Calcif Tissue Int (1997) 60:148–154

Calcified Tissue International

Osteoporosis and Bone Mineral Metabolism Disorders in Cirrhotic Patients Referred for Orthotopic Liver Transplantation

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Received: 7 March 1996 / Accepted: 24 June 1996

Abstract. The purpose of this study was to determine the prevalence of osteoporosis, to estimate the bone turnover and hormonal status, and to identify the factors associated with bone disease in patients with end-stage liver disease who were referred for orthotopic liver transplantation.

A prospective study was performed on 58 cirrhotic patients (6 with primary biliary cirrhosis, 14 with alcoholic cirrhosis, and 38 with posthepatitic cirrhosis), who were referred for orthotopic liver transplantation. Patients, excluding those with primary biliary cirrhosis, were classified in Child-Pugh groups according to the severity of liver disease (class B [28 patients], class C [24 patients]). Biochemical parameters of bone mineral metabolism and standard liver function tests were measured in all patients. Additionally, serum osteocalcin, urinary hydroxyproline/creatinine ratio, serum intact parathyroid hormone, serum 25-hydroxyvitamin D, serum 1,25-dihydroxyvitamin D, follicle-stimulating hormone, and luteinizing hormone levels were determined in patients and controls within the same age range. Plasma testosterone, sex hormone-binding globulin levels, and free testosterone index were obtained for all men included in the study.

Bone mass of the lumbar spine and femur were measured by dual X-ray absorptiometry (DPX-L), and were expressed as a standard deviation of mean values (*Z*-score) from a sex and age-matched control group. Spinal X-rays were obtained to assess vertebral fractures. Osteoporosis was considered as a factor in spinal bone mineral density with a *Z*-score below 2 or at least one vertebral fracture.

Twenty-five patients (43%) had osteoporosis, with lower bone mass measurements in the lumbar spine than in the femoral neck ($P < 0.005$). Alcoholic and Child-Pugh C patients showed the lowest femoral bone mineral density values. Cirrhotic patients showed lower osteocalcin levels than controls (14.3 ± 5.9 vs. 18.2 ± 8.1 ng/ml; $P < 0.05$) and showed increased urinary hydroxyproline (125.1 ± 51.5 vs. 107.9 ± 26.6 nM/mg creatinine; $P < 0.05$). Serum 25-hydroxyvitamin D, 1,25-dihydroxyvitamin D and parathyroid hormone levels were significantly lower in cirrhotic patients than in controls (10.3 ± 9.1 vs. 23.1 ± 26.6 ng/ml; $P = 0.000$), (12.9 ± 9.1 vs. 48.3 ± 11.5 pg/ml; $P = 0.000$), (16.6 ± 9.2 vs. 27.9 ± 8.2 pg/ml; $P = 0.000$), with no differences between Child-Pugh groups. Alcoholic Child-Pugh C patients showed the lowest 25-hydroxyvitamin D serum values (4.5 ± 2.2 ng/ml; $P < 0.05$). Male patients had lower testosterone levels than controls (302.5 ± 229.4 vs. 556.7 ± 146.5 ng/dl; $P = 0.000$), with increased sex hormone-binding globulin values. Levels of testosterone and gonadotropin were related to Child-Pugh classification. No correlation was found between bone mass and hormonal values.

A significant decrease in bone mass, particularly in the lumbar spine, is seen in end-stage cirrhotic patients. Reduced bone formation and significant disorders of bone mineral metabolism, such as vitamin D deficiency, reduced parathyroid hormone levels, and hypogonadism are involved. Moreover, severity and etiology of the liver disease are the main risk factors for developing bone loss and mineral metabolism disorders in patients referred for orthotopic liver transplantation.

Key Words: Cirrhosis — Osteoporosis — Hypoparathyroidism — Hypogonadism.

Liver transplantation has become the treatment of choice for patients with life-threatening liver disease. However, the posttransplantation period may be complicated by the development of osteoporotic fractures, which cause great morbidity. Available data indicate that the prevalence of skeletal fractures after liver transplant ranges from 17% to 65% [1–7]. As the number of patients undergoing liver transplantation will increase in the future, it is necessary to assess and to prevent the main risk factors for developing such a complication. Few studies have addressed this problem. However, pretransplant bone disease has been identified as one of the factors in the development of osteoporosis and fractures in the postoperative phase [3, 4]. It is known that patients with chronic liver disease suffer metabolic bone disease, mainly osteoporosis. Although much attention has been focused on primary biliary cirrhosis, other liver diseases have also been recognized as important causes predisposing bone disease [8–14].

In order to clarify the metabolic bone disorders in patients with end-stage liver disease, this study was aimed at determining the prevalence of osteoporosis, estimating the

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bone turnover, and identifying the major risk factors associated with osteodystrophy.

Patients and Methods

Patients

The study was performed on 58 caucasian patients with chronic advanced liver disease (male/female 39/19; mean age ± SD: 50 ± 7.6 years, range 32–60 years), during assessment for orthotopic liver transplantation (OLT), between January 1992 and December 1993. Six patients had primary biliary cirrhosis, 14 had alcoholic cirrhosis, 35 had posthepatitic HCV cirrhosis, and three had posthepatitic HBV cirrhosis. The existence of cirrhosis was established by histological examination of the liver in all the patients. All patients, excluding those with primary biliary cirrhosis, were classified according to the Child-Pugh score [15] as follows: class B (28 patients), class C (24 patients).

All patients studied were accepted in the transplant program and survived until the operation. Patients who had previously received drugs, which may have influenced bone metabolism (corticosteroid, calcitonin, oestrogen, bisphosphonate, or sodium fluoride) were excluded from the study. Three patients with serum creatinine levels greater than 1.3 mg/dl (normal upper range) were excluded from the analysis of biochemical markers of bone turnover and hormonal determinations.

None of the patients had a previous history of thyroid or parathyroid disease. All patients with primary biliary cirrhosis were taking 1000 to 1500 mg of calcium per day, and two low doses of vitamin D per os (266 μg of 25-hydroxyvitamin D weekly). Seven patients were receiving spironolactone and thirty-four were receiving spironolactone and furosemide.

Biochemical and Hormonal Determinations

After an overnight fast, a sample of venous blood was taken from all patients for measurement of biochemical parameters. In addition to standard liver function tests, serum levels of calcium, phosphate, magnesium, alkaline phosphatase, and creatinine were measured by standard procedures.

Serum osteocalcin was measured in all patients and in 29 healthy control subjects by immunoradiometric methods (CIS Elsa-Osteo, Gif-sur-Yvette, France). Serum intact parathyroid hormone was measured by immunoradiometric assay (Allegro Intact PTH, Nichols Institute Diagnosis, San Juan de Capistrano, CA) in all patients and in 31 controls who were within the same age range. Serum 25-hydroxyvitamin D was determined in all patients and in 40 healthy controls, who were within the same age range, by a competitive protein-binding assay (Nichols Institute Diagnosis, San Juan de Capistrano, CA); serum 1,25-dihydroxyvitamin D was measured by a radioreceptor assay (Nichols Institute Diagnosis, San Juan de Capistrano, CA) in 29 patients and in 42 healthy controls of similar ages. Vitamin D metabolites were obtained from patients and controls in the same season.

Plasma testosterone and sex hormone-binding globulin levels were determined in the 39 men included in the study and in 36 healthy males who were within the same age range. Testosterone levels were analyzed by RIA (Bio-Merieux, France) and sex hormone-binding globulin was measured by immunoradiometric methods (Orion Diagnostica, Finland). The free testosterone index was obtained by dividing the plasma testosterone value by the plasma sex hormone-binding globulin level in each male patient or control and multiplying by 100 [16].

Follicle-stimulating hormone and luteinizing hormone levels were measured in 57 healthy controls (18 male and 39 female) and in 36 patients (17 male and 19 female) who were within the same age range, by immunoradiometric methods (Immunotech, Marselle, France).

A two-hour fasting urine sample was obtained the same day between 8 and 10 AM in 47 patients and in 51 controls. Urinary hydroxyproline was measured by high performance liquid chromatography and was expressed as a hydroxyproline/creatinine ratio. Urine creatinine determination was performed in the Cobas Mira S analyzer using an assay based on a modified Jaffé method.

Bone Mineral Density and X-ray Measurements

Bone mineral density of the lumbar spine (L_2–L_4) and femur was measured by dual X-ray absorptiometry using a bone mineral analyzer DPX-L (Lunar Radiation Corporation, Madison, WI) and was expressed as g/cm^2. The in vitro and in vivo coefficients of variation for the lumbar spine were 0.5% and 0.8%, respectively, and for the proximal femur (neck, Ward's triangle, and trochanter) the coefficients were 2.1%, 1.2%, and 1.2% in vitro and 2.3%, 1.4%, and 1.2% in vivo, respectively. The lumbar and femoral bone mineral density data were compared to those seen in 832 healthy control subjects (308 male/524 female) from the same geographical area and were expressed as a standard deviation of mean values from a sex- and age-matched control group (*Z*-score).

Standard X-rays of the thoracic and lumbar spine were obtained in all patients to disclose vertebral fractures. The evaluation was performed by an independent observer who was unaware of the patients' clinical conditions. Vertebral fracture was defined as a reduction of 20% or more in the anterior, middle, or posterior height as compared with the adjacent, undeformed vertebral body. Fractures attributable to major trauma were not recorded.

Osteoporosis was considered a value for lumbar bone mineral density two standard deviations or more below the mean obtained in the sex- and age-matched control group (<2 *Z*-score), or by the presence of at least one atraumatic vertebral fracture.

Statistical Analysis

Results were expressed as means ± SD (standard deviation of the mean). The statistical significance between means was calculated by Student's *t* test, analysis of variance (ANOVA), or Mann-Whitney U test when appropriate. Differences between proportions were assessed by the chi-square test and correlations were calculated by multiple regression analysis. Values of $P < 0.05$ were considered significant.

The study was approved by the Ethical Committee of the Hospital Clínic i Provincial and the patients provided informed consent for the procedures.

Results

Clinical and Biochemical Analysis

Clinical and biochemical data of patients included in the study according to the etiology of liver disease are shown in Table 1. Alcoholic cirrhotics were significantly younger and had significantly higher bilirubin levels and a lower prothrombin ratio than posthepatitic cirrhotics. Cirrhotic patients showed serum calcium levels in the lowest range but these levels rose to normal when calcium levels were corrected by serum albumin values. However, both groups of patients distributed similarly between B and C groups of the Child-Pugh classification. In addition, Child-Pugh C patients showed significantly lower magnesium levels than Child-Pugh B patients (1.7 ± 0.2 vs. 1.9 ± 0.2 mg/dl; $P = 0.14$). Primary biliary cirrhosis patients showed an analytical picture of cholestasis.

Biochemical Markers of Bone Turnover

Cirrhotic patients showed significantly lower mean osteocalcin levels (14.3 ± 5.9 vs. 18.2 ± 8.1 ng/ml; $P < 0.05$) and

Table 1. Clinical and biochemical data

	Posthepatitic cirrhosis	Alcoholic cirrhosis	Primary biliary cirrhosis
Number	38	14	6
Age (years)	52.4 ± 5.9	43.4 ± 7.6[a]	50.5 ± 6.8
Sex (M/F)	26/12	13/1	0/6
Menopausal status	12/12	1/1	3/6
Child-Pugh score			
Class B	22	6	—
Class C	16	8	—
Alkaline phosphatase (IU/L)	258 ± 95.6	300.8 ± 86.9	1133 ± 439[c]
Bilirubin (mg/dl)	2.9 ± 1.6	6.3 ± 4.7[b]	12.5 ± 7.1[c]
Aspartate aminotransferase (IU/L)	107.6 ± 49.4	63.2 ± 27.1[b]	134.3 ± 47.8
Alanine aminotransferase (IU/L)	76 ± 43.5	42.8 ± 26[b]	120.8 ± 42.7[c]
Prothrombin index (%)	56.2 ± 13.5	41.9 ± 17[b]	88.3 ± 13.5[d]
Serum calcium (mg/dl)	8.4 ± 0.6	8.5 ± 0.6	9 ± 0.8[c]
Serum phosphate (mg/dl)	3.5 ± 0.6	3.5 ± 0.6	4 ± 0.4[c]
Serum magnesium (mg/dl)	1.9 ± 0.2	1.8 ± 0.4	1.9 ± 0.1
Serum creatinine (mg/dl)	0.8 ± 0.3	0.7 ± 0.2	0.5 ± 0.3[c]

Data are expressed as means ± SD.
P values for differences between posthepatitic and alcoholic cirrhosis, [a]$P = 0.000$, [b]$P < 0.05$
P values for differences between women with posthepatitic cirrhosis and primary biliary cirrhosis, [c]$P < 0.05$, [d]$P = 0.000$

showed increased urinary hydroxyproline/creatinine ratio than controls (125.1 ± 51.5 vs. 107.9 ± 26.6 nM/mg creatinine; $P < 0.05$). There were no significant differences between alcoholic and posthepatitic cirrhotics in these two parameters. Child-Pugh C but not Child-Pugh B patients showed significantly lower osteocalcin serum levels (12.8 ± 5.9 ng/ml; $P < 0.05$) and increased hydroxyproline excretion (140.3 ± 45.3 nM/mg creatinine; $P = 0.000$) than controls. Primary biliary cirrhosis patients had higher hydroxyproline excretion than controls (180.7 ± 63.9 vs. 107.9 ± 26.5 nM/mg creatinine; $P = 0.000$) with no significant differences in osteocalcin levels.

Hormonal Analysis

Serum 25-hydroxyvitamin D and 1,25-dihydroxyvitamin D levels were significantly lower in cirrhotic patients in comparison with controls (10.3 ± 9.1 vs. 23.1 ± 8.8 ng/ml; $P = 0.000$ and 12.9 ± 9.1 vs. 48.3 ± 11.5 pg/ml; $P = 0.000$) (Fig. 1). In fact, serum 25-hydroxyvitamin D levels were below normal values in 37 patients (64%) and serum 1,25-dihydroxyvitamin D in 18 out of 29 patients (62%). As shown in Figure 1, there were no significant differences in 25-hydroxyvitamin D levels between cirrhotics from Child-Pugh B and C groups. Only alcoholic cirrhotic Child-Pugh C patients had significantly lower 25-hydroxyvitamin D levels (4.5 ± 2.2; $P < 0.05$). Finally, 25-hydroxyvitamin D levels were clearly lower in primary biliary cirrhosis patients with respect to the control group (9.7 ± 3.1 vs. 23.1 ± 8.8 ng/ml; $P < 0.01$). No significant correlation was found between 25-hydroxyvitamin D and serum albumin levels.

Parathyroid hormone circulating levels were significantly lower in cirrhotics patients than in controls (Fig. 2), being below the reference values in 25 out of 58 (43%) cirrhotic patients. There were no significant differences in parathyroid hormone levels between alcoholic and posthepatitic cirrhotics or between Child-Pugh B and C cirrhotic patients. Parathyroid hormone levels in primary biliary cirrhosis patients ranged within the reference values. No significant correlation was found between parathyroid hormone levels and serum magnesium values, nor between parathyroid hormone levels and 25-hydroxyvitamin D or 1,25-dihydroxyvitamin D levels.

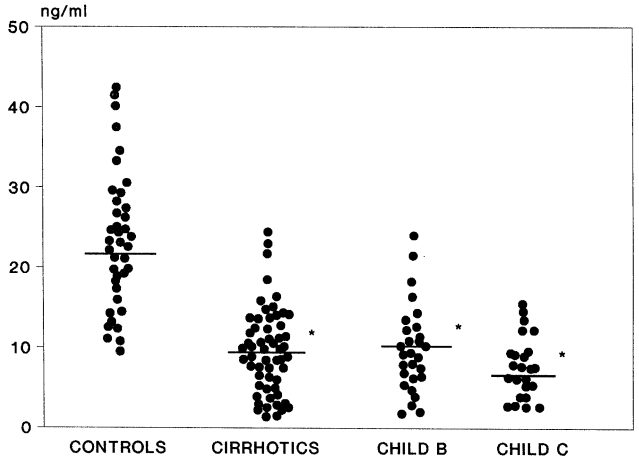

Fig. 1. Serum 25-Hydroxyvitamin D levels in controls, in cirrhotic patients, and in Child-Pugh B and C cirrhotic patients. *P* value for differences between patients and controls, $*P = 0.000$.

Whereas total testosterone levels were significantly reduced in cirrhotic patients in comparison with controls (Fig. 3), sex hormone-binding globulin was significantly increased, thus resulting in a marked reduction in the free testosterone index in cirrhotic patients (10.4 ± 6.4 in cirrhotics vs. 79.1 ± 25.9% in controls; $P = 0.000$) (Fig. 3). In fact, 23 of 39 (59%) male patients showed reduced testosterone levels. Total testosterone levels were significantly lower in Child-Pugh C than in Child-Pugh B patients, without significant differences between alcoholic and posthepatitic cirrhotics. Serum levels of follicle-stimulating hormone and luteinizing hormone were significantly higher in

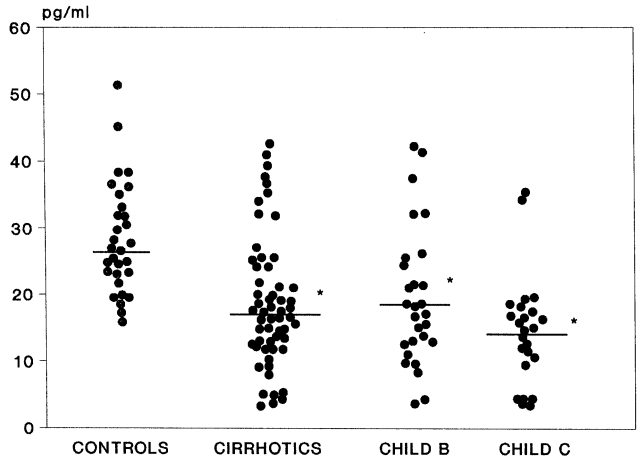

Fig. 2. Serum intact parathyroid hormone levels in controls, in cirrhotic patients, and in Child-Pugh B and C cirrhotic patients. *P* value for differences between patients and controls, $*P = 0.000$.

Child-Pugh B cirrhotic patients than in controls (Table 2). Among postmenopausal women, Child-Pugh C patients showed significantly lower levels of follicle-stimulating hormone and luteinizing hormone than controls and Child-Pugh B patients (Table 2).

Bone Mineral Density and Fractures

Twenty-five patients (43%) had osteoporosis; 12 patients by densitometric criteria, 10 by radiological criteria, and three by both criteria. Fifteen patients showed lumbar bone mineral density below 2 Z-score but only five patients had femoral bone mineral density with a 2 Z-score below ($P < 0.05$).

The clinical and biochemical data were similar in patients with and without osteoporosis. For all hormonal parameters, including vitamin D metabolites, parathyroid hormone levels, and testosterone values, no differences were found between both groups. Moreover 13 of the men with osteoporosis were hypogonadal, but also 10 men without osteoporosis showed low testosterone levels. There were no differences in the etiology of the liver disease or in the Child-Pugh score between osteoporotic and nonosteoporotic groups. However, Child-Pugh C patients showed significantly lower femoral bone mineral density values than Child-Pugh B patients (Fig. 4). In addition, alcoholic patients had significantly lower bone mineral density of the femoral neck (Z-score -0.7 ± 1.3 vs. $+0.04 \pm 0.9$ SD; $P < 0.05$), trochanter (Z-score -0.4 ± 1.2 vs. $+0.5 \pm 1.1$ SD; $P < 0.05$), and Ward's triangle (Z-score -1.1 ± 1.3 vs. -0.1 ± 1.1 SD; $P < 0.05$) than patients with posthepatitic cirrhosis. No correlation was found between bone mass and the biochemical markers of bone turnover or hormonal values.

Discussion

The current study shows that patients with end-stage liver disease, referred for orthotopic liver transplantation, have a high prevalence of osteoporosis, with the lumbar spine being the most intensely affected site. Furthermore, the subgroup of patients with the most severe hepatic dysfunction have the most reduced femoral bone mass. In addition, significant disorders of mineral metabolism, such as vitamin D deficiency, reduced serum parathyroid hormone levels, and hypogonadism, were frequently observed.

A high proportion of patients exhibited reduced bone mineral density in the lumbar spine indicative of osteoporosis. Our data support the findings of other series that described low bone mass in cirrhotic patients [2, 3, 8–10]. Moreover, the current study provides additional data concerning the femoral bone mass in these patients. Lumbar bone mineral density was more affected than femoral bone mineral density. However, femoral bone mineral density values were related to the Child-Pugh score. In addition, when bone mineral density data were analyzed according to the etiology of liver disease, alcoholic patients showed lower femoral bone mineral density values than the other cirrhotic patients. Our results support the finding that end-stage liver disease and chronic alcohol consumption may exert simultaneous damaging effects in cortical bone, without excluding the possibility that hypogonadism may also have an impact [12, 17].

Contradictory results have been reported with respect to the bone turnover state in chronic liver disease. However, most data indicate that decreased bone formation contributes to bone loss [8, 18]. The low levels of osteocalcin, a biochemical marker of bone formation, found in our patients suggest impaired osteoblastic activity in end-stage liver cirrhosis. Moreover, in the present series osteocalcin levels were also related to the severity of liver disease, since the most severely affected patients had the lowest osteocalcin values. This observation suggested a progressive decline in osteoblastic function associated with the progression of liver disease. On the other hand, urinary hydroxyproline values were increased in our patients, especially in the most severely affected, which suggested increased bone resorption. However, it should be noted that urinary hydroxyproline is not a specific indicator of bone resorption since it may be elevated in other processes with increased collagenolysis, such as liver cirrhosis [19]. Therefore, we can not assume that there was increased bone resorption in patients from the present study since no other markers of bone resorption were determined.

In the present report, severe abnormalities in the regulation of mineral metabolism, including low vitamin D and parathyroid hormone levels and a marked hypogonadism, were found in cirrhotic patients. Although there are some conflicting results [2, 3, 9, 12, 20, 21], the present study clearly shows that in end-stage cirrhotic patients, particularly alcoholics, serum 25-hydroxyvitamin D is below normal values. The absence of bone biopsy in these patients does not definitely exclude alternative bone diseases such as osteomalacia. Decreased circulating levels of vitamin D binding protein, as a cause for low vitamin D levels in our patients, seems unlikely, since in the present series there was no relationship between vitamin D and albumin levels [21]. However, other causes of vitamin D deficiency, such as decreased sunlight exposure, reduced dietary intake, intestinal malabsorption, or decreased liver hydroxylase activity, should be considered in the group of end-stage cirrhotic patients [11, 22–24].

Another interesting finding was the low parathyroid hormone levels found in this group of cirrhotic patients. The cause of low parathyroid hormone values in the current study remains uncertain. Although the cause of low values could be attributed to the low magnesium levels observed in some of the patients [25–27], we did not find a correlation

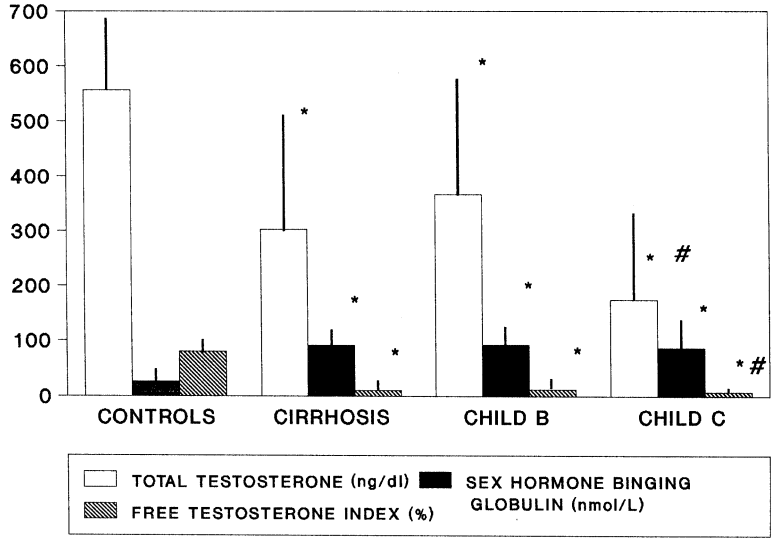

Fig. 3. Plasma testosterone, sex hormone-binding globulin levels, and free testosterone index in controls, in cirrhotic patients, and in Child-Pugh B and C cirrhotic patients. Data are shown as mean and SD. *P* value for differences between patients and controls, $^{*}P = 0.000$; *P* value for differences between Child-Pugh groups, $^{\#}P < 0.01$.

Table 2. Serum gonadotropin levels

	Controls	Cirrhotics	Child B	Child C
N				
Men	18	17	10	7
Women	39	19	6	7
FSH (IU/L)				
Men	3.7 ± 1.6	5.7 ± 4.3	5.7 ± 3.1[a]	5.7 ± 5.9
Women	53.1 ± 22.1	23.2 ± 24.2[b]	51.3 ± 20.2	9.9 ± 12[b,c]
LH (IU/L)				
Men	2.7 ± 1.6	4.7 ± 2.6[a]	5.4 ± 2.8[a]	3.6 ± 2.2
Women	27.9 ± 8.9	14.1 ± 13.8[b]	27.4 ± 11.7	4.7 ± 6.6[b,c]

Data are expressed as means ± SD
[a]$P < 0.05$ vs. control group, [b]$P < 0.000$ vs. control group, [c]$P < 0.01$ between Child-Pugh groups
FSH follicle-stimulating hormone, LH = luteinizing hormone

between both parameters. However, it is known that intracellular magnesium values are better indicator levels than serum values [28]. Therefore, this hypothesis suggesting a low parathyroid hormone secretion induced by hypomagnesemia cannot be totally excluded. On the other hand, the low parathyroid hormone levels may also be indicative of a dysfunction in the up-regulation of mineral metabolism in these patients, particularly in end-stage liver failure, since increased regulatory values of parathyroid hormone would be expected to accompany subnormal vitamin D metabolites. But we still must consider the possibility of an alternative explanation. The role of low parathyroid hormone levels in the development of osteoporosis in these patients is unknown and should be clarified through further study.

Hypogonadism was found in a high proportion of patients, with more than half of the male patients showing decreased testosterone values. In addition, testosterone levels were related to liver failure; the most severely affected patients had the lowest testosterone values. Hypogonadism is a common disorder among cirrhotic patients [29–31] and some studies have shown a relationship between hypogonadism and osteoporosis in these patients [32, 33]. Hypogonadism in these patients was probably caused by the combined effects of both a central (hypothalamus–pituitary) and a gonadal failure, which is in agreement with other studies [30, 31]. Decreased plasma testosterone values and the lack of consistent gonadotropin suppression in less severely affected patients (Child-Pugh B), is compatible with gonadal failure. However, in the most severely affected patients (Child-Pugh C), a central dysfunction may also be possible, as suggested by inappropriately low levels of gonadotropin [33, 34]. A relationship was not found between the presence of osteoporosis and hormonal disturbances in these series, probably because of the high prevalence of both processes.

In conclusion, patients with end-stage liver cirrhosis have reduced bone mass and therefore have increased risk for developing bone fractures. Although low vitamin D levels and hypogonadism are highly prevalent in these patients, the severity and etiology of the liver disease are the main risk factor for developing bone loss and bone mineral metabolism disorders, without excluding the possibility of osteomalacia. Our results suggest that correcting vitamin D deficiency and hormonal disorders, prior to liver transplantation, may be of benefit in the treatment of coexistent bone disease.

Acknowledgments. We are grateful to Javier Fernandez for his technical assistance. The study was supported by a research grant from the Fondo de Investigación Sanitaria FISS 92/0341.

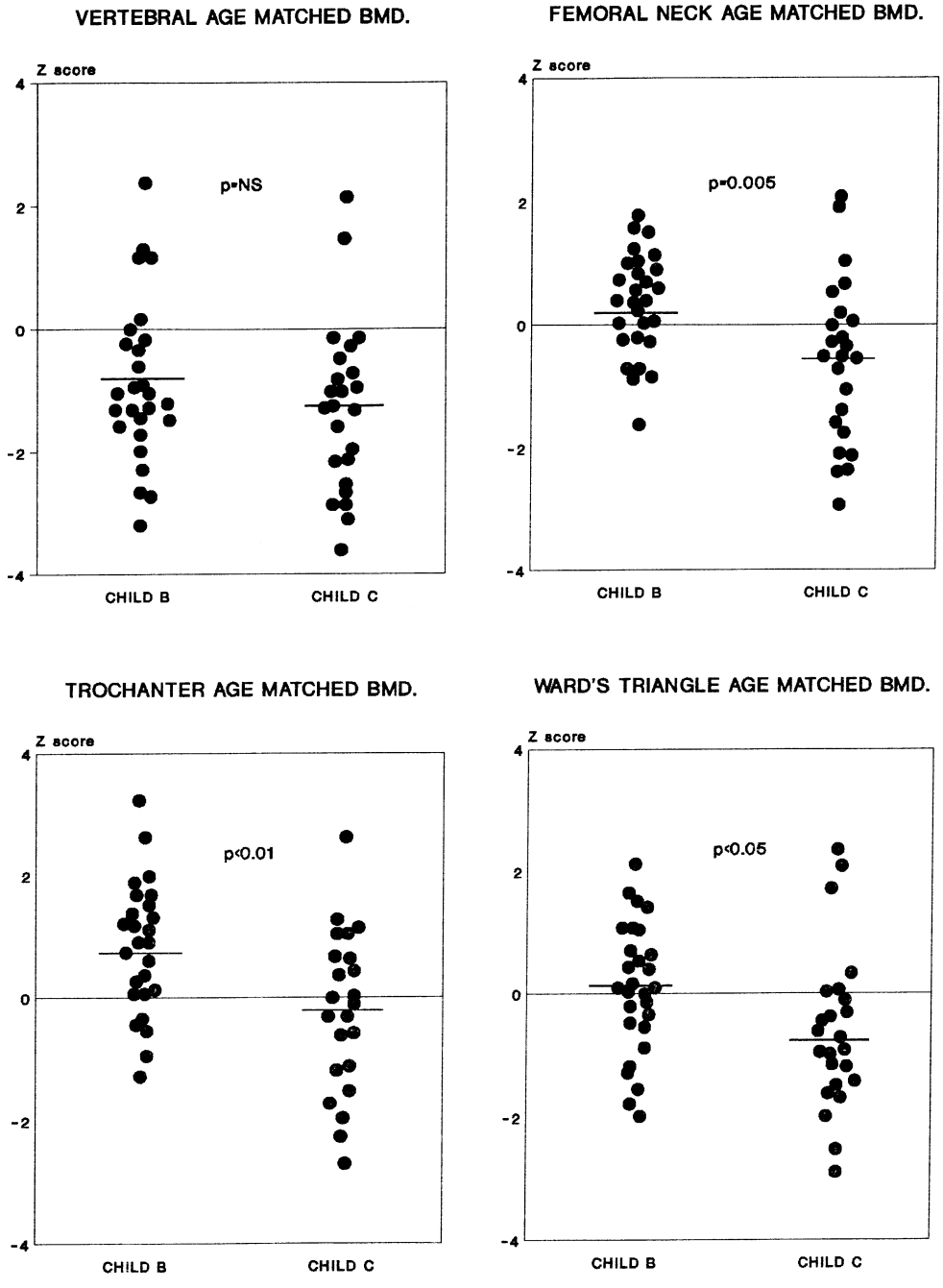

Fig. 4. Bone mineral density of the lumbar spine and proximal femur in Child-Pugh B and C cirrhotic patients.

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