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CLINICAL RESEARCH / KLİNİK ARAŞTIRMA

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Evaluation of Bone Metabolism in Patients with Chronic Liver Disease due to Chronic Hepatitis B or C Infection

Kronik Hepatit B veya C Enfeksiyonuna Bağlı Kronik Karaciğer Hastalığı Olan Hastalarda Kemik Metabolizmasının Değerlendirilmesi

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Abstract

Objective: Osteoporosis in chronic liver disease is couldn't be determined exactly. We aimed to investigate how the severity of liver function disorders affects bone mineral density (BMD) and the hormonal parameters associated with BMD in chronic hepatitis and cirrhosis patients.

Methods: A total of 32 patients (16 females) with chronic hepatitis associated with hepatitis B virus and hepatitis C virus and 32 patients (14 females) with liver cirrhosis were enrolled. Vitamin 25-hydroxy-D 3, calcium, parathyroid hormone (PTH), testosterone, estradiol, and dehydroepiandrosterone sulfate (DHEAS) levels evaluated. All patients underwent lumbar and femur neck BMD assessments.

Results: In patients with cirrhosis, the osteoporosis rate was 40.6 and the osteopenia rate was 28.1; in patients with hepatitis, the osteopenia rate was 43.8% and there were no osteoporotic patients. In the cirrhosis group, vitamin D levels were significantly lower than those in the hepatitis group ($p<0.05$). Calcium, PTH, testosterone, and estradiol levels were similar between the groups. DHEAS levels were lower in the cirrhosis group. In subgroup analyses; estradiol levels in cirrhotic women were lower than women with hepatitis. A positive correlation was observed between albumin levels and the femur T-score ($p=0.002$). There was no significant relationship between BMD and etiologic agent use, hepatic activity index, fibrosis and Child-Pugh score.

Conclusion: In cirrhotic patients, osteoporosis rates were significantly higher. The absence of a complete correlation between liver fibrosis and child stage and BMD signs that different factors play roles in osteoporosis development. In patients with cirrhosis, low vitamin D and DHEAS levels and in female patients with cirrhosis, impairment of estradiol were found to be important factors in osteoporosis.

Keywords: Chronic hepatitis, cirrhosis, bone mineral density, vitamin D, calcium

Öz

Amaç: Kronik karaciğer hastalığında görülen osteoporozun biyolojik mekanizması karmaşıktır ve nedeni kesin olarak belirlenememiştir. Kronik hepatit ve sirozlu hastalarda, karaciğer fonksiyon bozukluğunun derecesinin kemik mineral yoğunluğunu (KMY) ve onunla ilişkili bazı hormonal parametreleri nasıl etkilediğini araştırmayı amaçladık.

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Öz

Yöntem: Hepatit B virüs ve hepatit C virüs'e bağlı kronik hepatiti olan 32 hasta (16 kadın) ile sirozlu 32 hasta (14 kadın) çalışmaya alındı. Vitamin 25-hidroksi-D3, kalsiyum, parathormon (PTH), testosteron, östradiol, dehidroepiandrosteron sülfat (DHEAS) seviyeleri değerlendirildi. Tüm hastalarda, lomber ve femur boynu KMY değerlendirmeleri yapıldı.

Bulgular: Siroz hastalarında osteoporoz oranı %40,6 ve osteopeni oranı %28,1 idi; hepatit hastalarında osteopeni oranı %43,8 idi ve hiçbir osteoporotik hasta yoktu. Siroz grubunda, D vitamini düzeyleri hepatit grubundan anlamlı derecede daha düşüktü ($p<0,05$). Kalsiyum, PTH, testosteron ve östradiol düzeyleri gruplar arasında benzerdi. Ancak, DHEAS düzeyleri siroz grubunda düşüktü. Alt grup analizlerinde; sirozlu kadınlarda östradiol düzeyleri hepatitli kadınlara göre daha düşüktü. Albümin seviyesi ve femur T-skoru arasında pozitif bir korelasyon görüldü ($p=0,002$). KMY ve etken, hepatik aktivite indeksi, fibrozis ve Child-Pugh skoru arasında anlamlı bir ilişki saptanmadı.

Sonuç: Sirozlu hastalarda, osteoporoz oranları anlamlı derecede yüksek bulundu. Karaciğer fibrozis derecesi ve Child skoru ile KMY arasında tam bir korelasyon olmaması, osteoporoz gelişiminde farklı faktörlerin rol oynadığını göstermektedir. Sirozlularda D vitamini ve DHEAS düzeylerinin düşük olması ve kadın sirozlularda östradiol düşüklüğü osteoporozda önemli faktörler olarak bulundu.

Anahtar Kelimeler: Kronik hepatit, siroz, kemik mineral yoğunluğu, vitamin D, kalsiyum

Introduction

The biological mechanisms of osteoporosis in chronic liver disease are complicated and are yet to be clarified. Osteoporosis, a condition often experienced by patients with cirrhosis, is a serious condition that causes morbidity and immobility[1]. Recent studies that have focused on metabolic bone diseases in patients with cirrhosis have suggested that these patients, who are asymptomatic, need to be scanned in order to start therapy in the early phase[2,3].

In this study, we evaluated the correlation between the severity of liver disease and bone mineral density (BMD), together with the nature of the biochemical and hormonal changes that may occur in patients with chronic hepatitis and cirrhosis with an etiology of hepatitis B virus (HBV) or hepatitis C virus (HCV) infection. We assessed how the severity of liver function disorders affected BMD.

Materials and Methods

The Ethics Committee of the University of Health Sciences Türkiye, İstanbul Haseki Training and Research Hospital, İstanbul, Türkiye approved this study (decision no: 11290, date: 13.09.2007). Informed consent was obtained from each patient.

Patient Selection

A total of 64 patients aged 18-65 years were included. Of these, 32 patients (16 females) had liver cirrhosis secondary to HBV or HCV infections and 32 (14 females) were non-cirrhotic. Patients were excluded if they had chronic renal failure, diabetes mellitus, any malignancy, chronic diseases that may cause secondary osteoporosis, or a history of alcohol abuse were excluded. Postmenopausal women who received hormone replacement therapy and those who had received any medications in the last six months that may have influenced BMD were also excluded from the study.

The diagnosis of cirrhosis was based on liver biopsy, imaging evidence of parenchymal changes, or portal hypertension. The hepatic activity index (HAI) and degree of fibrosis were determined according to the Child-Pugh score of patients with cirrhosis and the Knodell classification of liver biopsy results in chronic hepatitis patients[4].

Both groups were assessed for osteoporotic risk factors: body mass index (BMI), smoking, coffee consumption, physical activity, exercise habits, exposure to the sun, and past medications. The number of pregnancies, lactation history, and duration of menopause were recorded for female patients.

Smoking behavior was described as either "smoker" or "non-smoker". Coffee consumption was categorized as none, rarely, or often (often: more than 2 cups/week, rarely: less than 2 cups/week). Physical activity was rated as light, moderate, or active (light physical activity: sedentary lifestyle; active: having a job that requires bodily exertion or a habit of physical activity, moderate: those between these two groups). Exposure to sunlight was defined as weak in those whose skin had no contact with sunlight (for example, veil or burqa wearers) and medium in those who had contact with sunlight only on the face and hand areas. Those with high exposure to sunlight were defined as normal.

Biochemical Parameters

The factors known to influence bone density were measured: 25-hydroxycholecalciferol [25(OH)D3], albumin-adjusted calcium, parathyroid hormone (PTH), testosterone, estradiol, and dehydroepiandrosterone sulfate (DHEAS). Total bilirubin and albumin levels and prothrombin time were determined to be used in the Child-Pugh scoring.

The 25(OH)D3 was measured using the high-performance liquid chromatography technique in the HPLC (Thermo-Finnigan, USA) device and with the help of the vitamin D3 ClinRep HPLC kit (Chemicals + Instruments GmbH, Munich, Germany). Calcium, albumin, and total bilirubin levels were measured using the Abbott C16000 device (65205, Wiesbaden, Germany), and the PTH level was determined using the Immulite 2500 autoanalyzer (LL554EL, UK). Testosterone, estradiol, and DHEAS levels were determined using the Abbott Architect Ci 2000 SR device (Wiesbaden, Germany). The Amax400 device (IDA Business Park, Bray, Co. Wicklow, Ireland) was used to establish prothrombin time.

Measurement of Bone Mineral Density

All patients underwent AP spine (lumbar, L1-4) and femur neck BMD measure ments using a Norland DEXA (dual energy X-ray absorption) Bone Densitometer (Norland Corp, Fort Atkinson, Wisconsin). Osteoporosis and osteopenia were defined according to the World Health Organization criteria [osteoporosis: T-score below -2.5 standard deviation (SD); osteopenia: T-score between -1.0 and -2.5 SD][5].

The BMI of the patients was calculated as weight/surface measurement=kg/m². The BMI values of the patients were classified as follows: under 18 kg/m² = underweight, between 18-25 kg/m²=normal weight, between 25-30 kg/m²=overweight, between 30-40 kg/m²=obese, and those over 40 kg/m² = morbid obese.

Statistical Analysis

All statistical analyses were performed using SPSS-16. The results were calculated as means ± SD. The Student's t-test was applied to differentiate between the averages of the two independent groups, and where the SD was greater than the average and/or the number of cases within the groups was small, the non-parametric Mann-Whitney U test was also applied. Analysis of variance was employed to compare the average values of more than two groups. For the comparison of the inter- group ratios, the non-parametric chi-square test was applied, and the correlation studies between two variables were carried out using Pearson's correlation test, the Levene's test, the Spearman correlation analysis, and Kruskal-Wallis analysis methods. A multiple regression analysis was performed for the possible variables of BMD measurement: age, sex, BMI, pregnancy, lactation, physical activity, exposure to sunlight, Child-Pugh score, fibrosis all biochemical parameters; a value of $p<0.05$ was accepted as indicating statistical significance.

Results

Demographic and Clinical Features

The demographic features, except for age, were similar in both groups (Table 1). Both groups were similar in terms of the other generally accepted osteoporosis risk factors ie physical activity status, smoking habits, coffee consumption, exposure to sunlight, and sedentary lifestyle ($p>0.05$). When female patients with cirrhosis were compared with female patients with hepatitis, there was no significant difference between the number of pregnancies and the duration of lactation ($p>0.05$). However, when compared with the length of menopause, the duration was significantly longer in patients with cirrhosis than in those with hepatitis ($p=0.013$). In the cirrhosis group, the Child-Pugh score was between A5 and C11. There were 19 (59%) patients in child A, 7 (22%) in child B, and 6 (19%) in child C. The average score was 6.62±1.84. Twenty-five out of 32 patients in the hepatitis group underwent liver biopsy. The average HAI score was 5.64±3.16 (range 0-13) and the fibrosis grade was 1.36±1.22 (range 0-3).

Table 1. Demographic features of the patients groups

Feature	Cirrhosis group	Hepatitis group	p
	(n=32)	(n=32)	
Sex (F/M)	16/16	14/18	>0.050
Age (years)	54.03±12.83 (18-65)	39.46±14.00 (18-65)	<0.001
Age / F	59.31±7.59	45.71±13.22	
Age / M	48.75±14.93	34.61±12.91	
HBV / HCV	19/13	20/12	>0.050
BMI (kg/m²)	28.15±4.87 (20-38)	28.59±6.62 (19-42)	>0.050

F: Female, M: Male, BMI: Body mass index, HBV: Hepatitis B virus, HCV: Hepatitis C virus

Bone Density Measurements

The femur T-score in patients with cirrhosis was measured as -2.14±1.38 (-4.28/0.21), the Z-score as -0.94±0.95 (-2.58/0.99); the lumbar T-score as -1.47±1.03 (-3.42 /-0.61) and the Z-score as -1.19±0.91 (-3.32/-0.36). In patients with hepatitis, the femur T-score was -0.72±1.09 (-2.45/-2.30) with a Z-score of -0.24±1.06 (-1.78/-2.62) and the lumbar T-score was -0.80±0.94 (-2.08/-2.21) with a Z-score of -0.62±0.94 (-1.95/-2.39). Although the femur T and Z-scores were lower in patients with cirrhosis than in those with hepatitis, no significant difference was observed between the lumbar T and Z-scores (Figure 1).

When BMD was evaluated for etiologic agent dependence, no significant difference was discovered (p>0.05).

In the cirrhosis group, BMD was normal in 10 patients (31.3%); 13 patients (40.6%) were osteoporotic and osteopenia was detected in 9 patients (28.1%). Among the hepatitis patients, 18 (56.2%) were normal, 14 (43.8%) were osteopenic, and none were osteoporotic. This situation was evaluated as highly significant (p<0.001) and it has been observed that there were more osteoporotic patients in the cirrhosis group than in the hepatitis group.

No relationship was found between BMD, HAI scores, and fibrosis grade in patients with hepatitis and between Child-Pugh score and BMD in the cirrhotic patients (p>0.05).

Biochemical and Hormonal Parameters

A positive correlation was observed between the femur T-score and albumin level in both groups (p=0.002). No significant correlation was found between femur Z and lumbar T-Z values (p>0.05) The bilirubin value had no significant relationship with the BMD in the cirrhotic patients (p>0.05).

When the hormonal parameters testosterone, estradiol, and DHEAS were examined, similar testosterone and estradiol levels were noted in both groups (p>0.05). DHEAS levels were significantly lower in the cirrhotic patients (p=0.001) (Table 2).

The average hormonal values of males and females in both groups were calculated. The resulting values indicated that the testosterone and estradiol levels of male patients with hepatitis and cirrhosis were similar, whereas the DHEAS levels in cirrhotic males were significantly lower than those in non-cirrhotic males. The testosterone levels in females were similar in both groups, but the estradiol and DHEAS levels were significantly lower in cirrhotic women than in non-cirrhotic women (Table 3). When the variables of PTH, vitamin D, and calcium, which indicate bone metabolism, were assessed, it was observed that the vitamin D-level was significantly lower in the cirrhosis group compared with the hepatitis group (p=0.045). The average calcium and PTH levels were similar between the groups (p>0.05) (Table 4).

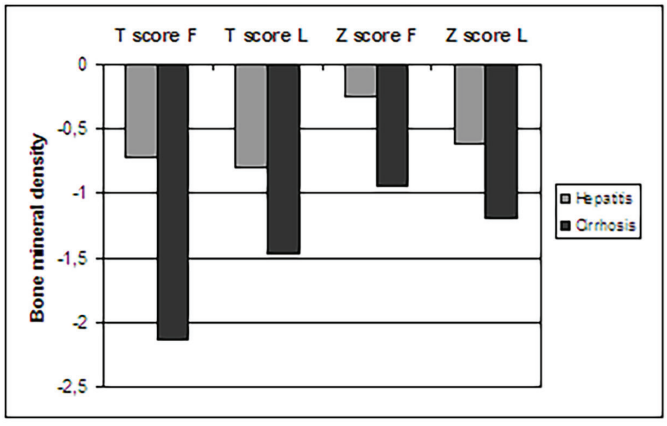

Figure 1. Comparison of the hepatitis and cirrhosis groups in terms of bone mineral density

Discussion

Studies conducted in the last 20 years have shown a prevalence of osteoporosis of 12-55% and a fracture incidence of 3-20% in patients with cirrhosis[6-18]. In accordance with these studies, we found an osteoporosis rate of 40.6% and osteopenia ratio of 28.1% in patients with cirrhosis, although none of our patients had experienced any fractures. Those with hepatitis also had an osteopenia ratio of 43.8%, but no osteoporotic patient was included in the group. The osteopenia ratio was approximately twice as high in the

Table 2. Comparison of the testosterone, estradiol and DHEAS levels

	Hepatitis (n=31) (Min.-Max.)	Cirrhosis (n=30) (Min.-Max.)	p
Testosterone*	3.90±4.20	3.51±3.62	>0.050
	(0.20-20.80)	(0.03-10.52)	
Estradiol**	46.69±6.10	38.19±3.95	>0.050
	(8.81-307)	(10-161)	
DHEAS***	213.09±147.60	96.19±123.50	0.001
	(4.64-475.30)	(14.56-618.40)	

*Testosterone: ((M: 2.8-8, F: 0.06-0.8 ng/mL), **Estradiol: (M: 25-107, F: 18-427 pg/mL), ***DHEAS: (F: 35-430, M: 80-560 ug/dL), DHEAS: Dehydroepiandrosterone sulfate, Min.: Minimum, Max.: Maximum

Table 3. Comparison of the hormone levels of the males and females in both patient groups

	Hepatitis M	Cirrhosis M	p	Hepatitis F	Cirrhosis F	p
	n=17	n=14		n=14	n=16	
Testosterone (ng/mL)	5.66±1.81	6.89±2.32	>0.05	1.76±5.27	0.52±0.45	>0.05
Estradiol (pg/mL)	25.05±9.49	38.10±20.36	>0.05	72.96±84.39	38.26±51.56	0.01
DHEAS (ug/dL)	275.27±130.54	148.18±165.14	0.01	137.57±134.48	50.68±33.47	0.01

DHEAS: Dehydroepiandrosterone sulfate

Table 4. Comparison of the Vit-D, PTH and calcium levels

	Hepatitis	Cirrhosis	p
	n=32	n=32	
Vit-D*	24.75±1.29	18.84±9.82	0.045
	(2.70-49.50)	(2.50-38.90)	
PTH**	57.34±5.07	64.09±2.71	>0.050
	(11.40-253.00)	(18.20-142.00)	
Calcium***	9.21±0.48	9.06±0.40	>0.050
	(8.4-10)	(7.9-9.8)	

*Vit-D: (10-50 ng/mL), **PTH: (11-67 pg/mL), ***Calcium: (8.6-10.2 mg/dL)
PTH: Parathyroid hormone, Vit-D: Vitamin D

hepatitis group than in the cirrhosis group. The interpretation of this finding may be that patients with hepatitis are further along the process of developing osteoporosis than those with cirrhosis.

Several studies exploring the state of osteoporosis in chronic liver diseases have suggested various etiopathogenic explanations. Ninkovic et al.[11] determined the risk factors for osteoporosis as low BMI and advanced age. Among our patients, the age of those with cirrhosis was greater than that of those with hepatitis, and the female patients with cirrhosis had a longer menopausal period. The BMI in both groups were similar. Giouleme defined the pathogenesis of osteoporosis as an "increased bone turnover" and although no relationship between the etiological agent and osteoporosis has been observed, a relationship between the grade of cirrhosis and the grade of osteoporosis has been determined[19]. In a study by Crawford et al.[16] involving patients with cirrhosis awaiting liver transplantation, a correlation was noted between BMD and vitamin D deficiency and the severity of the disease[20]. There are other studies that support this finding[9,16]. However, in our study, no significant correlation was observed between Child-Pugh score and BMD. Cijevschi et al.[21], on the other hand, observed correlations between the nutritional status and chronic cholestasis and BMD in patients with cirrhosis.[21] The calcium-PTH-vitamin D axis plays a vital role in the pathogenesis of the osteometabolic diseases. The decrease in vitamin D levels goes hand in hand with an increase in PTH levels, and this probably contributes to the development of osteoporosis[22-24]. Studies focused on this point are also not in accordance with each other. Although vitamin D deficiency has been detected in many studies, its relationship with BMD has not been clarified[4,6]. There are studies emphasizing that increased PTH levels in patients with cirrhosis are observed parallel to degenerating liver function as well as studies that failed to observe any relationship between PTH levels and BMD[4,6].

In our study, when the bone metabolism parameters PTH, 25(OH)D3 and calcium were assessed, the 25(OH)D3 vitamin level was significantly lower in the cirrhosis group than in the hepatitis group. There were no significant difference between the hepatitis and cirrhosis patients with albumin-adjusted calcium levels. The results were similar for the PTH values. It is hypothesized that the lower 25(OH)D3 vitamin levels in patients with cirrhosis with no difference in PTH levels is a consequence of the Child A status of most of these patients.

Although *in vitro* and animal studies have shown that free bilirubin inhibits osteoblastic activity and its functions, no relationship between the levels of conjugated, non-conjugated, and total bilirubin and BMD has been determined in patients awaiting liver transplantation[25-28]. Boone et al.[29] suggested that hyperbilirubinemia disrupts osteoblastic function and raises osteoclast levels. We also found that bilirubin levels were higher in patients with cirrhosis than in patients with hepatitis, but we did not observe a relationship between bilirubin and BMD.

Floreani pointed to the contribution of hypogonadism to the etiopathogenesis of osteodystrophy in patients with

cirrhosis[30,31]. A study by Kaymakoğlu et al.[32] suggested that hypogonadism and feminization are correlated with the grade of cirrhosis. In Grandi et al.[33] study, low testosterone levels were found to be a major determinant of bone loss, whereas in another study, the PTH, vitamin D3, testosterone, and estrogen levels in patients with cirrhosis were similar to healthy individuals, although BMD was significantly reduced[34]. We observed similar testosterone and estradiol levels in the hepatitis and cirrhosis groups, but the DHEAS levels were significantly lower in the cirrhotic patients. Additionally, low estradiol levels were detected in women with cirrhosis in the subgroup analysis, no correlation between testosterone or estradiol and BMD was detected, but there was a negative correlation between DHEAS and BMD. When Tsuneoka et al.[23] compared chronic viral hepatitis and cirrhosis patients, he found that BMD was significantly lower in the cirrhosis patients and indicated that vitamin D and albumin levels correlate with BMD. In our study, only a positive correlation between the femur T-score and albumin was observed.

In a study by Schiefke et al.[35], no difference was observed between HBV and HCV as etiologic agents in terms of osteoporosis. We also note that BMD was not influenced by the etiologic agent. Schiefke et al.[35] detected a relationship between high PTH levels and histologic changes of the liver and emphasized that PTH pointed to a shift in metabolic balance toward bone resorption in chronic hepatitis patients. We did not find any significant relationship between HAI and fibrosis and BMD.

Study Limitations

The limitations of our study include its small sample size and cross-sectional design. Further research with larger patient cohorts is needed to achieve a better understanding of this topic.

Conclusion

In conclusion, the osteoporosis ratio in patients with cirrhosis was in accordance with the literature. However, there was no correlation between liver fibrosis or Child-Pugh score and BMD. This result suggests that other factors, such as low vitamin D and DHEAS levels, influence the development of osteoporosis in female patients with cirrhosis.

Ethics

Ethics Committee Approval: The Ethics Committee of the Turkish Health Sciences University, Istanbul Haseki Training and Research Hospital, İstanbul, Türkiye approved this study (decision no: 11290, date: 13.09.2007).

Informed Consent: Informed consent was obtained from each patient.

Footnotes

Authorship Contributions

Surgical and Medical Practices: A.T.K., M.K., Y.S., M.Ko., Z.A., Ş.P., Concept: A.T.K., M.K., Y.S., M.Ko., Z.A., Ş.P., Design: A.T.K., M.K., Y.S., M.Ko., Z.A., Data Collection or Processing: A.T.K., Z.A., Analysis or Interpretation: A.T.K., Ş.P., Literature Search: A.T.K., Ş.P., Writing: A.T.K., M.K., Y.S., M.Ko., Z.A., Ş.P.

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