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Bone Mineral Density and Bone Turnover Markers in Chronic Liver Disease

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Aim of this study to detect the effect of chronic liver diseases on bone mineral density and bone turnover markers. Sixty two patients with chronic hepatitis C viral (HCV) infection were included in the study. They were 37 males and 25 females, their ages ranged from 27 to 68 years. They were divided into two groups. The first group consisted of 37 patients with chronic hepatitis (22 males and 15 females, age range: 27-59 years) and the second group consisted of 25 patients with liver cirrhosis (16 males and 9 females, age range: 34-68 years). Thirty three healthy subjects age and sex matched with the patients were taken as control group. For all patients and controls Bone Mineral Density (BMD) g cm^{-2} of the lumbar spines and the left proximal femur were measured by dual energy X-ray absorptiometry (DEXA) and serum levels of osteocalcin, C- terminal propeptide of type I collagen (CICP), osteoprotegrin (OPG) and soluble receptor activator of nuclear factor (sRANKL) NF-KB ligand and urinary deoxypyridinoline (DPD) were assessed. The results showed that BMD at the proximal femur was normal among 35.1% of patients with chronic hepatitis, 36% of patients with liver cirhosis and 51.5% of controls with insignificant difference. Osteopenia was present among 43.2% of patients with chronic hepatitis, 32% of patients with liver cirrhosis and 39.4% of controls with insignificant difference. Osteoporosis was significantly more prevalent among patients with liver cirrhosis (323%) compared to controls (9.1%) p = 0.04. BMD of the lumbar spine was normal among 45.9% of patients with chronic hepatitis, 48% of patients with liver cirrhosis and 72.7% of normal control with insignificant difference. Osteopenia was present among 45.9% of patients with chronic hepatitis, 36% of patients with liver cirrhosis and 24.2% of controls with significant difference between chronic hepatitis and controls (p = 0.02). Osteoporosis was present among 8.1% of patients with chronic hepatitis, 16% of patients with liver cirrhosis and 3% of controls with insignificant difference. There was no significant difference as regard mean values of osteocalcin and CICP between chronic hepatitis (7.6±13.1 and 171.9±136.3, respectively), cirrhosis (7.3±3.7 and 246.5±160.2, respectively) and controls (3.4±3 and 224.2±122.1, respectively). Mean values of OPG were significantly higher in cirrhosis (8.9±9.1) compared to controls (4.9±3.9) (p = 0.03). As regard markers of bone resorption, there was no significant difference between the three groups. Mean urinary DPD levels among chronic hepatitis, cirrhosis and controls were: 40.3±29.8, 42.2±26.7 and 65.7±49.6, respectively. Serum levels of sRANKL among chronic hepatitis, cirrhosis and controls were: 0.5±0.5, 0.6±0.7 and 0.4±0.3, respectively. When we classify all patients and controls according to BMD of proximal femur and lumbar spine, into three groups: normal, osteopenia and osteoporosis, we did not found any significant difference as regard bone turnover markers between the three groups. When we do the same classsification for the patients with chronic hepatitis and cirrhosis each separately, we found that in patients with cirrhosis, mean CICP levels were significantly lower among patients with osteopenia of proximal femur (172±108.1) compared to patients with normal BMD (351.6±131.8) (p = 0.05). BMD is decreased in chronic liver disease, with the proximal femur most commonly affected and patients with liver cirrhosis are at higher risk than patients with chronic hepatitis.

Key words: Hepatitis C. virus, osteoporosis, osteoprotegrin, RANKLE

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INTRODUCTION

An important complication of chronic liver disease is osteodystrophy which includes osteoporosis and the much rarer osteomalacia. Both conditions are associated with significant morbidity through fractures resulting in pain, deformity and immobility. There is also a further significant increase in the risk of fractures following liver transplantation for end stage chronic liver disease (Eastell *et al*., 1998).

The mechanism of liver disease-associated bone mass loss is not fully understood but several factors are likely to contribute. Diminished bone formation has been suggested to be the main factor responsible for osteoporosis in alcoholic subjects with and without liver cirrhosis, but there are few published data on patients with viral cirrhosis without a history of alcohol consumption (Gonzalez-Calvin *et al*., 2004).

Bone loss occurs as a result of increased bone turnover and/or remodeling imbalance. The latter may be due to reduced formation or increased resorption or a combination of the two. Some studies have shown increased bone resorption, even in the absence of osteoporosis, in the presence of chronic liver disease whereas most others have shown decreased bone formation (Crosbie *et al*., 1999; Gallego-Rojo *et al*., 1998). Histologically, hepatic osteodystrophy is similar to postmenopausal and aging-related bone loss in that trabecular (cancellous) bone is more rapidly and severely affected than cortical bone (Collier *et al*., 2002). The etiology of hepatic osteodystrophy remains undefined. Potential inciting factors that either directly or indirectly alter bone mass include insulin growth factor-1 (IGF-1) deficiency, hyperbilirubinemia, hypogonadism (estrogen and testosterone deficiency), alcoholism, excess tissue iron deposition, subnormal vitamin D levels, vitamin D receptor genotype and osteprotegrin (OPG) deficiency (Collier *et al*., 2002).

Osteoporosis is a histologic diagnosis; however, clinical recognition relies on noninvasive imaging studies such as bone mineral density (BMD) measurements using dual X-ray absorptiometry (DEXA) and radiography, which enable an assessment of bone mass and fracture risk. Prospective studies have shown that the risk of fracture increases progressively with decreasing BMD, the risk of fracture increasing two to three fold for each standard deviation decrease in BMD (Marshall *et al*., 1996).

There is marked heterogeneity in BMD findings in chronic liver disease, ranging from no effect to a large BMD deficit. This controversial findings may contribute to different population studied and different etiologies of chronic liver diseases (Bernstein *et al*., 2003). Biochemical markers of bone metabolism have been shown to correlate with bone metabolism changes occurring during physiologic and pathologic stages of human development: accelerated growth and mineralization during puberty, menopause and a number of metabolic bone diseases (Simonet *et al*., 1997; Christenson *et al*., 1997).

The aim of this study is to detect the effect of chronic liver diseases on bone mineral density and bone turnover markers.

MATERIALS AND METHODS

The present study was conducted at the Medical Services Unit of the National Research Centre. Sixty two patients with chronic hepatitis C viral (HCV) infection selected from internal medicine and hepatology outpatient clinic participated in the study. They were 37 males and 25 females, their ages ranged from 27 to 68 years (mean: 47.4±8.5) They were divided into two groups. The first group consisted of 37 patients with chronic hepatitis (22 males and 15 females, age range: 27-59 years) and the second group consisted of 25 patients with liver cirrhosis (16 males and 9 females, age range: 34-68 years). Fifteen patients had past history of bilharziasis documented by history and bilharzial antibody in the serum = 1/32. HCV was diagnosed by positive hepatitis C virus antibody detected by third generation test (ELISA), with elevated transaminases level more than twice the upper limit of normal for more than 6 months duration. Liver cirrhosis was diagnosed clinically (ascites, lower limb oedema, hepatic encephalopathy), laboratory (serum bilirubin, albumin, prothrombin time) and by ultrasonographic findings (shrunken liver and/or portal hypertension and/or ascites). Patients with endocrine, cardiac, respiratory, rheumatic diseases or serum creatinine concentration greater than 2 mg dL^{-1} were excluded from the study. None of the patients had received calcium, vitamin D, corticosteroids or any medications related to bone mineral metabolism. Thirty three healthy subjects age and sex matched with the patients were taken as control group. All patients and controls were subjected to full history taking including history of alcohol or drug abuse, past history of schistosomiasis or exposure to canal water and thorough clinical examination by an internist and hepatologist including height and body weight assessment and Body Mass Index (BMI) was calculated by dividing body weight in kilograms per height in square meters. Laboratory investigations in the form of complete blood count, fasting blood sugar, ALT, AST, serum bilirubin and albumin and prothrombin time

and concentration and bilharzial antibody were also done. Abdominal ultrasound was done for all patients.

For all patients and controls Bone Mineral Density (BMD) g cm^{-2} of the lumbar spine and the left proximal femur (if unaffected by disease, otherwise the right proximal femur) was measured by dual energy X-ray absorptiometry (DEXA) with the use of Norland XR 46. The mean BMD value of the second, third and fourth lumbar vertebrae (lumbar spine BMD) and of the femoral neck of the proximal femur (femoral neck BMD) were used in the present analysis. T score >-1 was considered normal, T score between -1 and -2.5 was considered osteospenia and T score =-2.5 was considered osteoporosis (5). Serum levels of osteocalcin, C- terminal propeptide of type I collagen (CICP), osteoprotegrin (OPG)and soluble receptor activator of nuclear factor (sRANKL) NF-KB ligand and urinary deoxypyridinoline (DPD) were assessed for all patients and controls.

The study was approved by the ethical committee of the National Research Center and all patients gave written informed consent.

Laboratory methods: A 10 mL of fasted venous blood samples were taken from each subject in the study, the serum was separated by centrifugation and stored at -20°C for determination of osteocalcin, C-Terminal propeptide of type I collagen (CICP), osteoprotegrin (OPG)and soluble receptor activator of nuclear factor (sRANKL) NF-KB ligand. Random urine sample were taken also from each subject in the study and stored at -20°C for determination of deoxypyridinoline (DPD). A quantitative assay by enzyme linked immunosorbent assay (ELISA) using a solid phase amplified sensitivity immunoassay were used for the determination of the following parameters: Osteocalcin (Power and Fottrell, 1991)and the kit was supplied from BioSource Europe (Rue I`Industrie8, B-1400 Nivelles, Belgium), CICP (Sagges *et al*., 1992) and DPD (Eastell et, 1997) and their kits were supplied from METRA (Quidel corporation world wide headquarters 10165 Mc Kellar Court, San Diego, CA 92121 USA). The kit of OPG (Lipton *et al*., 2002) was supplied from Immunodiagnostik, Benshein And Biomedical, Wein and that of sRANKL (Hofbauer and Heufelder, 2001) was supplied from Biomedical Medizinprodukte Gmb H And Co K G, A -1210 Weinand Divischgasse.

Statistical method: Data was presented by means±SD and percentages. The compiled data were computerized and analyzed by EPI Info version 6.2 produced through the collaboration between CDC/WHO and by SPSS PC+, version 7.5. The following tests of significance were used: Analysis of variance (ANOVA) test between more than two means, t-test between means was used to analyze mean difference, Z test between percentages to analyze percent difference. Chi-Square test (X^2) was used to study the pattern of distribution of different variables.. A level of significance with $p \leq 0.05$ or ≤ 0.01 was considered significant, $p \leq 0.001$ was considered highly significant and $p > 0.05$ was considered insignificant.

RESULTS

Bone mineral density of HCV patients and control group: The results showed that there was no significant difference in the percentage of subjects with normal BMD or osteopenia of the proximal femur between chronic hepatitis, liver cirrhosis and normal control. Osteoporosis was significantly more prevalent among patients with liver cirrhosis (32%) compared to controls (9.1%), (p = 0.04). (Table 1).

As regard BMD of the lumbar spines, there was no significant difference in the percentage of subjects with normal BMD between chronic hepatitis, cirrhosis and controls. Osteopenia was present among 45.9% of patients with chronic hepatitis, 36% of patients with liver cirrhosis and 24.2% of controls with significant difference between chronic hepatitis and controls (p = 0.02.) Percentage of patients with osteoporosis was higher than controls but the difference was insignificant (Table 2).

Biochemical markers of bone turnover: Results of bone forming markers revealed there was no significant difference in the mean values of osteocalcin and CICP between chronic hepatitis, cirrhosis and controls. Mean values of OPG were higher among cirrhotics compared to controls (8.9±9.1 and 4.9±3.9, respectively) (p = 0.03). As regard markers of bone resorption (DPD and sRAMKL) there was no significant difference between the three groups (Table 3).

Biochemical markers of bone turnover and BMD: According to BMD of proximal femur and lumbar spine, we classify all patients and controls into three groups: normal, osteopenia and osteoporosis.

We found that osteoporosis of the proximal femur was more common among male than female (p = 0.002).

As regard biochemical markers of bone turnover there was no significant difference between the three groups (Table 4).

We classify the group of patients with chronic hepatitis and liver cirrhosis each separately according to BMD into: normal, osteopenia and osteoporosis and we did not found any significant differences as regard biochemical markers of bone turnover between the three

Table 1: BMD of proximal femur in patients with chronic hepatitis, cirrhosis and in normal control

T score of proximal femur (gm cm^{-2})	Chronic hepatitis (n = 37)	Cirrhosis (n = 25)	Controls (n = 33)	p-value
Normal (T>-1), n (%)	13 (35.1%)	9 (36%)	17 (51.5%)	NS
Osteopenia (T-1 to >-2.5), n (%)	16 (43.2%)	8 (32%)	13 (39.4%)	NS
Osteoporosis (T = 2.5),n (%)	8 (21.6%)	8 (32%)*	3 (9.1%)	0.04

*p is significant compared to control, NS: Non Significant

Table 2: BMD of lumbar spine in patients with chronic hepatitis, cirrhosis and in normal control

T score of lumbar spine (g m cm^{-2})	Chronic hepatitis (n = 37)	Cirrhosis (n = 25)	Controls (n = 33)	p-value
Normal (T>-1), n (%)	17 (45.9%)	12 (48%)	24 (72.7%)	NS
Osteopenia (T-1 to >-2.5), n (%)	17 (45.9%)*	9 (36%)	8 (24.2%)	0.02
Osteoporosis (T = 2.5), n (%)	3 (8.1%)	4 (16%)	1(3.1%)	NS

*P is significant compared to control NS: non significant

Tale 3: Biochemical markers of bone turnover in patients with chronic hepatitis, cirrhosis and in normal control

Biochemical markers of bone turnover (mean±SD)	Chronic hepatitis (n = 37)	Cirrhosis (n = 25)	Controls (n = 33)	p-value
Osteocalcin (ng mL^{-1})	7.6±13.1	7.3±3.7	3.4±3	NS
CICP (ng mL^{-1})	171.9±136.3	246.5±160.2	224.2±122.1	NS
Osteoprotegrin (pmol L^{-1})	5.7±3.9	8.9±9.1*	4.9±3.9	0.04
DPD (nmol mL^{-1})	40.3±29.8	42.2±26.7	65.7±49.6	NS
sRANKL (pmol L^{-1})	0.5±0.5	0.6±0.7	0.4±0.3	NS

*p is significant compared to control, NS: Non Significant, CICP: C-terminal propeptide of type 1 collagen. DPD: Deoxypiridinoline, sRANKL: Soluble receptor activator of nuclear factor kappa ligand

Table 4: Difference in biochemical markers of bone turnover between normal BMD, osteopenia and osteoporosis of proximal femur and lumbar spines of all patients and controls

Biochemical markers of bone turnover (mean±SD)		Normal BMD	Osteopenia	Osteoporosis	p-value
Osteocalcin (ng mL^{-1})	PF	6.7±12.7	5.7±3.6	6.6±4.4	NS
	LS	6.4±11.1	5.8±3.8	7.4±3.1	NS
CICP (ng mL^{-1})	PF	237.5±162.2	180.5±130.7	195.5±127.5	NS
	LS	238.9±151.7	176.1±138.9	132.9±48.3	NS
Osteoprotegrin (pmol L^{-1})	PF	7.9±8	5.3±4.5	5.2±3	NS
	LS	7±7.2	5.8±4.6	5.1±2.4	NS
DPD (nmol mL^{-1})	PF	43.5±46.4	57.2±32.2	35.1±25.6	NS
	LS	50.8±44	44.1±28.4	37.9±29.9	NS
sRANKL (pmol L^{-1})	PF	0.4±0.3	0.4±0.3	0.7±0.9	NS
	LS	0.5±0.4	0.4±0.3	0.9±1.4	NS

NS: Non Significant, CICP: C-terminal propeptide of type 1 collagen. DPD: Deoxypiridinoline, sRANKL: soluble receptor activator of nuclear factor kappa ligand, PF: Proximal femur LS: Lumbar spines

Table 5: Difference in biochemical markers of bone turnover between normal BMD, osteopenia and osteoporosis of proximal femur and lumbar spines in chronic hepatitis patients

Biochemical markers of bone turnover (mean±SD)		Normal BMD	Osteopenia	Osteoporosis	p-value
Osteocalcin (ng mL^{-1})	PF	10±22.1	6.7±4.1	6.2±3.9	NS
	LS	9.4±18.7	6.2±3.5	6±1.6	NS
CICP (ng mL^{-1})	PF	208.7±187.5	125.4±92.1	182.1±78.9	NS
	LS	224.1±164	110.1±75	154±52	NS
Osteoprotegrin (pmol L^{-1})	PF	7.92±4.7	4.3±3	6.2±3.4	NS
	LS	6.9±4.6	4±2.5	7.3±0.7	NS
DPD (nmol mL^{-1})	PF	34.4±26.3	51.4±32.3	19±12.3	NS
	LS	50.8±44	44.1±28.4	37.9±29.9	NS
sRANKL (pmol L^{-1})	PF	0.5±0.3	0.5±0.4	0.7±0.4	NS
	LS	0.6±0.4	0.4±0.3	0.3±0.2	NS

NS: Non Significant, CICP: C-terminal propeptide of type 1 collagen. DPD: Deoxypiridinoline, sRANKL: soluble receptor activator of nuclear factor kappa ligand, PF: Proximal femur LS: Lumbar spines

Table 6: Difference in biochemical markers of bone turnover between normal BMD, osteopenia and osteoporosis of proximal femur and lumbar spines in cirrhotics

Biochemical markers of bone turnover (mean±SD)		Normal BMD	Osteopenia	Osteoporosis	p-value
Osteocalcin (ng mL^{-1})	PF	6.8±3.5	6±3	8.6±4.3	NS
	LS	6.5±3.5	7.3±4.4	9.2±2.5	NS
CICP (ng mL^{-1})	PF	351.6±131.8	172±108.1*	188±169.5	0.05
	LS	295.2±129.9	261.8±197.4	106.4±34.2	NS
Osteoprotegrin (pmol L^{-1})	PF	14.2±13	5.7±3.4	5.7±3.1	NS
	LS	11±12.4	8.8±6.5	4.5±2.6	NS
DPD (nmol mL^{-1})	PF	25±17.3	56±29.3	44.2±27.5	NS
	LS	41.5±32.5	36.6±20.3	50.2±29.7	NS
sRANKL (pmol L^{-1})	PF	0.4±0.3	0.4±0.4	0.9±1.2	NS
	LS	0.5±0.4	0.5±0.4	1.2±1.7	NS

*p is significant compared to normal BMD, NS: Non Significant, CICP: C-terminal propeptide of type 1 collagen. DPD: Deoxypiridinoline, sRANKL: soluble receptor activator of nuclear factor kappa ligand, PF: Proximal femur LS: Lumbar spines

groups of chronic hepatitis patients (Table 5). In patients with cirrhosis, we found that mean CICP levels were significantly lower among patients with osteopenia of proximal femur (172±108.1) compared to patients with normal BMD (351.6±131.8), (p = 0.05) (Table 6).

DISCUSSION

Osteoporosis results from an abnormality in the remodeling process of bone in which bone resorption exceeds bone formation leading to a net loss of bone. Bone mineralization remains intact. Bone remodeling is normally characterized by the balanced coupling of osteoblast and osteoclast function. Even after growth has stopped, skeletal remodeling continues (Teitelbaum, 2002). This dynamic process involves resorption of bone on one bone surface and deposition of newly formed bone on the opposing surface. It is influenced by weight bearing and gravity, as well as by problems such as systemic disease. The cellular events are carried out by specific bone cells and are modulated by systemic and local hormones and peptides. These bone cells include osteoblasts, osteocytes and osteoclasts (Hay *et al*., 1991).

The reported prevalence of osteoporosis among patients with chronic liver disease ranges from 20 to 100%, depending on patient selection and diagnostic criteria. The pathogenesis is unclear and likely is multifactorial. Regardless of the etiology of bone disease in these patients, they have an increased incidence of bone pain and fractures. Present study revealed that osteoporosis of proximal femur is more common among cirrhotics than chronic hepatitis patients and controls and no statistically significant difference as regard osteoporosis of lumbar spines between the three groups. Osteoporosis is the predominant component of hepatic osteodystrophy and is present in 20-50% of patients with chronic liver disease, based on BMD measurements (Canalis *et al*., 1991), which is in agreement with our study. In the current study, it was found that osteoporosis of proximal femur was more prevalent than that of lumbar spines. However previous study reported that osteoporosis in patients with hepatic disease affects mainly trabecular bone and has been characterized by low bone turnover with reduced osteoblast function and low serum osteocalcin levels (Diamond-Hodgson *et al*., 1985). Ormarsdottir *et al*. (1999) reported higher prevalence of osteoporosis in female subjects with chronic liver disease than male subjects and suggested that female sex is one of the most important factors determining the outcomes in their study, on the other hand we found that osteoporosis of proximal femur was more common among male than female, which did not agree with results of previous studies. Many cases of osteoporosis in men are due to age-related bone loss, but at least half of the cases are due to some secondary cause including chronic liver diseases.

Ormarsdottir *et al*. (1999) in their study, found increased urinary excretion of DPD in patients with chronic liver diseases compared with the control, whereas serum osteocalcin levels were similar between the groups. These results suggest that the bone loss in patients with chronic liver disease is not due to the diminished bone synthesis but due to the increased bone resorption in these patients. In agreement with their finding, Crosbie *et al*. (1999) also found increased urinary excretion of DPD and normal serum osteocalcin levels in their subjects but in the present study, it was found that CICP was significantly decreased in cases of femur osteoporosis among cirrhotics and this finding indicates that the osteoporosis in chronic liver disease was not only due to increase bone resorption but it was also due to decrease bone formation.

Receptor activator of NF-kappaB (RANK) is a receptor that is present on the surface of osteoclast precursor cells. RANKL is expressed on the surface of osteoblast cells and binds to (is a ligand for) RANK. Binding of RANKL to RANK leads to the differentiation and maturation of the osteoclast precursor cells to mature osteoclast cells. This binding results in a cascade of events, which includes the activation of Nuclear Factor Kappa B (NF-Kappa B), hence its name. The absence of NF-Kappa B leads to the bone disease osteopetrosis (Roubenoff, 2003). OPG is made by osteoblasts (as well as a number of other cell types) and blocks both osteoclast formation and bone resorption. It also binds to RANKL (Receptor for Activation of Nuclear Factor Kappa B Ligand). When OPG binds to RANKL it prevents it from binding to RANK, resulting in the inhibition of osteoclast formation (Takayanagi *et al*., 2002). Factors other than gonadal hormones, vitamin D and vitamin D receptor genotypes likely play a role in the development of high turnover bone disease in patients with hepatic osteodystrophy. OPG, a member of the tumor necrosis factor receptor superfamily, has recently been found to regulate bone turnover. Produced by the liver, OPG inhibits osteoclast differentiation in vitro and in vivo. In a transgenic mice model, increased hepatic expression of OPG resulted in osteopetrosis, or increased bone density (Teitelbaum, 2000). In this study, it was found that the highest mean value of OPG was present among cirrhotics which mean that in our patients osteoporosis was mainly due to decreased bone synthesis rather than increased bone resorption and the high OPG level may be a compensatory mechanism to increase synthesis of resorbed bone.

Audi *et al.* (2002) in their study found no correlation between BMD and any individual hormonal or biochemical bone metabolism markers, which indicates that none of these parameters could predict bone mineralization status. This finding partially agree with that of the current study as most of the biochemical markers did not differ between normal BMD, ostoepenia and osteoporosis and this may limit the use of these markers in diagnosis of osteoporosis but they are useful for understanding the pathogenesis of osteoporosis. Biochemical markers can indicate bone activity but not absolute bone mass. Also bone mass varies from site to site, but biochemical markers reflect total activity (Caulfield, 1995). Collier *et al.* (2002) concluded that these serum bone markers may prove useful in assessing response to treatment in the future. However, as the levels are affected by the extent of hepatic fibrosis and none of these markers has been studied in patients with chronic liver disease, they cannot yet be recommended as a means of assessing bone loss and the risk of fracture in cirrhotic patients. Bone markers are more useful in directing and following therapy. Subgroups of osteoporotics can have excessive bone resorption or reduced bone formation. Those with excessive resorption will have elevated levels of bone turnover markers and in this group antiresorptive therapy (such as oestrogens, bisphosphonates or calcitonin) may be of use. Those with reduced bone formation will have low levels of bone turnover markers and in this group bone formation stimulating agents (such as anabolic steroids) may be useful (Price and Thompson, 1995). Once therapy has been instituted bone markers are very useful in monitoring response.

CONCLUSION

BMD is decreased in chronic liver disease, with the proximal femur most commonly affected and patients with liver cirrhosis are at higher risk than patients with chronic hepatitis. Further and large-scaled studies should be performed to reveal the exact mechanisms that underlie the etiology of osteoporosis with chronic liver disease. Subsequently, treatment strategies should be improved.

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