morbidity and mortality worldwide and may lead to various complications, such as liver failure, portal hypertension, hepatorenal syndrome, ascites, encephalopathy and esophageal variceal hemorrhage. Chronic liver disease is also a risk factor for osteoporosis, osteopenia and bone fractures.[1] Hepatic dystrophy is a term used to describe metabolic bone diseases, such as osteopenia, osteoporosis and osteomalacia, seen at various degrees due to chronic liver disease.[2] While osteomalacia is a rare condition accompanying chronic liver disease,[3] osteoporosis is more common (11–55%).[2–4] However, osteoporosis often remains unnoticed due to indolent clinical features and is often ignored in the presence of other complications. As a result, osteoporosis increases the risk for fractures, thus adversely affecting morbidity and quality of life.

In this study, the prevalence and risk factors of osteoporosis and vitamin D deficiency and their effects on survival were investigated in patients with chronic liver disease that were followed up in our clinic.

Materials and Methods

Two hundred and eighteen patients, who were diagnosed with chronic liver disease by physical examination, imaging techniques, endoscopy and in some cases histopathological methods, and who were in follow-up regularly at the hepatology and Transplantation Department of Yüksek İhtisas Research and Training Hospital, Ankara, a tertiary center, were included in this study. The data of these patients were analyzed retrospectively.

Exclusion criteria were patient age below 18 and over 70, glucocorticoid therapy for longer than three months, premature or surgical menopause, having diseases to affect bone metabolism (chronic renal disease, thyroid and parathyroid disease).

Weight and height measurements were used to calculate body mass index (BMI). Laboratory tests, including total bilirubin, albumin, serum 25-hydroxy (OH) D, serum parathyroid hormone (PTH) levels, were performed. Serum total Ca rather than ionize calcium were recorded and then were corrected for low albumin as this formula corrected Ca mg/dL=measured total Ca mg/dL+(0.8x[4-(albumin g/dL)]). Serum total 25-OH D level above 30 ng/mL was accepted as vitamin D sufficiency. The cut-off value <20 ng/mL was used to identify patients with inadequate vitamin D status. Patients were classified according to total 25-OH D level: ≤10 ng/mL severe deficiency, 11–20 ng/mL moderate deficiency, 21–29 ng/mL mild deficiency or ≥30 ng/mL normal vitamin D status.[5] Laboratory test of bone formation (osteocalcin) and marker of bone resorption (type 1 collagen) were also recorded.

Table 1. Baseline demographic and laboratory data of the patients

	Total number n=218 (%)	Osteoporosis + n=42 (%)*	Osteoporosis - n=61 (%)	p	Normal ranges
Sex					
Female	71(32.6)	16 (38.1)	19 (31.1)	0.69	
Male	147(67.4)	26 (61.9)	42(68.9)		
Age (years old) Mean±SD	50.4±11.7	52.5±10.6	49.3±11.2	0.38	
BMI (kg/m^2) Mean±SD	26.6±5.0	25.7±5.0	26.7±5.2	0.32	
Child-Pugh score					
A	89 (40.8)	18 (42.9)	29 (47.4)	0.42	
B+C	129 (59.2)	24 (57.1)	32 (52.6)		
MELD Na score Mean±SD	8.4±2.8	7.7±1.7	8.0±2.8	0.14	
Albumin (g/dL) Mean±SD	3.76±0.72	3.59±0.52	3.93±0.92	0.11	3.5–5.2
Total bilirubin (mg/dL) Mean±SD	1.72±1.31	1.58±0.98	1.79±1.47	0.99	0.3–1.2
Serum Ca (mg/dL) Mean±SD	4.5±3.2	4.44±3.19	4.14±3.2	0.67	8.6–10.2

*Osteopenic patients (n=115) are not included. SD: Standard deviation; MELD: Model for End-Stage Liver Disease; BMI: Body mass index.

All the data from the patients in this study, who underwent a BMD measurement of the lumbal spine (LS L1-L4), femoral neck (FN) and femur total with dual-energy X-ray absorptiometry (DEXA), were recorded.

The World Health Organization (WHO) categorizes bone disease based on bone mineral density (BMD) and reported as the T score.[6] A BMD <2.5 standard deviations below the young adult mean bone mass (T score of ≤–2.5) is defined as osteoporosis. A T score between –1 and –2.5 is defined as osteopenia. Severe or established osteoporosis is diagnosed when the T score is ≤–2.5 or in the presence of a fragility fracture.

Disease severity was graded according to the CP score and Model for End-Stage Liver Disease (MELD Na) score. Patients were followed-up for a median of 30.07±11.83 months after BMD measurement. The effects of osteoporosis and vitamin D levels on survival were evaluated.

This study was approved by the Ankara Yüksek İhtisas Research and Training Hospital local ethics committee.

Statistical Analysis

Frequency (percent) for categorical variables, mean ± standard deviation (median [minimum-maximum]), was given as descriptive statistics. The chi-square test and Kruskal-Wallis variance analysis were used to compare more than two independent groups for categorical variables and metric variables, respectively. Overall survival was estimated by Kaplan-Meier survival analysis. The log-rank test was used to compare survival estimates between subgroups. A p value <0.05 was considered as statistically significant.

Results

Clinical demographic and laboratory findings of the 218 patients are summarized in Table 1. One hundred forty-seven (67.4%) patients were male; the mean age was 50.4±11.7.

Identified etiologies were hepatitis B virus (HBV) in 67 (30.7%), cryptogenic in 43 (19.7%), Budd-Chiari syndrome in 25 (11.5%), hepatitis C virus in 20 (9.2%), HBV and HDV in 12 (5.5%), alcohol in nine (4.1%), hepatoportal sclerosis in nine (4.1%), Wilson disease in nine (4.1%), primary biliary cirrhosis (PBC) in six (2.8%), autoimmune hepatitis in three (1.4%) and other rarely seen etiologies in 15 (6.9%) patients. Patients were 40.8% Child A, 47.1% Child B and 12.1% Child C. Mean MELD Na score was 8.4±2.8. The patients had the diagnosis of chronic liver disease for a median of 48 months (6 month–468 months).

Table 2. Bone mineral density data of the patients

	n	%	T scores Median (range)
Lumbar spine L1-L4			
Osteoporosis	34	15.6	
Osteopenia	96	44	-1.20 ([-5.8]–[3.6])
Normal	88	40.4	
Femoral neck			
Osteoporosis	19	8.7	
Osteopenia	86	39.4	-0.9([-4.5]–[2.4])
Normal	113	51.8	
Total femur			
Osteoporosis	15	6.9	
Osteopenia	72	33	-0.6 ([-7.7]–[2.5])
Normal	131	60.1	
Either lumbar spine or femoral neck			
Osteoporosis	42	19.3	
Osteopenia	115	52.8	
Normal	61	28	

Serum vitamin D levels were measured in 122 of 218 patients. Mean serum 25-OH D level was low (14.26±9.44 ng/mL). Serum 25-OH D level was ≤20 in 102 of 122 patients (83.6%). Secondary hyperparathyroidism was identified in 35 (25.7%) of 136 patients whose PTH levels were measured. Bone formation marker increased in 30 (25.6%) of the 117 patients with osteocalcin level measurements. Bone resorption marker increased in 15 (12.5%) of 120 patients with Type 1 collagen measurements, bone turnover increased in total 38.1% of patients.

BMD results are presented in Table 2. Lumbar spine BMD measure-

Table 3. Survival according to osteoporosis

	1-year (%)	3-year (%)	Mean survival (months)	p
Osteoporosis	82.9	61.5	32.2±2.3	
Osteopenia	91.5	73.2	36.7±1.3	0.262
Normal	93.8	72.9	37.2±1.7	

Table 4. Survival according to 25-OH D level

25-OH D (ng/mL)	1-year (%)	3-year (%)	Mean survival (months)	p
≤10	85.7	62.8	34.4±2.0	
>10–≤20	90.9	77.8	36.2±2.1	0.308
>20	100	84.6	39.1±1.6	

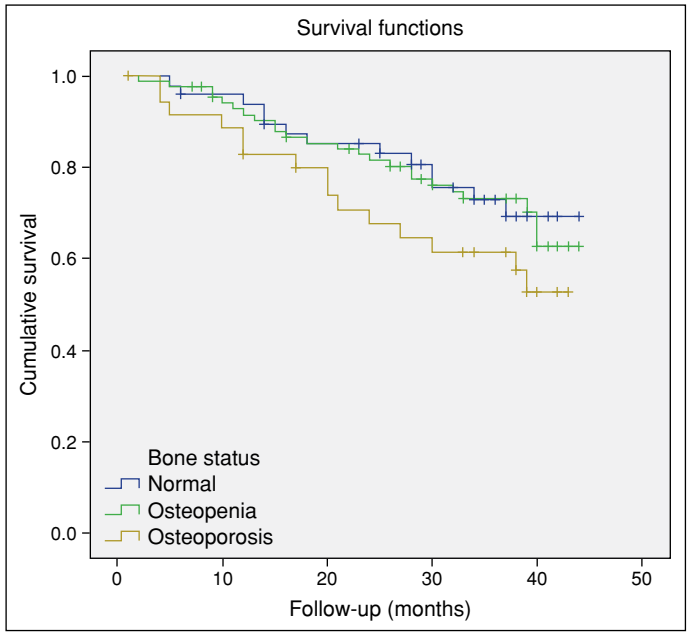

Figure 1. Survival according to bone mineral density status.

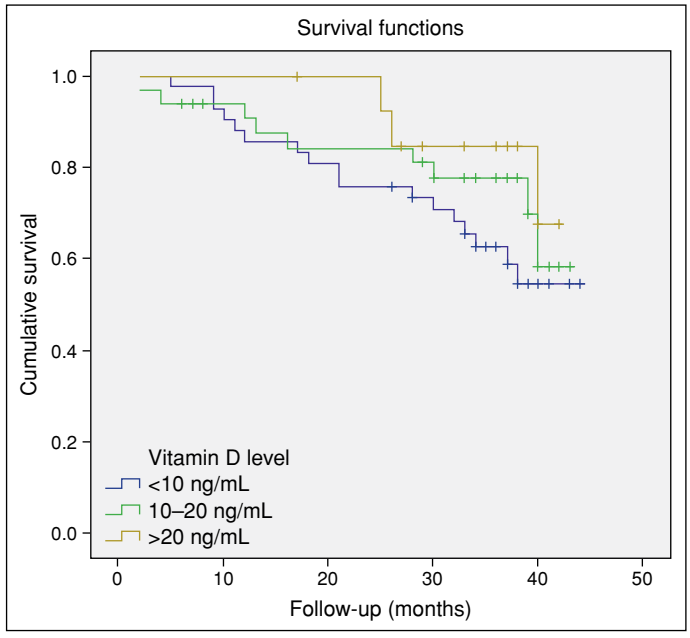

Figure 2. Survival according to 25-OH D level.

ments revealed a mean T score of -1.20 ([-5.8]–[3.6]). Accordingly, 96 patients had osteopenia (44%), 34 patients had osteoporosis (15.6%) and 88 (40.4%) patients were normal in 218 patients. FN BMD measurements performed in chronic liver disease patients according to the WHO classification revealed T scores of -0.9 ([-4.5]–[2.4]). In 218 patients, 86 patients had osteopenia (39.4%), 19 patients had osteoporosis (8.7%), while 113 patients were normal (51.8%).

When osteoporosis was described as a T score of <-2.5 on either FN or lumbar spine BMD measurements, 115 (52.8%) patients who had T scores between –1 and –2.5 were assessed to have osteopenia and 42 (19.3%) patients had osteoporosis.

Patients were grouped according to presence of osteoporosis (osteopenic patients were excluded from analysis). There was no statistically significant difference between osteoporosis (n=42) and non-osteoporosis groups (n=61) regarding gender (p=0.69), age (p=0.38), etiology (p=0.16), BMI (p=0.32), CP score (p=0.42), MELD Na score (p=0.14), albumin (p=0.11), total bilirubin (p=0.99), serum Ca (p=0.67) (Table 1); PTH (p=0.88), osteocalcin (p=0.92), collagen type 1 (p=0.25).

Although a statistically significant relation was not found between vitamin D levels and osteoporosis, serum vitamin D was ≤10 in 54.5% of the patients with osteoporosis and in 48.1% of the patients without osteoporosis (p=0.30).

Patients were followed-up for a median of 30.07±11.83 months after the time of the DEXA test. Fifty-four of 218 patients (24.8%) died during the follow-up period. None of them was associated with hepatic osteopathy.

One and three-year survival rates were estimated for patients with or without osteoporosis (Table 3). Mean survival in patients with or without osteoporosis were 32.2±2.3 months and 37.2±1.7 months, respectively (p=0.26) (Fig. 1).

Survival rates by vitamin D levels are presented in Table 4. Survival was insignificantly lower in patients with 25-OH D levels of ≤10 compared to the patients with 25-OH D levels of >20 (34.4±2.0 months vs 39.1±1.6 months) (p=0.308) (Fig. 2).

Discussion

Chronic liver disease may lead to various significant serious complications, including metabolic bone diseases, such as osteoporosis, osteopenia and bone fractures, which often remain unnoticed until late stages. In the literature, osteoporosis, osteopenia and bone fracture rates are reported as 12–55%, 26–70.6%, and 7–35% in chronic liver disease, respectively.[2–4,7,8] In our study, bone diseases (osteoporosis/osteopenia) were observed 72.1% (19.3%/52.8%) in Turkish patients with chronic liver disease, respectively.

Vitamin D deficiency is related to various factors, including osteoporosis, secondary hyperparathyroidism, increased bone turnover, increased bone mineral loss and increased risk for bone fractures, and it is fre-

quently seen in cirrhotic patients.[9] Vitamin D deficiency is widely (66–81%) distributed among patients with chronic liver disease.[9–14] In this study, we found that 83.6% of the patients had 25-OH vitamin D deficiency (≤20 ng/mL).

The risk for osteoporosis and fracture is reported higher in patients with cholestatic liver disease like PBC and primary sclerosing cholangitis and is lower in chronic active hepatitis, alcoholic liver disease, or hematochromatosis.[15] Statistically, we did not find any difference between the prevalence of osteoporosis and vitamin D levels among the etiological groups of chronic liver disease.

Many etiologic factors are assumed as part of the process leading to hepatic osteodystrophy, even if its origin is still far to be completely defined.[7] Risk factors that may cause bone mineral loss include female gender, chronic alcohol use, decreased physical activity,[2] malnutrition, low BMI, increased age, steroid use, hypogonadism, vitamin D and Ca deficiency.[3,16–18] Also, some studies showed that the severity of liver failure measured by Child-Pugh and MELD scores are correlated with osteoporosis grade and vitamin D insufficiency.[4,9,11,14] However, a few studies showed no effect of the Child-Pugh score and MELD scores on osteoporosis and vitamin D insufficiency.[19,20] We did not find a statistically significant difference between osteoporosis and non-osteoporosis groups according to demographic and laboratory parameters. Also, we did not find any statistically significant relationship between the Child-Pugh score or MELD Na score and osteoporosis or serum vitamin D levels. The male predominance, younger age average and having BMI mostly in the normal range in the study group may explain the statistical insignificance among the groups. Similarly, the predominance of normal albumin values and mean MELD Na scores among the groups may explain the statistical insignificance among studied parameters.

Vitamin D has a primary role in the regulation of hormone secretion, immune functions, cell proliferation and differentiation.[21] Vitamin D receptors are described in various tissues (endothelium, myocardium, skin, smooth muscle, lungs, kidney, prostate, colon, and breast) and T and B-lymphocytes, macrophages and dendritic cells.[22] 25-OH vitamin D levels have effects on immune system activity,[4,23,24] reduces pro-inflammatory cytokines production, increasing the phagocytic activity of macrophages and killer cells.[25,26] Thus, changes in 25-OH D vitamin levels have effects on immune system activity.[4,23,24] Studies have shown that active vitamin D increases cell differentiation, inhibits cancer cell proliferation, shows anti-inflammatory, pro-apoptotic and anti-angiogenic features.[25,26] Vitamin D improves cardiac functions and has anti-atherosclerotic effects[27,28] and inversely related to hypertension, obesity, diabetes and hypertriglyceridemia.[29] Thus, vitamin D is suggested to improve survival in cirrhosis through multiple mechanisms mentioned above. Studies that investigate the effects of osteoporosis and vitamin D deficiency on the survival of patients with chronic liver disease are limited. In our study, survival was insignificantly lower in patients with vitamin D deficiency and osteoporosis (Table 3, 4). The insignificance in survival function may be due to low MELD Na score among studied groups.

Biochemical markers of bone turn-over measured in urine and serum, which are required besides BMD for osteoporosis diagnosis, reflect the bone remodeling activity and may be considered surrogate markers.[2] Bone turnover markers (bone resorption and formation) are increased in osteoporotic patients and their levels are inversely related to BMD.[30] Studies conducted with bone turnover markers have found different results.[31,32] Thus, the clinical role of markers of bone remodeling in the diagnosis and management of osteoporosis in patients with chronic liver disease is still unclear. However, they may be useful for monitoring bone loss or assessing treatment response.[30] Although osteocalcin and collagen type 1 levels increased in our patients, there was no statistical significance.

The limitations of this study are described in the previous paragraphs in detail. Low MELD Na score and a similar level of osteoporosis risk factors among studied groups constrained our statistical analyses.

In conclusion, the prevalence of bone disease (osteoporosis/osteopenia and vitamin D deficiency) was found to be higher in cirrhotic patients. Although osteoporosis and vitamin D deficiency were found to decrease survival, this effect was not statistically significant. We suggest designing multi-institutional and/or multinational studies with larger and more heterogeneous patient groups would enable better testing of this phenomenon.

Ethics Committee Approval: This study was approved by the Ankara Yuksek Ihtisas Research and Training Hospital local ethics committee (12.10.2015/337).

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – HG, MAK, SOK; Design – HG, MAK, SOD, SOK; Supervision – HG, MAK; Materials – SOD, PC, MK, RD, DA; Data Collection and/or Processing – HG, PC, MK, RD, DA; Analysis and/or Interpretation – HG, MAK, SK, DO; Literature Search – HG, MAK, SK; Writing – HG, SK.

Conflict of Interest: The authors do not have any conflict of interest.

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