Effects of Cirrhosis on Bone Mineral Density and Bone Metabolism

Sirozun Kemik Mineral Yoğunluğu ve Kemik Metabolizmasına Etkileri

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Objective: The present study was undertaken to examine the correlation between the severity of liver disease and the presence and severity of bone disease in patients with hepatic cirrhosis.

Materials and Methods: Between January 2005 and February 2006, 40 patients with cirrhosis and 22 healthy controls were enrolled in a cross-sectional study. All subjects underwent standard laboratory testing and bone densitometric studies of the lumbar spine and femoral neck using dual X-ray absorptiometry (DEXA).

Results: Cirrhotic patients had lower serum follicle-stimulating hormone (FSH) levels than controls. Male patients had lower serum free testosterone (FT) levels than male controls. 25-hydroxyvitamin D (25-OHD3) levels were significantly higher in the controls as compared to patients with cirrhosis. In the cirrhotic group, 25-OHD3 concentrations did not differ significantly between patients with Child B and C class cirrhosis. As compared to the control group, cirrhotic patients had significantly elevated levels of urinary deoxypyridinoline (DPD). The cirrhotic patients also had a significantly lower mean spinal (SD) bone mineral density (BMD) than the control group. BMD of the lumbar spine (LS) was noted to be significantly lower in the Child C group than in the Child B group. In the cirrhotic patients, there was a positive correlation between the BMD T score of the femoral neck (FN) and albumin levels whereas there was a negative correlation between BMD T scores of the FN and age, bilirubin and prothrombin time (PT).

Conclusion: Osteopenia and osteoporosis are highly prevalent in individuals with liver cirrhosis. Cirrhotic patients should undergo routine bone densitometric assessment and, if necessary, be treated for osteoporosis.

Keywords: Cirrhosis, Osteoporosis, Bone mineral density

Anahtar Kelimeler: Siroz, Osteoporoz, Kemik mineral dansitesi
Introduction

Hepatic osteodystrophy is defined as bone disease associated with cirrhosis. It includes osteoporosis and, more rarely, osteomalacia [1,2]. Although cirrhosis is associated with a broad spectrum of bone diseases, the most common type of bone disease present in hepatic osteodystrophy is osteoporosis. Osteoporosis is a disorder characterized by a reduction in bone mass and micro-architectural deterioration of bone tissue with a resultant increased risk of fracture [2,3]. Osteoporosis is an important and common complication in individuals with cirrhosis. The association between metabolic bone disease and cholestatic liver disease has been previously studied and is well characterized. However, data regarding the association between bone disease and noncholestatic liver cirrhosis (NCLC) are relatively scant. The exact prevalence of osteoporosis in patients with hepatic cirrhosis is unknown [4]. The documented prevalence of decreased bone mass in patients with hepatic cirrhosis ranges from 12 to 55% and varies largely by the study population and the technique used for bone density measurement [5-7].

The pathogenesis of osteoporosis in hepatic cirrhosis remains incompletely understood. The pathophysiological basis of osteoporosis appears to be osteoblastic dysfunction rather than excessive bone resorption [8]. There is much controversy regarding the risk factors for osteoporosis in patients with hepatic cirrhosis, and several factors may be implicated in the development of osteoporosis and fractures. These factors include steroid treatment, alcohol abuse, smoking, immobility, hypogonadism, poor nutritional status, reduced muscle mass, premature menopause, and preexisting osteopenia [4,9]. Dual energy X-ray absorptiometry (DEXA) can precisely, rapidly, and noninvasively measure bone mineral density (BMD) [10].

The correlation between liver dysfunction (as assessed by a clinical scoring system) and the incidence of osteodystrophy is still controversial. The Child-Turcotte-Pugh (Child) classification is by far the most widely used and reported scoring system, as scores can be determined by an easily administered clinical assessment [11]. It assesses five variables, including serum levels of albumin and bilirubin, prothrombin time, ascites and encephalopathy, and divides patients into three classes (A, B and C).

The present study was undertaken to assess the correlation between the severity of liver disease and the presence and severity bone disease in patients with noncholestatic liver cirrhosis.

Materials and Methods

Patients

Forty consecutive cirrhotic patients at the Ataturk University Hospital were studied between January 2005 and February 2006. The study group consisted of 26 (65%) males and 14 (35%) females. Included cirrhotic patients had varied etiologies of their liver disease, including hepatitis B, hepatitis B+D, hepatitis C, hydatid cyst disease, cryptogenic cirrhosis. Of the patients with cirrhosis, 23 had chronic hepatitis B (HBV), 9 had chronic hepatitis C (HCV), 2 had HBV + chronic hepatitis D (HDV), 1 had a hydatid cyst and 5 had cryptogenic cirrhosis. With regard to the severity of liver disease, they were classified into three groups according to the Child score, as follows: class A (4 patients), class B (20 patients) and class C (16 patients). Fourteen healthy male and eight healthy female volunteers comprised the control group. No patients in the control group were taking any medications known to affect bone turnover and none had known metabolic bone disease or recent fractures.

The patients and the controls had diverse occupations, which ranged from manual labor to office work.

The hepatological diagnosis in each case was confirmed by examination of the appropriate biochemical, serologic and liver biopsy data. At the time of BMD evaluation, none of the patients were taking or had taken calcium, vitamin D or other treatments that could affect bone mass such as calcitonin, estrogens, sodium fluoride, biphosphonates or corticosteroids. Baseline exclusion criteria included having a history of an ileal resection, chronic renal failure, abnormal thyroid or parathyroid function, diabetes, malignancy, hypogonadism, postmenopausal status and any other known bone disorder other than osteoporosis or osteopenia. Demographic and disease information including age, gender, diagnosis and duration of disease were documented using a baseline questionnaire. Other informative data were gathered through review of the patients’ blood tests and DEXA scans. Patients were also asked about any history of pathologic fracture.

The study protocol was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee of our hospital. Patients and controls provided written informed consent before the investigation began.

Laboratory Analyses

Blood and urine samples were drawn in the morning after
Biochemical liver function tests, as well as the prothrombin index, serum calcium and inorganic phosphate levels were measured by automated procedures. The calcium level was corrected according to albumin level as previously described (the total calcium was raised 0.8 mg/dl for each 1 g/dl decrease in serum albumin below 4.0 g/dl) [12]. Bone alkaline phosphatase (BALP) activity was estimated by heat inactivation (Olympus AU-2700).

Serum assays were performed using commercially available kits. Serum assays included measurements of intact parathyroid hormone (I-PTH) (chemiluminescence, E-170, Roche, Germany), 25-hydroxyvitamin D (25-OHD3) and free testosterone (fT) (RIA, Biosource-EUROPE-SA, Belgium). Urinary deoxypyridinoline (DPD) was measured by chemiluminescence enzyme labeled immunoassay with a commercially available kit (Immulite-2000, DPC-USA). At day 3-5 of the menstrual cycle, plasma levels of follicle-stimulating hormone (FSH), luteinizing hormone (LH), estradiol (E2) were measured by immunoassay using a commercially available kit (Immulite-2000, DPC-USA). Detection of HBsAg, anti-HBc, and Anti-HDV was performed by using commercial enzyme immunoassay kits (Diapro, SEAC-ALIRAD, Italy).

**Bone Mineral Density Measurements**

BMD of the lumbar spine and the left hip and femoral neck were measured by dual-energy x-ray absorptiometry, using a QDR-4500W densitometer (Hologic Inc, Waltham, Mass). Lumbar spine (LS) and femur neck (FN) BMD were measured with DEXA scans in all cases. Results of BMD were expressed as the number of standard deviations from the mean peak value of a reference population of the same sex and race (T score). Osteopenia is defined by the World Health Organization (WHO) as a T score between −1 and −2.5, and osteoporosis as a T score less than −2.5, using the lowest T score present in the lumbar spine (L1–L4) or femoral neck [12]. Lateral thoracolumbar radiographs (T5-L5) were performed and evaluated to search for the presence of spinal compression fractures.

**Statistical Analysis**

All collected data were analyzed. Results were presented as mean ± standard deviation or frequencies [n (%)]. Differences between groups were compared using the Mann-Whitney and Kruskal-Wallis tests. For correlation analysis, we used Pearson’s test and Spearman’s test. P values lower than 0.05 were considered significant. All statistical analyses were performed using the Statistical Package for the Social Sciences Version 10.0 for Windows (SPSS Inc., Chicago, IL).

**Results**

The clinical and demographic characteristics of all and gender-based sub-groups are shown in table 1. No statistically significant differences in age or body mass index were observed between patients and controls (P>0.05 for both). Serum biochemical liver function tests and prothrombin levels were higher in cirrhotic group than controls (P<0.05) (Table 1). There was also a significant difference between the patients and controls in terms of serum albumin (Alb), phosphate (P), and corrected calcium (P<0.05) (Table 1).

25-OHD3 levels were significantly higher in the controls (41.7±13.4 ng/l) than the cirrhotic group (21.9±21.5 ng/l; P=0.001) (Table 1). There were no significant differences in 25-OHD3 concentrations between patients with Child B (23.89±19.46 ng/l) and Child C (16.33±16.65 ng/l) cirrhosis (P>0.05) (Table 2).

Serum I-PTH, LH and E2 levels were higher in the study group than in the control group, but these differences were not found to be statistically significant (P>0.05) (Table 3). Male patients had significantly lower serum fT levels than control subjects (P<0.001)
citrasis (irrespective of the etiology), viral cirrhosis, cholestatic liver diseases, and primary biliary cirrhosis [15]. However, in many patients with cirrhosis, osteoporosis remains unrecognized and untreated. For this reason, hepatic osteodystrophy has become more important.

In this cross-sectional study, the bone mineral density measurements of the FN and LS were significantly lower in cirrhotic patients than in the healthy population. This reduction was more severe in the LS (trabecular bone) than in the FN (cortical bone), likely because the rate of turnover in cortical bone is much slower than that in trabecular bone. Previous studies have reported quite variable prevalence rates for osteopenia and osteoporosis in individuals with liver cirrhosis. Many of the differences between these various reports are due to the definitions of osteoporosis and osteopenia used, as well as the sites at which the measurements of BMD were made. Screening for low BMD with single site measurements can underestimate its frequency and severity, and is not a perfect predictor of BMD at other sites [16]. Due to the faster rate of renewal in trabecular bone than in cortical bone (it can be up to 8 times faster), sites with a high proportion of trabecular bone, such as vertebrae and hips, will be affected earliest. Vertebrae consist of 50% trabecular bone and the femoral neck consists of 30% trabecular bone, thus, changes in BMD will be apparent earlier and with more severity in the lumbar spine than at the femoral neck. The differences in bone composition between the LS and the FN can therefore explain the differences in BMD found between these sites [17]. In our study, the overall prevalence of osteopenia and osteoporosis in cirrhotic individuals was found to be 45% and 42.5%, respectively, according to WHO criteria. Overall, the cirrhotic patients had a significantly lower mean spinal BMD (-2.44±1.30) than femoral neck BMD (-1.11±1.82). In this study, we found an increase in the prevalence and severity of osteoporosis coincident with the progression of liver dysfunction. These results are supported by the findings of Sohki et al., who reported the prevalence of osteopenia and osteoporosis in cirrhotic individuals as 34.6% and 11.5%, respectively. The frequency of osteopenia at the lumbar level was lower (24%) than that of the femoral neck site (32.7%). In contrast, osteoporosis was found more often in the lumbar spine (8.7%) than at the femoral neck (2.9%). Additionally, the reduction in BMD correlated with the severity of liver disease as measured by the Child class [5]. No correlation between BMD and the clinical severity of the cirrhosis was noted in a study performed by Chen et al. [6]. Bonkovsky et al. [15] studied patients with chronic liver disease due to varied etiologies and reported a prevalence of osteopenia (defined as a BMD <2 SD below that of age- and sex-matched controls) ranging from 13 to 39%. They reported the prevalence of osteopenia at the LS and the FN to be 26% and 13%, respectively. Diamond et al. [18] reported a prevalence of spinal osteoporosis (defined as a BMD <2 SD

(Table 4). Cirrhotic patients had significantly elevated DPD levels in comparison to control subjects (P<0.001) (Table 1).

As expected, the biochemical markers of liver function such as albumin, prothrombin time (PT) and bilirubin were found to differ significantly between control subjects and cirrhotic patients and also among the cirrhotic sub-groups (P<0.05) (Table 1).

There were no individuals with spinal compression fractures in either the patient or the control group. Overall, the cirrhotic patients had a significantly lower mean (SD) spinal BMD (-2.44±1.30 g/cm²) than the control group (-0.54±1.40 g/cm²; P<0.001). Although the mean femoral neck BMD and T score values were lower in the study group than in the control group, these differences were not found to be statistically significant (Table 5). Among cirrhotic patients, the rate of osteoporosis was found to be 45.2% as compared to 0% in the control group. BMD of the LS was significantly lower in the Child C group than in the Child B group (P<0.05) (Table 2).

According to the WHO criteria, T values between -1 and -2.5 were classified as osteopenia [13]. Eighteen out of the forty included patients’ T score values were less than -1, whereas in the control group, 6 individuals were osteopenic (P<0.05).

In the cirrhotic patient group, a positive correlation was found between the BMD T score of the FN and Alb (r=0.351, P=0.026) (Figure 1). A negative correlation was found between the BMD T score of the FN and age, bilirubin and PT levels (r=-0.499, p=0.001; r=-0.346, p=0.029; r=-0.111, P=0.496, respectively) (Figures 2 and 3). No statistically significant relationship was observed between BMD and other biochemical parameters.

### Discussion

With the improvement in survival of patients with liver cirrhosis and with advances made in liver transplantation, the clinical significance of hepatic osteodystrophy has increased. Osteoporosis is the most common form of bone disease in individuals with liver cirrhosis [5, 14]. The risk of osteoporosis and associated fractures has been shown to be increased in patients with liver cirrhosis (irrespective of the etiology), viral cirrhosis, cholestatic liver diseases, and primary biliary cirrhosis [15]. However, in many patients with cirrhosis, osteoporosis remains unrecognized and untreated. For this reason, hepatic osteodystrophy has become more important.

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### Table 2. Bone mineral density and serum concentrations of 25-hydroxyvitamin D in patients stratified by Child score (mean ± SD)

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<tr>
<th>Child score</th>
<th>Bone mineral density P</th>
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<tr>
<td>B</td>
<td>-2.71±1.13</td>
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<tr>
<td>C</td>
<td>-2.94±1.44</td>
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<tr>
<td>D</td>
<td>-2.94±1.79</td>
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<tr>
<td>B</td>
<td>23.61±9.46</td>
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<tr>
<td>C</td>
<td>15.33±6.05</td>
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[Imagery and references are not provided in the text, and the content is structured to mimic the original text layout.]
The loss of bone mass in cirrhosis is likely multifactorial, and several risk factors may be involved. Changes in parathyroid hormone (PTH) concentrations may influence the development of osteoporosis in patients with liver cirrhosis irrespective of the cause of the cirrhosis [7,18]. Kirch et al. [20] found elevated PTH concentrations may influence the development of an overall prevalence rate of 37.8% for osteopenia and of 12.8% for osteoporosis.

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The osteodystrophy associated with hepatic cirrhosis is due to a defect in alpha-hydroxylation of vitamin D (leading to the formation of 1, 25-OHD3) by the kidney due to a decrease in the levels of its primary substrate, 25-OHD3, which is produced by the liver. This decrease in 25-OHD3 concentration may be caused by the reduced availability of vitamin D, inadequate conversion of vitamin D to 25-OHD3, accelerated metabolism of 25-OHD3, or urinary loss of 25-OHD3 with its transport protein [24]. The factors contributing to vitamin D deficiency in cirrhotic patients are more likely related to poor absorption or availability of dietary sources of vitamin D, particularly in patients with cholestasis and malabsorption of fat-soluble vitamins or decreased sun exposure due to poor general health and mobility [25]. The importance of decreased serum 25-OHD3 levels in chronic liver disease patients is not well known. Two previous studies found no correlation between serum 25-OHD3 levels and BMD values [12,19]. In contrast to these studies, Diamond et al. [26] reported a significant correlation between decreased levels of 25-OHD3 and low BMD values in their patients with chronic liver disease. In addition, Ormarsdottir et al. [27] concluded that bone loss in patients with advanced liver disease is associated with decreased levels of 25-OHD3. Although we found a decreased level of serum 25-OHD3 in our subjects, we did not find a significant correlation between serum 25-OHD3 levels and BMD values, which is in agreement with the findings of most other studies. Diamond et al. [28] have suggested that subnormal 25-OHD3 levels in patients with advanced liver disease are related to a reduced synthesis of carrier proteins in the liver. We did not measure levels of the vitamin D carrier protein specifically, but the correlation between serum albumin (which is a marker of reduced protein synthesis in the liver) and serum 25-OHD3 we found in this study corresponds with Diamond’s suggestion and may explain the fact that low 25-OHD3 levels were not identified as an independent risk factor for osteoporosis in patients with cirrhotic liver disease.

We found that serum corrected calcium levels significantly decreased with the progression of the liver dysfunction. The growing evidence that low bone mass is not related to abnormalities in vitamin D metabolism in liver diseases, however, requires further research.

An association between male hypogonadism and osteoporosis has been previously described [29]. Serum testosterone is a strong independent predictor of bone density in men and declines with the progression of liver disease [17]. Although free testosterone (which comprises only 1–3% of total testosterone) is biologically active, it is rapidly cleared, thus protein-bound testosterone is the major source of androgens available for utilization in tissues. The two major risk factors for the development of osteoporosis reported by Diamond et al. [18] were cirrhosis itself and hypogonadism. In our study, patients with physical signs of hypogonadism were excluded. Child B and C patients had lower FT values than controls, but we did not find a correlation between FT values and BMD. We did not measure the vitamin D carrier protein specifically. An increase in sex hormone-binding globulin (SHBG) levels is seen with cirrhosis, occurring as a consequence of decreased androgenic suppression and increased estrogenic stimulation of SHBG production by the liver, and contributes to a reduction in bioavailable testosterone [30]. Therefore, we suggest that serum 25-OHD3 levels are not a predictive marker for BMD values in patients with chronic liver disease.

We also found increased serum BALP levels in cirrhotic patients. Previous studies have described some crossreactivity (about 16%) between bone and liver alkaline phosphatase [31]. This, however, may lead to falsely elevated serum levels of BALP in patients with significant elevations in total alkaline phosphatase (elevations that are at least twice the upper limit of normal) [32]. In our study, none of the patients had serum total alkaline phosphatase levels higher than twice the upper limit of normal. Incremental increases in BALP levels in cirrhotic patients may reflect higher bone formation rates. Although we found increased serum BALP levels in our subjects, we did not find a significant correlation between serum BALP levels and BMD values. We have no explanation for the higher levels of BALP in the cirrhotic patients as compared to healthy individuals.

In addition to markers of bone formation (i.e., BALP), objective resorption markers were also measured in this study. We measured urinary DPD as a biochemical marker of bone resorption, which has some advantages over other markers of osteo-

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<th>Table 3. Luteinizing hormone, follicle-stimulating hormone, estradiol and intact parathyroid levels in female subjects (mean ± SD)</th>
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<tr>
<td><strong>Luteinizing hormone (mlU/ml)</strong></td>
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<td>5.5±3.6</td>
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<td><strong>Follicle-stimulating hormone (mlU/ml)</strong></td>
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<td><strong>Intact parathyroid hormone (pg/mL)</strong></td>
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<th>Table 4. Free testosterone levels in male patients (mean ± SD)</th>
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<td><strong>Free testosterone (pg/mL)</strong></td>
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<td>6.8±6.1</td>
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clastic function in patients with liver cirrhosis because it is found almost exclusively in bone and teeth, but not in human liver fibrosis. Hence, most of the DPD in urine is assumed to originate from bone [33, 34]. One study in patients with primary biliary cirrhosis (PBC) showed that urinary DPD levels correlated with levels of the serum amino terminal propeptide of type III collagen, an index of liver fibrogenesis, suggesting that DPD may be correlated with liver collagen metabolism [35]. We found that cirrhotic patients had significantly elevated DPD levels as compared to control subjects. There was no correlation observed, however, between DPD levels and bone mineral density.

In the present study, a positive correlation was found between BMD and Alb in the cirrhotic patient group. In contrast, a negative correlation was found between BMD and age, bilirubin and PT levels. In addition, no statistically significant relationship was observed between BMD and Ca, P, or GGT.

In conclusion, osteopenia and osteoporosis are highly prevalent in individuals with liver cirrhosis. Trabecular bone is clearly more affected than cortical bone. The main reason for this increased prevalence may be the augmented bone resorption observed in these patients. Other factors, such as FT, 25OHD3, and PTH may play an important role in bone mass loss in these patients. Larger studies with frequently repeated clinical measurements and more sensitive biochemical or laboratory measures of disease activity, performed over a course of many months or years, are needed to determine the precise effect of liver disease stage on BMD. Due to this high prevalence of metabolic bone disease among cirrhotic patients, these patients should undergo routine bone densitometric assessment and, if necessary, receive anti-osteoporotic therapy.

Conflict interest statement The authors declare that they have no conflict of interest to the publication of this article.

References


