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BRIEF ARTICLE

Hepatic osteodystrophy and liver cirrhosis

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Abstract

AIM: To investigate the correlation between hepatic osteodystrophy and osteoporosis in patients with liver cirrhosis.

METHODS: Bone mineral density of the patients (n = 55) and that of the control group (n = 30) were measured by dual-energy X-ray absorptiometry. All the women in the study were premenopausal. Deoxypyridinoline, pyridinoline and urinary Ca^{2+} were measured as bone destruction markers, while alkaline phosphatase (ALP), osteocalcin and insulin-like growth factor-1 (IGF-1) were measured as bone formation markers. Furthermore, interleukin-1 (IL-1), IL-6, tumor necrosis factor α (TNF-α), vitamin D3, direct bilirubin, albumin, cortisol and parathyroid hormone (PTH) levels were measured. The independent Student t test and χ^2 test were employed in comparing both groups, and the Pearson correlation test was used to determine associations.

RESULTS: Comparing cirrhosis and control groups, lumbar total T-score (-1.6 ± 1.2 g/cm^2 *vs* -0.25 ± 1.3 g/cm^2, P < 0.001), lumbar total Z-score (-1.2 ± 1.23 g/cm^2 *vs* -0.6 ± 1.3 g/cm^2, P < 0.001), total femur T-score (-0.05 ± 1 g/cm^2 *vs* -0.6 ± 0.9 g/cm^2, P = 0.003) and total femur Z-score (-0.08 ± 1.5 g/cm^2 *vs* 0.7 ± 0.9 g/cm^2, P = 0.003) showed significantly lower values in the cirrhosis group. Blood ALP level (109.2 ± 57 U/L *vs* 62.6 ± 32.5 U/L, P < 0.001), IL-6 level (27.9 ± 51.6 pg/mL *vs* 3.3 ± 3.1 pg/mL, P = 0.01), TNF-α level (42.6 ± 33.2 pg/mL *vs* 25.3 ± 12.3 pg/mL, P = 0.007) and direct bilirubin level (0.9 ± 0.7 mg/dL *vs* 0.3 ± 0.2 mg/dL, P < 0.001) were significantly higher in the cirrhosis group. IGF-1 level (47.7 ± 26.2 ng/mL *vs* 143.4 ± 53.2 ng/mL, P < 0.001), osteocalcin level (1.05 ± 2.5 ng/mL *vs* 7.0 ± 13 ng/mL, P = 0.002) and 24 h urinary Ca^{2+} (169.6 ± 227.2 mg/dL *vs* 287 ± 168.6 mg/dL, P = 0.003) were significantly lower in the cirrhosis group. Urinary deoxypyridinoline/creatinine (9.4 ± 9.9 pmol/μmol *vs* 8.1 ± 5.3 pmol/μmol, P = 0.51), urinary pyridinoline/creatinine (51.3 ± 66.6 pmol/μmol *vs* 29 ± 25.8 pmol/μmol, P = 0.08), blood IL-1 level (3.4 ± 8.8 pg/mL *vs* 1.6 ± 3.5 pg/mL, P = 0.29), vitamin D3 level (18.6 ± 13.3 μg/L *vs* 18.4 ± 8.9 μg/L, P = 0.95), cortisol level (11.1 ± 4.8 μg/dL *vs* 12.6 ± 4.3 μg/dL, P = 0.15) and PTH level (42.7 ± 38 μg/dL *vs* 34.8 ± 10.9 μg/dL, P = 0.27) were not significantly different.

CONCLUSION: Hepatic osteodystrophy is an important complication encountered in patients with liver cirrhosis and all patients should be monitored for hepatic osteodystrophy.

Key words: Liver cirrhosis; Osteoporosis; Hepatic osteodystrophy

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INTRODUCTION

Liver cirrhosis develops when the liver parenchyma takes a nodular form as a result of fibrosis arising from delayed wound-healing in chronic liver damage. Osteoporosis, characterized by a reduced bone mass and an increase in bone fracturability due to distortion of bone tissue microstructure, is a multifactorial disease and the most common bone disease. Dual energy X-ray absorptiometry is a method of measuring bone mineral density which has been become the standard in many centers and is a highly accurate X-ray method.

It is known that liver diseases may lead to bone disease[1]. Although chronic liver disease is associated with a broad spectrum of bone diseases, the most common type of hepatic osteodystrophy is osteoporosis. If an increase in bone resorption exceeds bone formation, or decreased bone formation is present together with normal bone destruction, then in advanced cases, bone mass will decrease and the risk of fracture will increase[2]. Increased cytokine levels in chronic liver disease and liver cirrhosis contribute to the development of hepatic osteodystrophy. Levels of interleukin-1 (IL-1), IL-6 and tumor necrosis factor α (TNF-α) are higher in patients with alcoholic hepatitis and liver cirrhosis than gender- and age-matched controls[3]. It is thought that a reduction in growth factors, such as insulin, or an excess of growth inhibitors such, as bilirubin, in patients with cirrhosis causes osteoblastic function disorder[4]. Low bone formation and a high resorption rate in chronic liver disease patients results in osteoporosis. It has been shown that serum osteocalcin decreases depending on reduction of osteoblast function. A decrease in serum osteocalcin levels and an increase in deoxypyridinoline (DPD) level can be explained by lower bone turnover[4-7].

Osteopenia is more frequent than osteomalacia in the primary biliary cirrhosis (PBC)-associated metabolic bone diseases in patients in North America[8]. Osteoclastic activity may be increased in premenopausal PBC women. In these people there is a disorder in the formation of new bone. Calcium and vitamin D metabolism is often normal in anicteric PBC patients[8]. Osteoporosis is a common complication of cholestatic liver disease. In primary sclerosing cholangitis (PSC), the cause of osteoporosis is multifactorial. The pathophysiological mechanism of osteoporosis has not been identified clearly yet[9,10].

The aim of this study was to establish the osteoporosis risk in liver cirrhosis, and to investigate the role of IL-1, IL-6, TNF-α, osteocalcin, insulin-like growth factor-1 (IGF-1), alkaline phosphatase (ALP), parathyroid hormone (PTH), cortisol and 25(OH)D3 in bone metabolism, and to investigate urinary DPD, pyridinoline and Ca^{2+} levels, which are biochemical markers of bone cycling.

MATERIALS AND METHODS

Our study comprised a cohort of 85 patients, 55 men and 30 premenopausal women (older than 18 years) with liver cirrhosis, and a control group (15 men and 15 women). The etiology was 37 hepatitis B, 10 cryptogenic, 2 PBC, 2 cardiac, 2 hepatitis C and 2 Wilson diseases in the patients with liver cirrhosis. The diagnosis of liver cirrhosis was done by biochemical and serological tests, abdominal ultrasonography, upper gastrointestinal endoscopy. Liver biopsy could not performed because of ascites. Twenty-four patients had Child-Pugh stage C (score 11.2), 17 patients had Child-Pugh stage B (score 7.9), 14 patients had Child-Pugh stage A (score 5.6) cirrhosis. Previous diseases, fracture anamnesis, smoking, using of alcohol or coffee were investigated in all cases included in the study. There was no history of diabetes mellitus, hypertension, goitre, early menopause, surgical menopause, hyperparathyroidism or Cushing's syndrome in any of the study subjects, and none. took any drug associated with increased risk of osteoporosis (anticoagulant, oral contraceptive, steroid, thiazide, diuretics, *etc.*).

Height, weight and body mass indexes (BMI) of all cases were calculated. Blood samples were analyzed in the laboratory department. Urea, creatinine, aspartate aminotransferase (AST), alanine aminotransferase (ALT), ALP, gamma glutamyl transpeptidase, Ca^{2+}, P^{+}, bilirubin and albumin levels were measured on an Abbott Aeroset device. Plasma cortisol, thyroid stimulating hormone, free T4, parathyroid hormone (PTH) and alpha-fetoprotein (AFP) levels were determined on a Modulator E 170 autoanalysator by electrochemiluminescence method. IGF-1 was measured on an Immulite 2000 autoanalyser, cytokines (IL-1, IL-6 and TNF-α) on an Immulite 1000 autoanalyser and vitamin D3 on an Agilent 1100 autoanalyser by HPLC.

Hydroxychloric acid was added to 24 h urine for determination of pyridinoline and DPD, markers of bone destruction, by HPLC. Calcium was also determined in 24 h urine. *Clearance* of creatinine was calculated as (24 h urine volume × urine creatinine)/(plasma creatinine × 1440). Bone mineral density measurements were conducted in the triangle of L1-L4 vertebrae and femoral neck, trochanteric major, intertrochanteric region. The results were calculated as g/cm^2. T and Z scores for all subjects were analyzed.

Statistical analysis

Statistical assessment was carried out by SPSS 13.0. The independent Student *t* test and χ^2 test were used for comparing the groups. The Pearson correlation test was used to determine associations.

RESULTS

Seventeen female and 38 male patients with liver cirrhosis and 15 female and 15 male controls were included in the study. There were no significant differences in BMI and gender between the patients and the controls. The mean age of the patients was significantly higher than in the control group (mean, 44.8 years *vs* 34.8 years, Table 1). All the women included in the study were premenopausal, and none took alcohol or coffee. There was no fracture anamnesis. T- and Z-scores were significantly lower in

the cirrhosis group than in controls when bone mineral densities were compared (Table 1). IL-6 and TNF-α were significantly higher in the liver cirrhosis group, but there was no significant difference in IL-1 (Table 1). ALP levels were significantly higher in the cirrhosis group, but IGF-1 and osteocalcin were significantly lower compared to the control group (Table 1). There were no significant differences in DPD/creatinine and pyridinoline/creatinine levels, nor in blood cortisol, PTH and vitamin D levels (Table 1). There were no significant differences in sedimentation rate, AFP and C-reactive protein levels. Prothrombin time and direct biluribin were significantly higher and albumin level significantly lower in the cirrhosis group (Table 1).

Table 1 Clinical features and laboratory test results of the liver cirrhosis and control groups

	Cirrhosis (n = 55)	Control (n = 30)	P-value
Lumbar total T-score (g/cm^2)	-1.6 ± 1.2	-0.25 ± 1.3	< 0.001
Lumbar total Z-score (g/cm^2)	-1.2 ± 1.2	-0.6 ± 1.3	< 0.001
Total femur T-score (g/cm^2)	-0.05 ± 1	0.6 ± 0.9	0.003
Total femur Z-score (g/cm^2)	-0.08 ± 1.5	0.7 ± 0.9	0.003
Age (yr)	44.8 ± 12.9	34.8 ± 8.2	< 0.001
BMI (kg/m^2)	25.5 ± 4.3	25.5 ± 3.7	0.970
IL-1 pg/mL	3.4 ± 8.8	1.6 ± 3.5	0.290
IL-6 pg/mL	27.9 ± 51.6	3.3 ± 3.1	0.010
TNF-α pg/mL	42.6 ± 33.2	25.3 ± 12.3	0.007
AFP (ng/mL)	2.6 ± 16.9	2.6 ± 1.1	0.100
Direct biluribin (mg/dL)	0.3 ± 0.2	0.9 ± 0.7	< 0.001
CRP (mg/L)	5.8 ± 5.9	5.4 ± 11.3	0.800
Osteocalcin (ng/mL)	1.05 ± 2.5	7.0 ± 13	0.002
IGF-1 (ng/mL)	47.7 ± 26.2	143.4 ± 53.2	< 0.001
ALP (IU/L)	109.2 ± 57	62.6 ± 32.5	< 0.001
24 h urinary Ca^{2+} (mg/dL)	169.6 ± 227.2	287 ± 168.6	0.003
Deoxypyridinoline/creatinine (pmol/μmol)	9.4 ± 9.9	8.1 ± 5.3	0.510
pyridinoline/creatinine (pmol/μmol)	51.3 ± 66.6	29 ± 25.8	0.080
Cortisol level μg/dL	11.1 ± 4.8	12.6 ± 4.3	0.150
PTH level μg/dL	42.7 ± 38	34.8 ± 10.9	0.270
Vit D3 level μg/L	18.6 ± 13.3	18.4 ± 8.9	0.950
Albumin (g/dL)	2.5 ± 0.5	4 ± 0.4	0.001
Prothrombin time (s)	17.1 ± 5.2	11.7 ± 1.7	< 0.001
Sedimentation rate (h)	18.8 ± 10.6	11.6 ± 9.6	0.030

BMI: Body mass index; IL: Interleukin; TNF: Tumor necrosis factor; AFP: α-fetoprotein; CRP: C-reactive protein; ALP: Alkaline phosphatase; IGF: Insulin-like growth factor.

DISCUSSION

Hepatic osteodystrophy is an important health problem encountered in patients with liver cirrhosis[1,2]. The reported prevalence of osteoporosis among patients with liver cirrhosis ranges from 20% to 50% depending on patient selection and diagnostic criteria, and the prevalence of fracture ranges from 5% to 20%[9]. In the present study, osteoporosis was found in 37% of patients in accordance with the literature. The fact that all the female patients were premenopausal allowed reliable examination of the effect of liver cirrhosis on osteoporosis. Diamond *et al*[5] found in their 2 separate studies that the prevalence of osteoporosis was 30%-48% in patients with chronic liver disease of different etiologies.

Hepatic osteodystrophy is defined as bone disease associated with chronic liver disease[5,6,11,12]. The mechanism of hepatic osteodystrophy encountered in liver cirrhosis patients has not been clearly determined. Osteoporosis has been reported in patients with cholestatic liver, chronic viral hepatitis, alcoholic liver, hemochromatosis and benign and malignant tumors of the liver[13]. In our study, the prevalence of osteoporosis was determined as 37% from the T-scores in lumbar vertebrae. Lumbar total BMD T-score and Z-score in patients with cirrhosis were significantly lower than those of the control group ($P = 0.003$).

IL-1, IL-6 and TNF-α cytokines are the cytokines most associated with postmenopausal osteoporosis[14]. These cytokines can affect bone metabolism through either increasing osteoclast formation or increasing osteoclast activity. In addition, the cytokines can block osteoblast function directly and increase formation of other cytokines[9]. IL-1, IL-6 and TNF-α levels were higher in patients with alcoholic hepatitis or liver cirrhosis compared to gender- and age-matched controls[13]. The incidence and severity of osteoporosis is increased in patients with chronic hepatitis or intestinal diseases. Inadequate nutrition, use of steroids, and cytokines have roles in this outcome. Pfeilschifter *et al*[15] concluded that these cytokines were strong resorptive agents. In the present study, IL-1, IL-6 and TNF-α levels were higher than those of the control group. It is thought that increased IL-6 and TNF-α levels were effective in promoting hepatic osteodystrophy in our patients with liver cirrhosis.

Menon *et al*[16] have shown that there is a positive correlation between serum bilirubin level and bone destruction ratio. In the present study, increased serum bilirubin levels in patients with osteoporosis concur with studies in the literature. Gillberg *et al*[17] have established that idiopathic osteoporosis exists together with a reduced IGF-1 level. It was thought that reducing growth factors, such as insulin, or increasing bilirubin in cirrhosis patients induces an osteoblastic function disorder[4]. In our study, we found significantly lower IGF-1 levels in the liver cirrhosis group ($P < 0.001$), and direct bilirubin levels were significantly higher ($P < 0.001$).

In recent studies it has been reported that there is no abnormality in Ca^{2+}, phosphorus and vitamin D metabolism in patients with PBS, which was unexpected[18]. However in some studies vitamin D was lower. In our study, in accordance with the literature, vitamin D levels were not higher than the healthy group suggesting that vitamin D metabolism was normal in the liver cirrhosis group.

In another study conducted by Karan *et al*[19], 24 patients with liver cirrhosis developing after hepatitis were compared with 22 healthy controls, and osteocalcin levels were non-significantly lower in the patient group. In the study of Capra *et al*[20], comprising 20 people with cirrhosis and 22 healthy controls, osteocalcin levels in the cirrhosis group were lower than in the control group,

whereas plasma calcitonin levels in the cirrhosis group were higher than in the control group[20].

In most studies, ALP levels in chronic liver patients were elevated, including the study of Karan *et al*[19]. It is necessary to measure enzyme function of osteoblasts (bone ALP) for diagnosis of osteoporosis. If liver-gallbladder disorders can be excluded, serum total ALP levels only can be used as an index of bone formation. In contrast, bone specific isoenzyme of ALP (BAP) is inside the osteoblast membrane and if osteoblast activation exists it is excreted into the circulation. Thus, measurement of BAP is more accurate and is affected less by non-bone pathologies.

Low bone formation and a high resorption ratio in chronic liver patients results in osteoporosis. It has been shown that serum osteocalcin decreases with reduction in osteoblast function. A reduction in serum osteocalcin and an increase in urine DPD can be explained by lower bone turnover[4-7]. Monegal *et al*[21] have established that serum osteocalcin in patients with PBC is low. They emphasized that this was associates with a reduction in bone formation. Guañabens *et al*[22] have found that the volume of bone decreases because of a reduction in bone formation in PBC.

Osteoclastic activity may be increased in premenopausal women with PBC. In these patients there is a disorder in formation of new bone. Calcium and vitamin D metabolism in anicteric patients with PBC is often normal[9]. Osteoporosis is a common complication of cholestatic liver disease. The causes of osteoporosis in PSC are multifactorial. The pathophysiological mechanism of osteoporosis has not been identified clearly yet[10].

In the present study, we investigated osteocalcin and ALP as measures of bone formation. Osteocalcin levels were lower than those of the control group ($P = 0.002$), whereas ALP levels were higher ($P < 0.001$). Lower osteocalcin levels exhibit lower osteoblastic activity. A higher ALP level, which is a bone formation marker, can be associated with cholestasis, while lower serum osteocalcin levels may be associated with a reduction in bone formation. Urine 24 h calcium levels in the liver cirrhosis patients were significantly reduced, and could be associated with inadequate nutrition in these patients, or might indicate that osteoclastic activity did not increase, or even decrease, to reduce bone formation.

PTH stimulates both bone resorption and bone formation, but it is known that if it remains at a high level, osteoclasts are stimulated, whereas osteoblasts are inhibited. Some authors have been reported that hepatocellular dysfunction increases serum PTH levels, while some authors reported no change or even a reduction[23]. In addition to the studies reporting that serum PTH levels in liver cirrhosis patients are higher than that of controls, there exists some studies indicating that the PTH level is lower[23]. In the present study, although there was an increase in PTH levels in the liver cirrhosis group, it was not statistically significant.

Urinary DPD/creatinine and pyridinoline/creatinine level were non-significantly increased in the cirrhosis patients. This finding suggests there may be more bone resorption than normal. Both insulin and IGF-1 have an influence on osteoblast function and contribute to bone formation. IGF-1 levels in the cirrhosis group were significantly lower in the study. This implied that IGF-1 reduction is an important factor in progression to hepatic osteodystrophy. There is an increase in the urinary hydroxyproline/creatinine ratio especially in advanced stages of liver cirrhosis[20]. The urinary deoxypyroline/creatinine ratio and serum bone ALP levels increase in osteoporosis developing from hepatitis C virus-associated liver cirrhosis[4]. Increased activity of the osteoprotegerin system can be associated with increased TNF-α and IL-6 levels[24,25].

In conclusion, metabolic bone diseases are important complications of chronic liver diseases. The bone mineral density of patients with liver cirrhosis is reduced. A decreased osteocalcin level in patients with liver cirrhosis means reduced bone formation, which, in turn, may contribute to development of osteoporosis. Increased TNF-α and IL-6 levels in patients with cirrhosis may contribute to the development of hepatic osteodystrophy. Decreased IGF-1 levels in patients with liver cirrhosis may contribute to the development of osteoporosis. Early scanning for osteoporosis in patients with liver cirrhosis will reduce the risk of morbidity and mortality. As advanced hepatic osteodystrophy is difficult to treat and adversely affects both the quality of life and the long-term prognosis of patients with chronic liver disease, special care is required in order to prevent the development of clinical bone disease in individuals with advanced hepatic disease.

COMMENTS

Background

Liver cirrhosis develops when the liver parenchyma takes a nodular form as a result of fibrosis arising from delayed wound-healing in chronic liver damage. Osteoporosis, characterized by a reduced bone mass and an increase in bone fracturability due to distortion of bone tissue microstructure, is a multifactorial disease and the most common bone disease. In North America, osteopenia is more frequent than osteomalacia in patients with metabolic bone diseases associated with primary biliary cirrhosis. In primary sclerosing cholangitis, the causes of osteoporosis are multifactorial. The pathophysiological mechanism of osteoporosis has not been identified clearly yet.

Research frontiers

Metabolic bone diseases are important complications of chronic liver diseases. Increased cytokine levels in chronic liver disease and in cirrhosis contributes to the development of hepatic osteodystrophy. This study compared bone mineral density and cytokines in patients with liver cirrhosis and controls.

Innovations and breakthroughs

Cytokines have a role in hepatic osteodystrophy. Screening and treatment of symptoms are very useful for patients with liver cirrhosis.

Applications

Early diagnosis of osteoporosis by scanning in patients with liver cirrhosis will reduce the risk of morbidity and mortality. Therefore life quality will be better in patients with liver cirrhosis.

Peer review

The manuscript investigated the correlation between hepatic osteodystrophy and osteoporosis by comparing 55 patients with liver cirrhosis and 30 healthy controls and there are several comments and suggestions. This is an interesting study as the pathogenesis of hepatic osteodystrophy has not been studied extensively.

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