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The Frequency of Osteoporosis in Patients with Liver Cirrhosis in Erzurum and Surrounding

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Abstract: Here**,** it was aimed to investigate whether the frequency of osteoporosis in patients with liver cirrhosis increases compared to the healthy population. DEXA (dual energy x-ray absorptiometry) test was applied to 50 patients with liver cirrhosis and 50 healthy people of similar age who were followed in the Gastroenterology Clinic of Atatürk University Medical Faculty Hospital. L1-L4 T scores were determined from the DEXA test results. In addition, age, gender, disease etiology, complications, Child-Pugh score, sodium-corrected MELD (Model for End-stage Liver Disease) score, serum vitamin D and corrected serum calcium levels were obtained from all patients. The mean age of the patient group with liver cirrhosis was 58.18±10.67 years. The mean age of the control group was 59.82±11.54. When compared in terms of age distribution, no statistically significant difference was found between the two groups ($p>0,05$). The mean DEXA test T scores of the patient group with liver cirrhosis was -1.58±1.44 SD and the mean of the DEXA test T scores of the control group was calculated as -1.01±1.32 SD. When compared in terms of T scores, a statistically significant decrease was found in the patients with liver cirrhosis compared to the control group ($p<0.05$). Liver cirrhosis may be a risk factor for the development of osteoporosis and these patients should be followed up for osteoporosis.

Keywords: Liver Cirrhosis; Osteoporosis; Chronic Hepatitis B Infection.

1. Introduction

Liver cirrhosis is one of the common causes of morbidity and mortality in developed countries. Liver cirrhosis is not considered as a disease alone today. It is accepted as a dynamic process that includes the treatment of clinical symptoms and complications (1). There is no single definition that includes all the details, but it is a definition in generally accepted morphological terms. Cirrhosis of the liver is considered to be a disease characterized by simultaneously developing parenchymal necrosis, regeneration and fibrosis resulting in lobular deterioration and nodules. As a result, liver cell failure and portal hypertension are the clinical definition of liver cirrhosis (2).

The main complications expected in liver cirrhosis are; portal hypertension, esophageal varicose bleeding, ascites, SBP (spontaneous bacterial peritonitis), splenomegaly and hypersplenism, HE (hepatic encephalopathy), hepatorenal syndrome, hepatopulmonary syndrome, malnutrition,

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coagulopathy, hepatic osteodystrophy, hematological disorders and hepatocellular carcinoma (3).

Hepatic osteodystrophy is a condition characterized by loss of bone mass and deterioration of its structure, especially in cholestatic chronic liver diseases. Although its pathogenesis is multifactorial, it is not clear. Its histological structure is similar to that of postmenopausal osteoporosis, and trabecular bone structure is more affected by cortical bone structure. Factors thought to be directly or indirectly effective IGF-1 (insulin-like growth factor-1) deficiency, hyperbilirubinaemia, hypogonadism (estrogen and testosterone deficiency), alcohol use, excessive iron accumulation, low vitamin D level, vitamin D receptor genotype, osteoprotegrin deficiency and immunosuppressive therapy before and after liver transplantation (4).

Osteoporosis is a condition that causes an increased risk of fractures, characterized by a decrease in bone mass and deterioration in microarchitecture. The World Health Organization defines osteoporosis as a BMD (Bone Mineral Density) of 2.5 SD or less than the average for a healthy young adult age group of the same age and gender. This value is also expressed as the T score of -2.5 SD or less (5).

DEXA is the most commonly used BMD measurement tool in the diagnosis of osteoporosis. Although any skeletal region can be measured, measurements on the lumbar vertebra and femur are generally evaluated. The T score is obtained by comparing the calculated amount of mineralization with the healthy young adult population (20-30 years old). The healthy young adult populations T score is considered to be 0 SD. T score of -1 SD and above indicates normal BMD. A range of -1 SD and -2.5 SD is considered osteopenia, while a value of -2.5 SD and below is considered osteoporosis (6).

2. Material and Methods

Between 01.07.2019 and 31.12.2019, 50 patients who were admitted to the gastroenterology outpatient clinic of Atatürk University Medical Faculty Hospital or hospitalized in our gastroenterology clinic were prospectively applied DEXA test. Fifty patients who were admitted to our general internal medicine and endocrinology outpatient clinics between 01.07.2019 and 31.12.2019 were included in the control group. DEXA test was performed in these patients and the frequency of osteoporosis was determined. In addition, age, gender, disease etiology, complications, Child-Pugh score, sodium-corrected MELD score, serum vitamin D and corrected serum calcium levels of all patients were determined through routine examinations requested from our patients. In the light of the data obtained, the frequency of osteoporosis in liver cirrhosis patients in and around Erzurum was analyzed and compared with the data of the healthy control group of the same age group.

2.1. Statistical analysis

All data obtained were recorded in Microsoft Excel 2013 program. SPSS (Statictical Package for Social Sciences) 20.0 statistics program was used in the analysis of the data. Group distributions were found to be normal with the Kolmogorov-Smirnov test in SPSS. Then, the data of the patient and control groups were analyzed with Student's t-test.

3. Results

Of the 50 patients diagnosed with liver cirrhosis included in our study, 32 (64%) were male and 18 (36%) were female. Of the 50 patients included in the control group, 15 (30%) were male and 35 (70%) were female. The mean age of the patient group diagnosed with liver cirrhosis was 58.18±10.67, while the mean age of the control group was 59.82±11.54. When compared in terms of age distribution, no statistically significant difference was found between the two groups (p: 0,463).

The mean BMI (Body Mass Index) of the patient group diagnosed with liver cirrhosis was calculated as 27.62±3.65 kg/m^2 and the mean BMI of the control group was calculated as 29.46±5.26 kg/m^2. When compared in terms of BMI, a statistically significant higher was found in the control group compared to the patient group (p: 0.045). In the patient group with a diagnosis of liver cirrhosis, 9 (18%) patients were smokers, 21 (42%) were non-smokers, and 20 (40%) patients became smokers at some point in their life, but quit before the last year. In the patient group with a diagnosis of liver cirrhosis, 7 patients (14%) were using alcohol, and 43 (86%) patients were not using alcohol. Of the 18 female patients in the liver cirrhosis group, 5 were in the premenopausal period and 13 were in the postmenopausal period. Of the 35 female patients in the control group, 6 were in the premenopausal period, while 29 were in the postmenopausal period.

When the patient group diagnosed with liver cirrhosis was examined etiologically, it was seen that 20 (40%) patients were most frequently due to chronic HBV infection, the second most common was 13 (26%) patients were considered cryptogenic, and the third most common was 4 (8%) patients due to chronic HCV infection. Detailed information about the etiological distribution of patients with liver cirrhosis is shown in figure 1.

In the liver cirrhosis patient group, 27 (54%) people were in the Child-Pugh A group, 14 (28%) were in the Child-Pugh B group, and 9 (18%) were in the Child-Pugh C group. When the new sodium-corrected MELD scores of the same group were calculated, it was found that 18 (36%) patients had a score of 9 and below, 24 (48%) patients had a score between 10 and 19, and 8 (16%) patients had a score between 20 and 29.

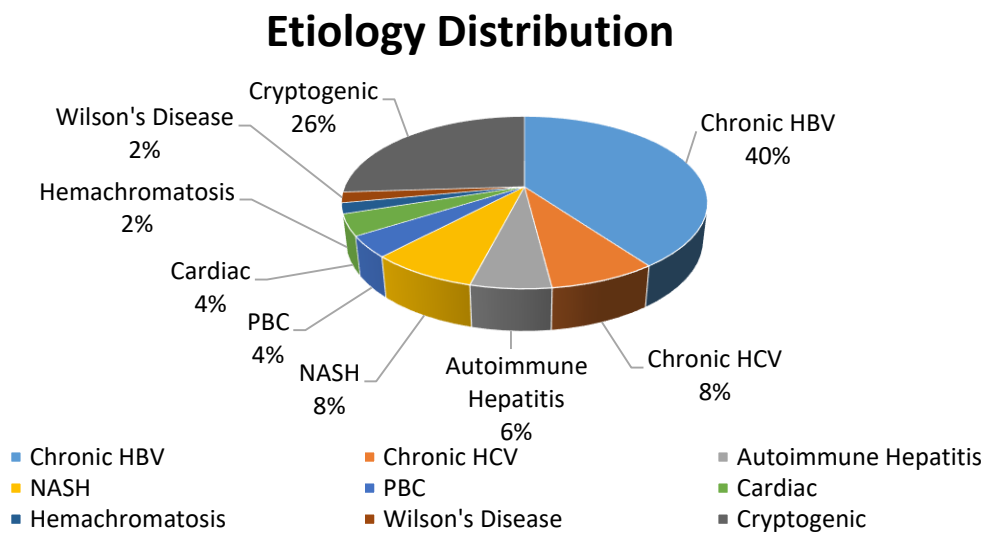

Figure 1: Etiological distribution of the patient group with liver cirrhosis.

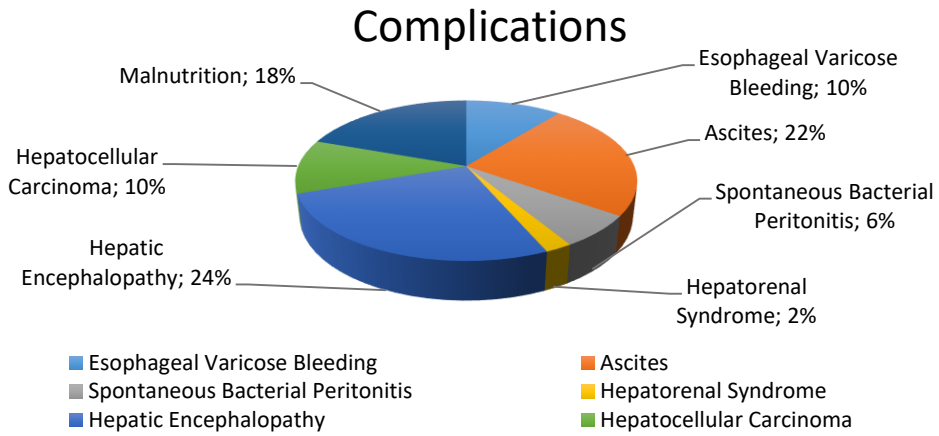

Figure 2: Complications in patients.

While the mean vitamin D level was 18.76±9.89 ng/ml in the group with liver cirrhosis, it was found as 23.48±14.15 ng/ml in the control group. When compared in terms of vitamin D levels, no statistically significant difference was found in both groups (p: 0.056). The mean corrected calcium value was 9.27±0.46 mg/dl in the patient group with liver cirrhosis and 9.29±0.59 mg/dl in the control group. When compared in terms of corrected calcium levels, no statistically significant difference was found between the two groups (p:0.83).

Complications developing in the patient group diagnosed with liver cirrhosis are shown in detail in figure-2. When the patients with EVB (Esophageal Varicose Bleeding) were examined, it was seen that 1 (2%) patient was male and 4 (8%) patients were female. When compared in terms of gender, the rate of EVB in sick females was found to be statistically significantly higher than in males (p: 0.031). In the patient group with a diagnosis of liver cirrhosis, 10 (20%) patients used entecavir, 8 (16%) patients used tenofovir, 8 (16%) patients used furosemide, and 1 (2%) patient used enoxaparin. When the T scores in the DEXA test of patients using entecavir and those not using it were compared, no statistically significant result was found (p:0.78). When the T scores of the DEXA test of the patients using and not using tenofovir were compared, a statistically significant low T score was found in patients who did not use the drug (p:0.008). When the T scores of the patients using furosemide and those who did not use the DEXA test were compared, no statistically significant difference was found (p:0.4).

In the liver cirrhosis group, patients with normal BMD, ostopenic and osteoporotic were grouped according to their etiology. 6 (12%) patients with liver cirrhosis due to chronic HBV infection had normal BMD and 14 (28%) patients had low BMD. The most common etiology in the group with low BMD was found to be chronic HBV infection.

When the DEXA test T scores of the patient group diagnosed with liver cirrhosis were examined, it was observed that it ranged from -4.4 to 3.1 SD. The mean of the T scores was calculated as -1.58±1.44 SD. When the DEXA test T scores of the control group were

examined, it was observed that it ranged from -3.6 to 1.6 SD. The mean of the T scores was calculated as -1.01±1.32 SD. When compared in terms of T scores, a statistically significant decrease was found in the patient group with a diagnosis of liver cirrhosis compared to the control group (p: 0.042).

4. Discussion

Osteoporosis is an important disease that causes an increase in mortality and morbidity, especially in postmenopausal women in our country and in the world. There are risk factors that should be evaluated before the diagnosis of osteoporosis. High BMI is considered to be a risk factor in many diseases other than osteoporosis. In contrast, one of the risk factors in osteoporosis is low body mass index (7). In our study, the mean BMI of the control group was found to be statistically significantly higher than the average BMI of the patient group with liver cirrhosis.

Many conditions such as chronic viral hepatitis, alcohol, hereditary metabolic diseases, NASH (Nonalcoholic Steatohepatitis), cardiac diseases, autoimmune diseases and toxic diseases can be involved in the etiology of liver cirrhosis. The most common etiology causes in the world and in our country are viral hepatitis and alcohol (8). In a study conducted by H. Enomoto et al in Japan on 48 621 cases, the most common (48.2%) chronic HCV infection in the etiology of liver cirrhosis, chronic alcohol use was the second (19.9%) and the third (11.5%) chronic HBV infection has been detected (9). In another study conducted by D. Kim et al. in the USA with 100 000 cases, the most common (32.1%) chronic HCV infection in the etiology of liver cirrhosis, chronic alcohol use was the second (61.1%) and the third (2.6%) chronic HBV infection has been found (10). In our study, in the etiology of liver cirrhosis, the most common (40%) chronic HBV infection, the second (26%) cryptogenic and the third (8%) chronic HCV infection were found. It was thought that the high rate of cryptogenic etiology in our study was due to the low number of patients in our study. In our study, liver cirrhosis due to chronic alcohol use was not detected. It was thought that the reason for this situation was the low alcohol consumption of our countries people due to religious and cultural reasons and the population of our study was limited to 50 patients.

Expected complications in patients with liver cirrhosis are portal hypertension, EVB, ascites, SBP, splenomegaly and hypersplenism, HE, hepatorenal syndrome, hepatopulmonary syndrome, malnutrition, coagulopathy, hepatic osteodystrophy, hematological disorders and HCC. Complications that develop may cause an increase in the mortality and morbidity of the patients. Sometimes patients can be diagnosed because of a complication that develops while living their lives without being aware of liver cirrhosis (11).

In the study conducted by J.C. Lai et al. on 1044 patients with liver cirrhosis, the frequency of HE was found to be 41% and the frequency of ascites as 36% (12). In our study, the frequency of HE was found to be the most common complication with 24% (12 patients) and ascites as the second most common complication with a frequency of 22% (11 patients). In our study, the frequency of HE and ascites development was lower than the study of J.C. Lai et al. The reason for this is thought to be the regular follow-up of the patients with liver cirrhosis in our region and the compliance of the patients with the recommendations and treatments.

In the study conducted by T.W. Sherpa et al. on 50 patients diagnosed with liver cirrhosis, the incidence of malnutrition was found to be 74%, the incidence of EVB as 22%, and the incidence of SBP as 8% (13). In our study, the frequency of malnutrition in the patient group was found to be 18%, the frequency of EVB as 10% and the frequency of SBP as 6%. In our study, according to the study of T.W. Sherpa et al., the frequency of malnutrition and EVB is significantly lower, but the frequency of SBP development is almost similar.

62 patients (23%) were diagnosed with HCC in a study conducted by H. Oka et al. with 260 patients with liver cirrhosis (14). In our study, HCC developed in 10% of the patients. In our study, the frequency of HCC development is lower than that of H. Oka et al. In the study conducted by S.W. Lee et al with 97 patients with esophageal varicose bleeding, recurrent bleeding was detected in 14.4% (15). There was no statistically significant difference in gender between the groups with and without recurrent bleeding. In the study conducted by B. Kraja et al on 139 patients with esophageal varicose veins, 24% of the patients developed EVB (16). On the other hand, 14.7% of the patients with EVB are female and 85.3% are male. In our study, the frequency of EVB was found to be 10%. 80% of these patients are female and 20% are male. It was found that the EVB was statistically significantly higher in female patients compared to male patients.

Patients diagnosed with osteoporosis should be examined in terms of secondary causes. Oral nucleotide/nucleoside analogues, which are antiviral drugs, can be used to provide treatment in patients with chronic HBV infection. Tenofovir, one of these drugs, is thought to cause a decrease in BMD. Hydroxylation of vitamin D in the kidney is completed in the proximal tubule. Tenofovir is thought to cause abnormalities in the proximal tubule, leading to a decrease in vitamin D levels and, consequently, osteoporosis (5).

In the study conducted by M.T. Wei et al on 1224 Asian patients with chronic HBV infection, 276 patients used tenofovir, 335 patients used entecavir and 613 patients did not use either drug. In the 8-year follow-up, the frequency of osteopenia/osteoporosis was found to be 13.17% in the tenofovir group, 15.09% in the entecavir

group and 10.17% in the group not using drugs. There was no statistically significant difference between these 3 groups in terms of osteopenia / osteoporosis (17). In our study, the mean T score in the DEXA test was found to be -0.37±1.18 SD in patients using tenofovir and -1.81±1.38 SD in patients not using it. When the T scores in the DEXA test of the patients using and not using tenofovir were compared, a statistically significant low T score was found in patients who did not use the drug, contrary to the data in the literature. It was thought that this was due to the limited number of patients in our study and the weakness of the power to represent the general population. n the DEXA test, the mean T score was found to be -1.73±1.33 SD in patients using entecavir and -1.59±1.39 SD in patients not using entecavir. A statistically significant result was not found when T scores in the DEXA test of patients using entecavir and those who did not use it.

A study on osteopenia/osteoporosis was conducted by L.S. Lim et al on 6481 women using loop diuretic drugs and those who did not. A statistically significant decrease was found in the DEXA test T score levels in patients using loop diuretics compared to patients not using loop diuretics (18). In our study, when the T scores of the patients using furosemide and those not using it were compared, a statistically significant difference was not found in accordance with the literature.

Hepatic osteodystrophy is a bone metabolism disorder especially seen in those with cholestatic chronic liver disease. Factors thought to have an effect on osteoporosis are IGF-1 deficiency, hypogonadism (estrogen and testosterone deficiency), alcohol use, low vitamin D level, osteoprotegrin deficiency, and immunosuppressive drugs used before/after liver transplantation. The reasons for low vitamin D levels; disruption of hydroxylation in the liver, malabsorption, disruption of the enterohepatic cycle and increased urinary excretion. Osteoporosis that develops in patients with liver cirrhosis can cause an increase in morbidity and mortality with bone fractures (19).

In a study conducted by Y. Karoli et al on 72 patients with liver cirrhosis, the most common etiology in the group with low BMD was found to be chronic HCV infection (20). In our study, in contrast to the study of Y. Karoli et al, the most common etiology in the group with low BMD among 50 patients with liver cirrhosis was chronic HBV infection.

In a study conducted by V. Goral et al, when the DEXA test was compared in terms of T scores, a statistically significant decrease was found in the patient group with a diagnosis of liver cirrhosis compared to the control group (21). In our study, when the DEXA test T scores were compared, a statistically significant decrease was found in the patient group with a diagnosis of liver cirrhosis compared to the control group, similar to the literature data.

5. Conclusions

In our study, the number of patients considered cryptogenic was found to be higher when compared with the data in the literature. In our region, patients diagnosed with liver cirrhosis and whose etiology cannot be determined should be reviewed and carefully examined. It was observed that the vitamin D levels of the patients participating in our study were below the level considered optimal by the World Health Organization. Because of the long winter season in our region, wearing clothes that cover almost the entire body and the low number of sunny days throughout the year explain the low vitamin D level. We should follow the vitamin D levels of the patients in our region and arrange their treatment when necessary. In addition, we must inform the patients about the appropriate contact method with sunlight for vitamin D synthesis to occur. We should follow the patients who apply to our polyclinics closely in terms of complications. We should find and treat patients with HE, if any, by finding the underlying causes. When compared in terms of gender, the rate of EVB in sick women was found to be statistically significantly higher than the sick men. Female patients with esophageal varices should be followed up more closely in terms of EVB. The fact that our study was limited to 50 patients weakens the strength of this finding. Male and female patients can be compared in terms of EVB in future studies with higher populations. The DEXA test T scores of patients with entecavir, tenofovir and furosemide among patients with liver cirrhosis included in our study were analyzed. When compared with patients who did not use these drugs in the same group, their effects to increase the development of osteodystrophy were not observed. However, there are findings in the literature that they predispose to osteoporosis in larger studies on these drugs. Therefore, patients should be carefully monitored for osteoporosis while using drugs such as entecavir, tenofovir and furosemide.

Liver cirrhosis can predispose to the development of osteoporosis. These patients should be closely followed up for osteodystrophic complications and treated early. Studies with higher populations are required to clearly reveal the relationship between chronic HBV infection and osteodystrophy.

Conflict of Interests

Authors declare that they have no financial interests or personal conflicts that may affect the study in this article.

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Author Contributions

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and/or Interpretation - Menekşe B.; Literature Search- Menekşe B., Topdağı Ö., Sanalp Menekşe T.; Writing Manuscript- Menekşe B.; Critical Review- Topdağı Ö., Sanalp Menekşe T.

Ethical Approval

The Ethics Committee's approval of the Atatürk University Faculty of Medicine is obtained for the study. (Decision number 4-A of 24.05.2019 dated meeting no: 07).

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