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Prevalence of osteoporosis, osteopenia and vitamin d deficiency in cirrhotic patients.

Kadri Atay[1], Ibrahim Hatemi[1*], Emre Durcan[1], Tugce Eskazan[1], Selma Bozcan[1], Tuncay Sahutoglu[2], Billur Canbakan[1], Sebati Ozdemir[1], Murat Tuncer[1], Abdullah Sonsuz[1]

[1]Department of Gastroenterology, Istanbul University Cerrahpasa Faculty of Medicine, Turkey

[2]Department of Nephrology, Sisli Etfal Training and Research Hospital, Turkey

Abstract

Background and aims: Osteoporosis (OP) is a major complication of cirrhosis. It can cause morbidity and mortality due to an increased fracture risk. The aim of this study is to determine the frequency of OP and vitamin D deficiency among patients with cirrhosis and to identify the risk factors associated with OP in these patients.

Methods: A single center retrospective study of the patients diagnosed with cirrhosis between January 2010 and January 2015 who were underwent Bone Mineral Density assessment using dual energy X-ray absorptiometry in 3 months from the diagnosis of cirrhosis. Demographic and biochemical factors, severity of underlying liver disease, history of fragility fracture, smoking status and alcohol use were collected from the patient file. Multivariate binary logistic regression analyses were used to assess risk factors for OP.

Results: Among the 126 patients (Male/Female, 55%/45%, median (range) age: 56 ± 13 (20-87) years), most (47.6%) were Child-Pugh A. The most common causes of cirrhosis were cryptogenic and hepatitis B was (37% and 34 % respectively). The prevalence of OP and osteopenia and vitamin D deficiency was 31% and 36% and 84.9% respectively. Previous fragility fractures had occurred in 6.3%. In multivariate logistic regression analysis (r^2 of the model was 0.18) revealed that female sex (OR (95% CI): 2.8 (1.096-7.15), p=0.03) and older age (OR (95% CI): 1.039 (1.003-1.076), p=0.03) were independent predictors of OP. Lower BMI (OR (95% CI): 0.91(0.836-1.008), p=0.06) tended to have an independent association with OP.

Conclusions: Osteoporosis and vitamin D deficiency are common metabolic complications in patients with chronic liver diseases. More than one fourth of our cirrhotic patients had osteoporosis, and 6.3% had a history of fracture. This study suggests the need of an accurate screening of bone mineral density in patients with liver cirrhosis to plan an adequate osteoporosis management.

Keywords: Osteoporosis, Vitamin D, Liver cirrhosis.

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Introduction

Osteoporosis is characterized by reduction bone mass without alteration the composition that eventually leads to higher tendency of fractures [1]. The incidence and awareness of osteoporosis is increasing, with the current estimates of prevalence reaching up to 200 million patients worldwide [2-4]. Osteoporosis can be associated with and/or complicate a variety of diseases, one of which is chronic liver disease [5]. As a result of impairment in nutritional and biosynthetic status in chronic liver disease, osteoporosis represents the most common type of bone disorder, and epidemiological data suggests that the prevalence of osteoporosis is about 4% to 21% in patients with chronic liver disease and 10% to 43% in liver transplantation patients [6-14]. Studies on the pathogenesis of osteoporosis point at both decreased bone synthesis and enhanced bone resorption in cirrhotic patients [7,12-14]. In addition to hepatocellular dysfunction, steroids, alcohol abuse, malnutrition, restriction in exercise, hypogonadism, smoking and pre-existing osteopenia are among the known risk factors for osteoporosis. With the fact that both waiting time and the number patients with cirrhosis who are waiting for transplantation are increasing, proper strategy for screening and prevention/treatment of osteoporosis at pre-transplantation stage could result in better morbidity and mortality outcomes [6]. The effects of sex, menopausal status, and etiology of liver disease on osteoporosis in patients with advanced liver disease are not sufficiently studied. Most of the data about osteoporosis is coming from Primary Biliary Cholangitis (PBC) patients. Therefore, we conducted this study to determine the Bone Mineral Density (BMD) in patients with

advanced liver disease other than PBC and to determine the risk factors of osteoporosis among cirrhotic patients.

Patients and Methods

We performed this retrospective study in a tertiary out-patient Gastroenterology clinic. We reviewed the files of adult patients with the diagnosis of cirrhosis except PBC from January 2010 to January 2015. Cirrhosis was diagnosed based either on liver biopsy (METAVIR stage F4) or radiological evidence of a nodular liver and portal hypertension. Severity of the underlying liver disease was assessed using Child-Pugh score. Exclusion criteria were to be younger than 18 years old.

Measurements

We recorded demographic characteristics, disease characteristics (etiology and duration of cirrhosis, Child-Pugh class), smoking history, body mass index (kg/m^2), and laboratory results including blood count, albumin, International Normalized Ratio (INR), 25-hydroxy vitamin D, intact parathyroid hormone, creatinine, calcium, and phosphorus. Bone densitometry at the lumbar spine (L1-L4) and femoral area were measured by dual energy X-ray absorptiometry (DEXA) within 3 months of diagnosis. Metabolic bone disease was defined according to World Health Organization (WHO) criteria: Osteopenia: T score between-1 and-2.5 standard deviation, osteoporosis: below-2.5 SD or a history of fragility fracture [15]. Subjects were grouped according to presence and absence of osteoporosis. We calculated estimated Glomerular Filtration Rate (GFR) levels using the chronic kidney disease epidemiology Collaboration Equation-Creatinine Formula (CKD-EPI) and corrected for body surface area [16]. Regarding the use of drugs that have affected BMD, none of the patients have received previously calcium or vitamin D supplements, neither bisphosphonates. Vitamin D deficiency was defined as to have a level of ≤ 20 ng/ml. The classifications of the subject according to the BMI was as follows: normal (19-25 kg/m^2), overweight (26-30 kg/m^2), obese (31-40 kg/m^2) or morbidly obese (>40 kg/m^2).

Statistical analysis

We determined the normality of distributions of continuous variables using the Kolmogorov-Smirnov test and compared categorical variables with Chi square or Fischer's exact tests and continuous variables using Student's t test or Mann-Whitney U test. We tested the correlations between variables using Pearson's or Spearman's tests as needed. We performed multivariate binary logistic regression analyses to assess independent associations with presence of osteoporosis. We used factors which had significant ($p<0.05$) or borderline ($p<0.25$) associations with osteoporosis as covariates in the regression analyses. We did not include factors with collinearity in the regression analyses. In all analyses, we accepted a two-sided p value of<0.05 as statistically significant. Statistical analysis was performed using IBM SPSS Statistics software for windows, Version 19.0.

Results

Baseline characteristics

A total of 126 patients (M/F, 55%/45%) with a mean age of 56 ± 13 (range, 20-87)) were enrolled in the study. The demographic and baseline characteristics of the patients are shown in Table 1. The most common causes of cirrhosis were cryptogenic and hepatitis B (37% and 34% respectively), followed by HCV (15.0%) and then alcohol abuse alone (11%) (Table 1). Almost half of the patients (47.6%) were at Child-Pugh A stage. The median (range) BMI was 27.7 (17-41) kg/m^2.

Prevalence of bone disease and fragility fractures

Overall, the prevalence of osteoporosis was 31% (39/126) in the whole group. Vitamin D deficiency was present in 84.9 % of all our study patients. Forty five (36%) patients had osteopenia. There was no significant association between abnormal DEXA findings and the etiology of cirrhosis. Osteoporosis was more frequent in females than males (39% and 24% respectively, p=0.003). Testosterone levels in men and serum LH levels of the whole patients with osteoporosis were significantly lower than those without osteoporosis patients (p=0.01 and p=0.05 respectively). The INR value of the whole patients and FSH levels in women osteoporosis group were significantly higher patients compared to the patients without osteoporosis (p=0.02 and p=0.03 respectively). Mean age, liver enzymes and the rest of the blood chemistry profile were similar in both groups (Table 2). Eight patients (6.3%) had a history of bone fractures. Seven of them had osteoporosis, one of them had femoral and the other six had lumbar low T scores. The remaining one patient had osteopenia in the lumbar area. Four of the fractures were occurred after trauma and the three were spontaneous fractures and one fracture was related to hepatocellular carcinoma metastasis. The location of the fractures was as follows: Three fingers, one tibia and radius fractures were related to trauma and three lumber vertebrae were spontaneous fracture.

Risk factors for bone disease in cirrhosis

We included age, gender, smoking, Child-Pugh score, CKD EPI, BMI and osteoporosis in multivariate analysis. In multivariate logistic regression analysis (r^2 of the model was 0.18) revealed that female sex (OR (95% CI): 2.8 (1.096-7.15), p=0.03) and older age (OR (95% CI): 1.039 (1.003-1.076), p=0.03) were independent predictors of osteoporosis. Lower BMI (OR (95% CI): 0.91 (0.836-1.008), p=0.06) tended to have an independent association with osteoporosis (Table 3).

A subgroup analysis was performed among men and women separately to assess the impact of gonado-pituitary hormones on metabolic bone disease in cirrhosis. Lower free testosterone among men (p=-0.37, p=0.01) and high serum FSH and low serum LH among women correlated with metabolic bone disease. (p=0.307, -404; p=0.03, 0.005 respectively). Also lower estradiol among women correlated with metabolic bone

disease but that was not statistically significant (p=-0.03, p=0.8).

Table 1. *Baseline characteristics of all patients.*

Variables		Number (%)
Age (years) (min-max)		56 (20-87)
Male/Female		55%/45%
Etiology	HBV	34.10%
	HCV	15.10%
	Cryptogenic	37.30%
	Alcohol	11.10%
Child-Pugh status	A	47.60%
	B	35.70%
	C	16.70%
BMI (kg/m^2) (min-max)		27.7 (17-41)
Vitamin D levels (ng/ml) (min-max)		12.4 (3-86)
CKD-EPI		79 ± 26
Femur total T-score		-0.7 ± 1.1
Vertebral L1-L4 T-score		-1.5 ± 1.3
Femur neck T-score		-1.0 ± 1.1
D vitamin deficiency		84.90%

BMI: Body Mass Index; CKD EPI: Chronic Kidney Disease Epidemiology Collaboration Equation; HBV: Hepatitis B Virus infection, HCV: Hepatitis C Virus infection.

Table 2. *The comparison group of osteoporosis and non-osteoporosis patients.*

Variables	Osteoporosis group (39)	Non-osteoporosis group (87)	P-value
Age (year)	59.2 ± 12.7	55.2 ± 13.2	0.1
Sex (male/female)	43.6%/56.4%	60.9%/39.1%	0.003
Body Mass Index	26.6 ± 4.2	28.1 ± 5.1	0.06
Parathormone	64 ± 24.5	55 ± 34.7	0.1
D vitamin levels (ng/ml)	11.9 ± 8.1	13.6 ± 13.3	0.4
Calcium	8.9 ± 0.7	8.9 ± 0.5	0.7
Phosphorus	2.8 ± 0.5	3 ± 0.5	0.1
Albumin	3.7 ± 0.7	3.7 ± 0.8	0.9
Testosterone (men) (nmol/L)	138 ± 76	267 ± 175	0.01
Estradiol (women)	56 ± 40	52 ± 45	0.8
Serum LH (women) (IU/L)	27 ± 20	47 ± 22	0.05
Serum FSH (women) (IU/L)	89 ± 57	135 ± 90	0.03
ALP	126 ± 58	110 ± 51	0.1
GGT	54 ± 37	65 ± 46	0.2
Total bilirubin	1.36 ± 1.03	1.63 ± 1.03	0.1
Direct bilirubin	0.78 ± 0.78	0.96 ± 0.95	0.1
INR	1.3 ± 0.2	1.2 ± 01	0.02
Smoking	38%	62%	0.3
D vitamin deficiency	85.10%	84.60%	0.5
Femur total T-score	-1.6 ± 0.9	-0.2 ± 0.9	0.0001
Vertebral L1-L4 T-score	-2.9 ± 0.4	-0.8 ± 1.0	0.0001
Femur neck T-score	-1.9 ± 0.9	-0.5 ± 0.9	0.0001
Child-Pugh score A	48.70%	47.10%	0.9
B	35.90%	35.60%	
C	15.40%	17.20%	

INR: International Normalization Ratio; LH: Luteinizing Hormone; FSH: Follicle-Stimulating Hormone.

Table 3. *Multivariate analysis risk factors for osteoporosis.*

Variables	Multivariate analysis Odds ratio (95% CI)	P-value
Age	1.039 (1.003-1.076)	0.03
BMI	0.91 (0.836-1.008)	0.06
Females	2.8 (1.096-7.15)	0.03
Smoking	2.2 (0.8-6.4)	0.4
CKD EPI	1.8 (0.7-4.7)	0.3
Child-Pugh score	1.1 (0.37-2.3)	0.8

BMI: Body Mass Index; CKD EPI: Chronic Kidney Disease Epidemiology Collaboration Equation.

Discussion

In this study, we evaluated the prevalence of osteopenia, osteoporosis, vitamin D insufficiency and risk factors for osteoporosis stratified according to the Child-Pugh classification in 126 cirrhotic patients due to hepatitis B, C, alcoholic or cryptogenic liver diseases. The majority of the cohort was in Child-Pugh A stage. Vitamin D insufficiency and abnormally low BMD measurements and prevalence of osteoporosis and osteopenia were present in 84.9% and 67% and 31% and 36% of all subjects respectively. Advanced age, female sex and low BMI status were associated with a higher risk for osteoporosis. In subgroup analysis, low testosterone levels in males and high FSH, and low LH levels in females were correlated with osteoporosis. The prevalence of osteopenia and osteoporosis across studies ranges from 11.5% to 48.1% and 1.9% to 36.6%, respectively [17-22]. Demographic characteristics, nutritional factors and underlying diseases may account for the different results. The prevalence of abnormal BMD results in our study were consistent with a previous large (489 patients with cirrhosis) cross sectional study, where Vargas et al. reported that 72% of their cohort had

low BMD [22]. Vargas et al. reported a higher rate of abnormal bone mineral density compared to our study. This could be explained by the fact that 78% of the patients included in their study had decompensated cirrhosis and 59% had alcoholic cirrhosis. In our study the ratio of patients with decompensated cirrhosis and alcoholic cirrhosis was significantly lower, yet abnormal bone mineral density was present in 67% of our patients. This also high rate could be explained by the nutritional factors and clothing habits that may be different in our country. Goral et al. reported osteoporosis in 37% of their 55 cirrhotic patients in Turkey. 41% of these patients had decompensated cirrhosis a ratio that is similar to our study [18]. Sokhi et al. carried a cross sectional study, investigating 104 cirrhotic patients on the waiting list for liver transplantation (51.9% male, median age: 54.4 years) reporting osteopenia in 34.6% and osteoporosis in 11.5% [19]. All patients in this study group were being treated with multivitamin supplements containing vitamin D. This may explain the lower rates of osteoporosis in this study compared to ours. Underlying cause of cirrhosis was not associated with osteoporosis; however the severity of liver disease was associated with osteoporosis. Advanced stages of cirrhosis reflect longer disease duration and more impairment in hepatocellular functions, which have been linked with bone disorders [23]. However we found no correlation between neither the stage nor the etiology of cirrhosis with the frequency of osteoporosis. Similar to our study Chinnaratha et al. found no correlation between neither the stage nor the etiology of cirrhosis with the frequency of osteoporosis [24]. The pathogenesis of bone disease that is seen in chronic liver disease, generally called hepatic osteodystrophy, is not clearly understood, but it shares similarities with postmenopausal and aging related bone loss, which is characterized by quicker loss of trabecular bone than of cortical bone [25]. Multiple factors have been implicated in hepatic osteodystrophy. The prevalence of hypogonadism is higher in chronic liver disease then in the general population, which is an established risk factor for osteoporosis. Reduced oestrogen in women and testosterone in men have been shown to be associated with lower bone mass in primary biliary cirrhosis and alcoholic cirrhosis patients, respectively [26,27]. In this study, low free testosterone levels in men and high FSH and low LH in women were significantly correlated with osteoporosis, whereas no correlation was found between osteoporosis and estradiol levels in women. Vitamin D has a critical role in bone mineral metabolism and low levels of vitamin D have been reported in chronic liver disease patients. However, studies in patients with primary biliary cirrhosis suggested that reduced vitamin D levels were not correlated with osteoporosis, and that treatment with vitamin D failed to restore or prevent the progression of bone loss [28-32]. Likewise, vitamin D levels were similar in osteoporotic and non-osteoporotic groups in this study. Vitamin D deficiency is a global health problem and with all the medical achievements of the present time, it is still epidemic. In the literature, reports have found vitamin D deficiency D in 40-100% of those tested, with proportions varying according to geographic area, latitude and specifics of the patient population [33-35]. In our society, probably because of the nutritional factors and clothing habits, vitamin D deficiency is also a common problem. In this regard, a study from Turkey by Hekimsoy et al., vitamin D deficiency rates was reported as 74.9% in among healthy subjects [36]. In our study, vitamin D deficiency rates were present in 84.9% of our patients. Pathologic fractures are the major complications of osteoporosis and the main outcome of clinical studies. However, in addition to BMD, advancing age, previous fracture history, glucocorticoid treatment, parental history of hip fracture, low body weight, current cigarette smoking, excessive alcohol consumption, rheumatoid arthritis and secondary causes of osteoporosis are some of the other important clinical risk factors for atraumatic fractures [37]. Therefore, data regarding the prevalence of fractures in cirrhotic patients with osteoporosis can inadvertently be expected to vary greatly, but in our cohort 6.3% of all patients had fractures, with up to 90% of them had low BMD results.

Limitations of this study include the retrospective nature and relatively low number of patients.

In conclusion, bone disorders are common/frequent in cirrhotic patients; however this issue may frequently be overlooked during the management of these patients. Low BMD is highly prevalent in patients with cirrhosis. Age, female gender, low testosterone in men, high FSH and low LH in women, low BMI are correlated with osteoporosis, whereas the underlying cause of liver disease, stage of cirrhosis and vitamin D levels were not associated with bone disease in cirrhotic patients. The findings from this study suggest that osteoporosis and osteopenia are indeed common in cirrhosis, therefore biochemical and BMD screening during routine follow up of these patients may be necessary.

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*Correspondence to

Ibrahim Hatemi

Department of Gastroenterology

Istanbul University Cerrahpasa Medical Faculty

Turkey