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Original Article

Osteodystrophy in Posthepatitic Cirrhosis

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This study investigated the incidence and severity of hepatic osteodystrophy in patients with posthepatitic liver cirrhosis, and the role of hepatocellular injury in bone loss. Twenty-four patients (15 females and 9 males, mean age 49 ± 13 years) with posthepatitic cirrhosis were enrolled in this study. The control group consisted of 22 healthy age and sex matched adults. The bone mineral density (BMD) was evaluated by dual energy x-ray absorptiometry of the L1-L4 vertebral bodies. A detailed questionnaire was used to assess the epidemiological findings. A statistically significant decrease in BMD of the patients was observed. There were no significant differences in the alkaline phosphatase, parathyroid hormone, calcitonin, 25-hydroxyvitamin D, osteocalcin, free testosterone, luteinizing hormone, follicle stimulating hormone, and estradiol levels, oral calcium intake, urinary calcium, phosphorus and hydroxypyroline excretion between patients and controls. The control group smoked more cigarettes, consumed more coffee and meat, and were exposed the sun light for a longer period than the study group. Multiple regression analysis showed that osteopenia depends significantly on the extent of liver disease. The data shows that the patients with posthepatitic cirrhosis had osteopenia, and that cirrhosis was a direct and independent risk factor.

Key Words: Liver cirrhosis, osteoporosis, bone mineral density

INTRODUCTION

Bone metabolism abnormalities observed in chronic liver disease are refered to as hepatic osteodystrophy. Osteodystrophy in liver cirrhosis consists of osteomalacia and/or osteoporosis. In general, there are secondary factors such as malabsorption and nutritional deficiencies that may cause bone changes in chronic liver disease.[1] The role of hepatocellular dysfunction in hepatic osteodystrophy is not clear.

Therefore, this study investigated the frequency and severity of hepatic osteodystrophy in patients with posthepatitic liver cirrhosis and determined the role of the hepatocellular failure in bone loss.

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MATERIALS AND METHODS

Twenty-four patients (15 females and 9 males, mean age 49 ± 13 years) with posthepatitic cirrhosis were enrolled in this study. The control group consisted of 22 healthy age and sex matched adults. The epidemiological features of patients and the control group are shown on Table 1. All patients were questioned according to recommendations of The Mediterranean Osteoporosis Study (MEDOS) group to determine the epidemiological factors regarding osteoporosis.[2] The questionnaire comprised of 19 subdivisions and 915 variables. Subdivisions of the questionnaire are shown on Table 2. As life-style factors are likely to change over a lifetime, the questionnaire aimed to obtain information over wide variety of ages and lifestyles, namely childhood, young adulthood and the recent past. All the patients' calcium intake was calculated according to their daily diet.

The urinary calcium levels were measured by the phosphomolibdic acid method. Urinary creatinine was measured as spectrophotometrically. The urinary hydroxyproline levels were measured spectrophotometrically using the method reported

Table 1. Features of Patients and the Control Group

	Patients	Control	*p*
Age (year)	49 ± 13	47 ± 8	N.S.
Sex (Female / Male)	15 / 9	15 / 7	N.S.
Etiology (Hepatitis B / Hepatitis C)	20 / 4		
Child classification (A / B / C)	10 / 10 / 4		

N.S.: not significant.

Table 2. Subdivisions of "The Mediterranean Osteoporosis (MEDOS) Study Questionnaire"

Subdivisions of the questionnaire
Interviewer, hospital and patient identification
Patient (control) identification
Sociodemographic data
Reproductive history and gynaecological status
Measurements: hieght, weight
Other findings: colour of skin, hair, and eye, mental score
Previous diseases and medical conditions at admission
Past fractures
Heredity
Other operations
Medication
Life style data
Condition during hospital stay
Circumstances around present hip fracture (case) or around fall (control)
Data on operation
Functional capacity
Evaluaton at time of discharge from hospital
General complication
In case of death

by Switzer B.R.[3] The serum parathyroid hormone, calcitonin, osteocalcin, free testosterone and 25-hydroxyvitamin D levels were measured by a radioimmunoassay. The luteinizing hormone, follicle-stimulating hormone, estradiol levels were measured by using the chemiluminescence assay method.

The bone mass density (BMD) of the first to fourth lumbar vertebrae was determined by a dual-energy X-ray absorptiometry diagnostic system. All the patients' plain radiographs of the dorsolumbar vertebrae were taken.

Statistical analysis was performed using a Student's t and X test. Correlation analysis was used to compare both the patients' and controls' biochemical parameters. A regression analysis method was used to evaluate the epidemiological data.

RESULTS

There were no individuals with compression fractures in either of the patients and control groups. The patients' BMD and T values were significantly lower than the control group (Table 3).

According to the WHO criteria,[4] T values between -1 and -2.5 were evaluated as osteopenia. Ten out of the 24 patients' T values were under -1. In the control group, 3 individuals were osteopenic ($p = 0.03$). If the T value was < -2.5, the bone fracture risk was considered to be quite. No patient in the control group had a T value < -2.5.

Table 3. Results of the Bone Mineral Density Measurements

	Patients	Control	*p*
BMD (g/cm^2)	0.675 ± 0.157	1.054 ± 0.126	0.045
T value	-0.8804 ± 1.373	-0.0095 ± 1.174	0.026
T percent	0.9088 ± 0.142	0.9942 ± 0.122	0.035

$p < 0.05$.

Table 4. Biochemical Findings

	Patients	Control	*p*
Calcium (mg/dl)	8.56 ± 0.58	9.81 ± 1.42	< 0.0001*
Calcium (corrected to albumin levels)	9.28 ± 0.77	9.81 ± 1.42	N.S.
Phosphate (mg/dl)	3.60 ± 0.53	4.08 ± 1.22	N.S.
Alkaline phosphatase (U/l)	86 ± 35	69 ± 22	0.05*
Albumin (g/dl)	2.48 ± 0.91	4.51 ± 0.44	<0.0001*
GGT (IU/l)	46 ± 42	23 ± 17	0.02*
AST (IU/l)	74 ± 53	20 ± 5	<0.0001*
ALT (IU/l)	57 ± 48	26 ± 12	0.005*
Bilirubin (mg/dl)	1.39 ± 0.99	0.48 ± 0.16	<0.0001*

*Significant, N.S.: not significant.

However, 4 patients in the study group had a T value < -2.5 ($p = 0.05$).

As hepatic dysfunction is classified according to Child's classification, 10 of the patients were Child A (compensated) and, 14 were Child B/C (decompensated). Nine patients with decompensated cirrhosis were osteopenic, while only one patient with compensated cirrhosis was osteopenic ($p = 0.007$). However, the BMD measures were not different significantly between the compensated and decompensated groups (0.985 ± 0.109 g/cm^2 and 0.945 ± 0.187 g/cm^2, respectively; $p > 0.05$).

The albumin levels of the patients were lower, and both the AST and bilirubin levels were higher than the control group. There were no significant differences in the other biochemical parameters and hormone levels between the two groups (Table 4, 5, and 6).

In assessing lifestyle factors, the control group consumed more coffee, smoked more cigarettes, ate more meat, and performed more physical activity than the patient group. Logistical regression analysis was used to evaluate the epidemiological data and the differences between the patient and control group for the osteopenia were found to be due to chronic liver disease ($p = 0.05$, predictive value=75.6%).

DISCUSSION

There are several studies which have reported that osteoporosis and skeletal fractures are more frequent among patients with chronic liver diseases.[5-7] However, regarding the BMD values, other authorities have reported no difference between patients with posthepatitic cirrhosis those without.[8] In this study, BMDs at the L1 - L4 vertebrae were significantly lower in patients with cirrhosis than the control group and there were more osteopenic individuals in the cirrhotic patients. In the control group, no patient had a very high fracture risk whereas four out of the 10 osteopenic patients with cirrhosis had T values < -2.5.

In the patients group, the alkaline phosphatase serum concentrations were higher than in the controls. The patient's serum gammaglutamyltransferase levels were also higher than in the controls'. As alkaline phosphatase originates from the liver such as gamma glutamyltransferase, it is possible that a high level of this enzyme is due

Table 5. Hormone Levels

	Patients	Control	*p*
Parathormone (pg/ml)	34 ± 20	34 ± 24	N.S.
Calcitonin (pg/ml)	3.69 ± 4.88	5.30 ± 5.88	N.S.
Osteocalcin (ng/ml)	3.69 ± 2.97	4.81 ± 3.11	N.S.
25-OH-D3 (ng/ml)	14.3 ± 7.9	18.7 ± 13.3	N.S.
Premenopausal women			
Estradiol (pg/ml)	37.67 ± 17.06	110.70 ± 114.47	N.S.
LH (IU/ml)	7.32 ± 6.84	8.38 ± 2.84	N.S.
FSH (IU/ml)	12.17 ± 4.25	19.73 ± 10.62	N.S.
Postmenopausal women			
Estradiol (pg/ml)	14.85 ± 12.14	12.85 ± 17.27	N.S.
LH (IU/ml)	14.79 ± 8.95	23.01 ± 8.04	N.S.
FSH (IU/ml)	89.62 ± 27.76	66.93 ± 41.35	N.S.
Free testosterone level of men (pg/ml)	18.23 ± 10.03	12.09 ± 6.42	N.S.

N.S, not significant.

Table 6. Oral Calcium Intake, Urinary Calcium, Phosphate and Hydroxyproline Excretions

	Patients	Control	*p*
Oral calcium intake (mg/day)	990 ± 420	898 ± 409	N.S.
Urinary calcium (mg/day)	132.49 ± 97.44	152.06 ± 82.02	N.S.
Urinary phosphate (mg/day)	640 ± 476	720 ± 200	N.S.
Urinary calcium/creatinin ratio	0.140 ± 0.10	0.132 ± 0.79	N.S.
Urinary hydroxyproline level (mmol/mol Cr)	21.88 ± 7.35	16.17 ± 12.54	N.S.

N.S, not significant.

to liver disease. There was no significant difference between the alkaline phosphatase levels in the patients who were osteopenic and who were not. These findings suggest that the osteoblastic activity was not lower in osteopenic patients.

The hydroxyproline excretion and urine calcium/creatinine ratios were not statistically different between the patients and the control group. This suggests that the bone turnover rates are similar. However, some authors reported that bone resorption was higher in chronic liver disease patients.[9]

The osteocalcin levels were lower in the patients than in the controls, but the difference was not statistically significant (Table 4). In some studies, it has been reported that the serum osteocalcin levels are higher in cirrhosis patients, which means that cirrhotic patients have high turnover osteoporosis.[10] However, some authors reported that the serum osteocalcin levels were lower in cirrhotic patients and the osteopenia in these patients was not due to a decrease in bone formation.[8,11]

In hepatocellular dysfunction, some authors reported that the serum parathyroid hormone levels were higher,[12] and others reported them as unchanged.[13] In some studies, it was shown that the calcitonin levels were higher.[14] In this study, there was no difference in the serum parathyroid hormone and calcitonin levels between the patients and controls. In addition, there was no correlation with the BMD values.

In our patients, hydroxyproline excretions were higher compared to the controls but the differences were not significant. There are conflicting results regarding hydroxyproline excretions.[5,13] No difference in the serum 25-hydroxyvitamin D levels were found between the patients and the controls. There was no correlation between the 25-hydroxyvitamin D levels with BMD values and the alkaline phosphatase enzyme levels.

In our patients, there was no correlation be-

tween the serum calcium, phosphorus, parathyroid hormone, 25-hydroxyvitamin D, osteocalcin levels and BMD values. These results are compatible with studies indicating that osteoporosis rather than osteomalacia cause the osteopenia in chronic liver disease.[5,13]

There was no difference in oral calcium intake and calcium excretion between the patients and controls, which means osteopenia is not related to calcium intake or excretion.

In chronic liver disease there is hypogonadism due to hepatocellular dysfunction.[15,16] The serum free testosterone and estradiol levels were not significantly different in the patients and controls.

In postmenopausal female patients, bone loss is more prominent than postmenopausal women in controls. In all 24 patients and 22 controls, there was a significant negative correlation between the BMD values and age, whereas only in patients or only in osteopenic patients has it been determined separately there was no correlation between the BMD values and age. This suggests that hepatocellular dysfunction increases bone loss in postmenopausal ages. In postmenopausal osteoporosis, the main pathophysiological process is a decrease in bone resorption.[17] In bone resorption some cytokines play a role such as interleukin 1 and interleukin 2.[18] These cytokines may increase bone resorption even though the serum parathyroid hormone and calcitonin levels were normal. This study suggests that chronic liver disease increases the risk of postmenopausal osteoporosis.

It is postulated that chronic liver disease and its complications might be responsible for activating some mediators.[18,19] It is further postulated that these mediators, such as some cytokines, might be the final common pathway leading to bone loss in parenchimal liver disorders.[20]

The results show that the patients with posthepatitic cirrhosis had osteopenia, and cirrhosis was a direct and independent risk factor.

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