J Bone Miner Metab (2008) 26:379–384
DOI 10.1007/s00774-007-0833-1

ORIGINAL ARTICLE

Aziza Mounach · Zhor Ouzzif · Ghizlane Wariaghli
Lahsen Achemlal · Imane Benbaghdadi · Aziz Aouragh
Ahmed Bezza · Abdellah El Maghraoui

Primary biliary cirrhosis and osteoporosis: a case-control study

Received: May 12, 2007 / Accepted: December 2, 2007

Abstract Osteoporosis is a common complication of chronic liver disease, from cholestatic disorders to autoimmune, alcoholic, and posthepatitic cirrhosis. Osteoporosis appears more striking in patients with primary biliary cirrhosis (PBC) because the disease usually affects elderly women, who are naturally prone to osteoporosis. Our aims were (1) to compare the prevalence of osteoporosis (T-score <–2.5 SD) between PBC patients and a group of age- and sex-matched controls consisting of healthy subjects from the general population; and (2) to identify the main risk factors for the development of bone loss. Thirty-three women with PBC (mean age, 47.3 ± 10.4 years) and 66 healthy subjects were enrolled in the study. Bone mineral density (BMD) was assessed at the lumbar spine by dual-photon X-ray absorptiometry. Bone metabolism was evaluated by measuring serum calcium corrected for serum albumin, 25-hydroxyvitamin D (25-OH vit D), parathyroid hormone, and osteocalcin. Vertebral fractures were analyzed using vertebral fracture assessment (VFA). The mean T-score was lower in the PBC group compared to healthy controls, with a significant statistical difference (–2.39 ± 0.93 and –1.47 ± 0.99 in lumbar spine and total hip, respectively, in the PBC group versus –0.99 ± 0.51 and –0.56 ± 1.14 in healthy controls ($P < 0.001$). The prevalence of osteoporosis was 51.5% in the PBC group versus 22.7% in healthy controls with a statistically significant difference ($P = 0.004$). BMD of the PBC group was significantly correlated positively with body mass index (BMI) and 25-OH vit D, and negatively with menopausal status, duration of disease, and parathyroid hormone (PTH) levels. Vertebral fractures were present in 9% of the patients. We found that osteoporosis is more prevalent in women with PBC than in the general population. BMI, menopausal status, duration of the disease, and vitamin D deficiency are the main risk factors for osteoporosis in this liver disease.

Key words primary biliary cirrhosis · bone mineral density · osteoporosis

A. Mounach (✉) · G. Wariaghli · L. Achemlal · A. Bezza · A. El Maghraoui
Rheumatology and Physical Rehabilitation Department, Military Hospital Mohammed V, PO Box: 1018, Rabat, Morocco
Tel. +212-3771-4419; Fax +212-3771-7032
e-mail: azizamounach@yahoo.fr

Z. Ouzzif
Biochemistry Department, Military Hospital Mohammed V, Rabat, Morocco

I. Benbaghdadi
Gastroenterology Department, Ibn Sina Hospital, Rabat, Morocco

A. Aouragh
Gastroenterology Department, Military Hospital Mohammed V, Rabat, Morocco

Introduction

Primary biliary cirrhosis (PBC) is a presumed autoimmune disease of the liver, which predominantly affects women over the age of 20 years. It affects women nine times more often than men. Metabolic bone disease is a well-known complication of PBC. The etiology of this disorder is complex and multifactorial. The clinical spectrum of the PBC is very broad, ranging from asymptomatic patients to end-stage cirrhotic patients awaiting organ transplantation. Recently, it has become common to diagnose PBC in postmenopausal women with minor cholestasis. It has been suggested that untreated women with PBC lose bone mass at a rate approximately twice that seen in age-matched controls [1]. In contrast to what was believed earlier, histomorphometric studies have shown unequivocally that osteoporosis is the major disorder [2,3], which can result in spontaneous or low-trauma fracturing that significantly impacts morbidity, quality of life, and even survival. Overall, the reported mean prevalence of osteoporosis and vertebral fractures in most series is around 35% [4,5] and 3%–20%, respectively [6]. Disagreements concerning the abnormalities of bone remodeling and turnover that result in bone loss have emerged. Thus, an increased bone turnover has been found in some patients with PBC, and the rate of bone turnover increased as hepatic disease and cholestasis worsened [7]. Conversely, it has been suggested that levels of

bone turnover in PBC may potentially be decreased by the effects of bilirubin or other substances that result from cholestasis [8,9]. Other factors, such as a genetic contribution to bone mass of several gene polymorphisms, have been involved [10,11].

The aims of the present study were, therefore, (1) to compare the prevalence of osteoporosis between PBC patients and a group of age and sex-matched controls consisting of healthy subjects from the general population; and (2) to identify the main risk factors for osteoporosis in patients with PBC.

Patients and methods

Patients

Thirty-three women (mean age, 47.3 ± 10.4 years) with PBC and 66 healthy females were included in this study. All subjects were asymptomatic for bone loss. Diagnosis of liver disease was achieved in two gastroenterology departments by biochemical, serological, and histopathological investigations. None of the patients had received any of the medications related to bone mineral metabolism, such as calcium, estrogen, hormone replacement therapy, vitamin D, corticosteroid, calcitonin, or bisphosphonates. Body weight and height were measured. Body mass index (BMI) was calculated as the weight (kg) divided by height (m^2). Patients and controls gave their informed consent to participation in the study.

Bone mineral density measurements

The bone mineral density (BMD) of the lumbar spine, total hip, and femoral neck was measured using dual-energy X-ray absorptiometry (Lunar Prodigy, General Electric, Madison, WI, USA) in all patients and controls. The phantom precision expressed as the coefficient of variation percentage was 0.08. Moreover, reproducibility has been assessed recently in clinical practice and showed a smallest detectable difference of 0.04 and 0.02 g/cm^2 for the spine and hips, respectively [12,13]. Osteopenia and osteoporosis were diagnosed in accordance with the World Health Organization criteria. Briefly, osteoporosis was defined as a BMD < 2.5 SD or more below the young adult mean value (T-score <–2.5) and osteopenia when the T-score was between –1 and –2.5. We used a Moroccan data reference curve to measure T-scores [14,15].

Clinical data and liver function

Age, duration of liver disease, menopausal status, histological stage, and severity of liver disease were assessed. The following measurements were performed to assess the severity of cholestasis and liver damage: serum concentration of bilirubin, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, and albumin, as well as the prothrombin index. The histological stage was recorded according to Ludwig's criteria [16].

Biochemical tests

Morning blood and urine samples were drawn after an overnight fast. Phosphate and total and ionized calcium were measured with an automatic technique. Serum 25 hydroxyvitamin D (25-OH vit D) was determined by radioimmunoassay (RIA) using a commercial kit (Diasorin, Stillwater, MN, USA). Serum osteocalcin, crosslaps (C-telopeptide, CTX), and parathyroid hormone (PTH) were measured in patients using electrochemiluminescence on an ELECSYS 2010 analyser (Roche Diagnostics, Mannheim, Germany).

Fracture assessment

Vertebral morphometry (vertebral fracture assessment) was used to identify vertebral fractures, defined as a reduction of 20% or more in the anterior, middle, or posterior height of the vertebral body.

Controls

The control group consisted of 66 young females extracted from the healthy general population (data used in the study of the Moroccan DXA reference database) [15]. The controls were age matched to the patients.

Statistical analysis

Analyses were performed with the Statistical Package for the Social Sciences (SPSS 13.0). All results were expressed as the mean ± SD. Student's *t* test for unpaired data and chi-square test were used, as appropriate. A P value ≤0.05 was considered significant. Correlation studies were performed with the Spearman test (nonnormal distribution).

Results

Clinical characteristics, bone mineral density values (g/cm^2), and T-scores of the PBC group and controls are illustrated in Table 1. All the patients with PBC and controls were females. The mean BMI of patients was significantly lower than controls ($P = 0.008$). Sixteen patients and 32 matched controls were menopausal at a mean age of 47.9 (5.2) and 47.4 (5.5) years, respectively. The mean BMD ($P < 0.001$) and T-score values ($P < 0.001$) of PBC patients were significantly lower at the lumbar spine, total hip, and femur neck than in controls. The prevalence of osteoporosis in PBC patients at the lumbar spine and or the total hip was 51.5% versus 22.7% in healthy controls ($P = 0.004$). The prevalence of osteoporosis and osteopenia according to the sites of measure of BMD is shown in Fig. 1. Figure 2 represents the prevalence of osteoporosis in different ages. Table 2

Table 1. Clinical and densitometric data of patients with primary biliary cirrhosis (PBC) and controls

	Patients with PBC $n = 33$	Controls $n = 66$	P
Age (years): mean ± SD	47.3 ± 10.4	47.3 ± 10.4	NS
Female sex: *n* (%)	33 (100)	66 (100)	NS
Weight (kg): mean ± SD	63.5 ± 12.9	66.8 ± 13.6	0.01
Height (m): mean ± SD	1.58 ± 0.1	1.58 ± 0.2	NS
Body mass index (kg/m^2): mean ± SD	25.4 ± 5.1	28.1 ± 4.7	0.015
Menopausal females: *n* (%)	16 (48.5)	32 (48.5)	NS
Age at menopause (years): mean ± SD	47.9 ± 5.2	47.4 ± 5.5	NS
Duration of menopause (years): mean ± SD	7.3 ± 6.5	7.0 ± 6.1	
Disease duration (years): mean ± SD	4.0 ± 3.6	—	
History of osteoporotic fracture: *n* (%)	3 (9.1)	—	
BMD (g/cm^2), mean ± SD			
Lumbar spine	0.887 ± 0.11	1.045 ± 0.17	<0.001
Total hip	0.830 ± 0.11	0.944 ± 0.13	<0.001
Femoral neck	0.803 ± 0.11	0.899 ± 0.13	0.001
T-score, mean ± SD			
Lumbar spine	–2.39 ± 0.93	–0.99 ± 1.51	<0.001
Total hip	–1.47 ± 0.99	–0.56 ± 1.14	<0.001
Femoral neck	–1.62 ± 1.02	–0.73 ± 1.18	<0.001

BMD, bone mineral density

Table 2. Liver and bone turnover data of patients with primary biliary cirrhosis

	Mean ± SD	Range	Number (percentage)
PBC histological stage			
I–II	—	—	12 (36.4)
III–IV			21 (63.6)
Serum alanine aminotransferase (U/l)	229.4 ± 326.2	[24–1700]	—
Serum alkaline phosphatase (U/l)	812.2 ± 979.2	[100–5160]	—
Gamma-glutamyltranspeptidase (U/l)	493.5 ± 566.5	[50–2400]	—
Bilirubin (mg/l)	41.3 ± 46.5	[5–200]	—
Albumin (g/l)	35.3 ± 6.7	[23.2–45.5]	—
25-OH D (ng/ml)	10.1 ± 5.7	[7–23.9]	—
1–25 $(OH)_2$ D (ng/ml)	24.8 ± 8.5	[12–38]	—
Parathyroid hormone (PTH) 1–84 (pg/ml)	37.1 ± 18.9	[14.1–79.8]	—
Osteocalcin (ng/ml)	12.7 ± 6.2	[2.3–28.6]	—
CTX (ng/ml)	0.2 ± 0.2	[0.001–0.6]	—

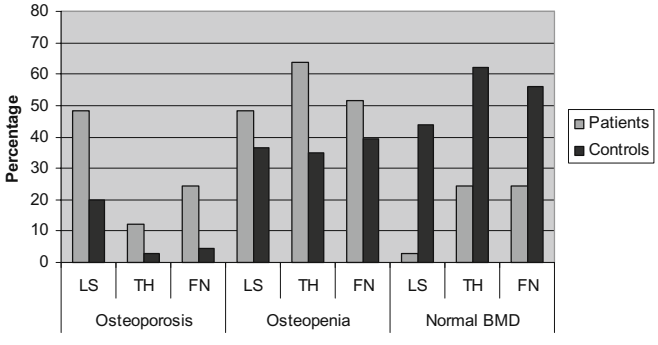

Fig. 1. Repartition of patients with primary biliary cirrhosis and controls according to bone mineral density (BMD). *LS*, lumbar spine; *TH*, total hip; *FN*, femoral neck

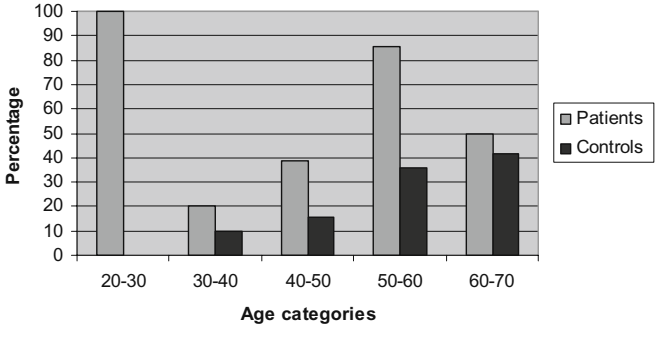

Fig. 2. Percentage of osteoporosis by age (decades) in patients with primary biliary cirrhosis (PBC) and controls

shows values of laboratory variables particularly relevant to calcium, phosphorus, hepatic function, and bone metabolism. The mean remodeling bone markers levels were within the normal reference ranges. All our PBC patients had low levels of 25-OH vit D (range, 7–23 ng/ml). Vertebral morphometry (VFA) showed a vertebral fracture in 3 patients (9%).

The clinical and laboratory data of PBC patients with and without osteoporosis are summarized in Table 3. No differences were found between osteoporotic and

Table 3. Clinical, biological, and histological parameters in patients with primary biliary cirrhosis with and without osteoporosis

	Osteoporotic patients (T-score ≤–2.5) (n = 17)	Nonosteoporotic patients (T-score <–2.5) (n = 16)	P
Age (years)	48.3 ± 11.3	46.2 ± 9.8	NS
BMI (kg/m^2)	24.6 ± 5.7	26.3 ± 4.59	NS
Menopause (%)	58.8	37.5	NS
Duration of menopause (years)	5.8 ± 3.67	9.8 ± 9.6	NS
Disease duration (years)	4.8 ± 4.3	3.1 ± 2.6	NS
Bilirubin (mg/l)	42.1 ± 54.7	40.4 ± 37.3	NS
ALAT (U/l)	183.5 ± 225.6	278.2 ± 409.6	NS
ASAT (U/l)	162.7 ± 186.6	245.3 ± 257.5	NS
Albumin (g/l)	36.3 ± 5.1	34.1 ± 9.1	NS
Histological stageI and II/III and IV	7/10	5/11	NS
PTH (pg/ml)	42.1 ± 17.8	33.0 ± 7.5	NS
25-OH vit D (ng/ml)	12.2 ± 7.8	17.2 ± 5.0	NS
Osteocalcin (ng/ml)	11.54 ± 6.76	13.61 ± 5.89	NS
CTX (ng/ml)	0.166 ± 0.172	0.221 ± 0.164	NS

Results are expressed as mean ± SD
NS, nonsignificant

Table 4. Correlation between BMD and different clinical, biological, and histological parameters in patients with PBC

	Lumbar spine BMD r	Total hip BMD r	Femoral neck BMD R
Age	–0.21	–0.08	0.12
BMI	0.18	0.39*	0.19
Menopause duration	–0.24	–0.22	–0.40*
Disease duration	–0.22	–0.27	–0.34*
Histological stage	–0.01	–0.02	–0.02
PTH 1–84	–0.25	–0.56**	–0.46*
25-OH vit D	0.54**	0.59**	0.58**
Osteocalcin	0.11	–0.003	0.11
CTX	0.05	–0.01	0.08

BMI, body mass index
* $P < 0.05$; ** $P < 0.01$

nonosteoporotic patients. Univariate and multiple regression analysis did not find any significant statistical association between 25(OH)D and osteoporosis. When comparing osteoporotic patients with non osteoporotic patients only in premenopausal women, we found a statistical difference in weight (53.4 kg ± 9.0 vs. 67.0 ± 8.9; $P < 0.001$) and BMI (21.0 ± 2.6 vs. 26.4 ± 4.3; $P < 0.001$, respectively).

BMD of PBC patients in total hip was significantly correlated, positively with BMI and 25-OH vit D and negatively with PTH. A significant negative correlation was found between BMD in femur neck and duration of menopause, disease duration, and PTH. BMD of PBC patients in lumbar spine was significantly correlated positively with 25-OH vit D. Significant correlations existed between BMD at the three studied sites. Pearson correlation coefficients were as follows: lumbar spine and femoral neck, I = 0.66; lumbar spine and total hip, $r = 0.67$; total hip and femoral neck, $r = 0.90$ (Table 4). PTH correlated negatively with 25 OH vit D ($r = –0.75$; $P = 0.013$).

Discussion

This study shows that osteoporosis is more prevalent in women with PBC than in the general population, and consequently these data confirm the association of PBC with low bone mass. Osteoporosis is the predominant component of hepatic osteodystrophy and is present in 20%–50% of patients with chronic liver disease (CLD), based on BMD measurements [17,18]. Osteomalacia, caused by concomitant vitamin D deficiency and calcium malabsorption, was traditionally considered to be the major bone disorder in patients with CLD, but is found in only a minority of patients [19].

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 [20]. The pathogenesis of osteoporosis in CLD is unknown, and there is much controversy about the risk factors for osteoporosis in CLD.

It has been shown that patients with cholestatic liver diseases, such as primary sclerosing cholangitis and PBC, have increased prevalence of osteoporosis compared to other chronic liver diseases [21,22]. Accordingly, Crosbie et al. [23] suggested that the high prevalence of osteoporosis rate (60%) in their study is the result of the large number of patients with either PBC or primary sclerosing cholangitis. The risk of osteoporosis in PBC has been shown to correlate with age, disease stage, BMI, and history of fractures [24–26].

Many series have evaluated bone metabolism in patients with PBC and most indicate a high turnover state even when trabecular bone volume and distal forearm BMD are still normal [27,28], although some reports indicate low bone turnover [4]. Reduced trabecular wall thickness and increased bone turnover are proportional to the severity of hepatic dysfunction and cholestasis [7]. As observed in our series, increased serum parathyroid hormone (PTH) level has been implicated, possibly in response to reductions in 25-OH vit D [29]. Although there is no consensus on optimal levels of 25-OH vit D as measured in serum, vitamin D deficiency is defined by most experts as a 25-OH vit D level of less than 20 ng/ml. Levels of 25-OH vit D are inversely associated with parathyroid hormone levels until the former reach 30 to 40 ng/ml, at which point parathyroid hormone levels begin to level off. All our PBC patients had low vitamin D levels (range, 7–23 ng/ml). Although Morocco is a sunny country, the prevalence of 25-OH vit D deficiency was found to be high among healthy Moroccan women in one study (83% having less than 30 ng/ml and 40% less than 15 ng/ml) [30]. However, the fact that 25(OH)D values were not measured in the controls in the present study is still a significant drawback to analyze the contribution of vitamin D status to PBC-associated osteoporosis. An osteoblast defect may also exist in PBC [7], although other studies show increased osteoblast activity [31]. One retrospective study did not find any osteomalacia or osteoporotic conditions in women with PBC aged 45–54 years, although indices of bone turnover were increased and similar findings were shown in women with PBC aged 65–74 years and those with age-related osteoporosis [32]. This finding suggests that some of the osteoporosis attributed to PBC may be the result of the concomitant aging process. Finally, it has been suggested that precipitation of calcium salts by unabsorbed fats within the intestinal lumen may contribute to the calcium malabsorption in chronic cholestasis. Other chronic cholestatic disorders such as primary sclerosing cholangitis (PSC) have not been as thoroughly studied, but histological examination in advanced cases again shows increased bone resorption, reduced formation, and no osteomalacia [33].

We found that duration of menopause and BMI were significantly correlated with osteoporosis. This finding apparently confirms previous results [34–37] in which chronic liver disease per se, and not a specific etiology, should be responsible for hepatic osteodystrophy. However, it has been reported that severe PBC cases have a low BMI. As two-thirds of patients in our series were in stage III and IV, this can explain why low BMI represented the major risk factor of osteoporosis, especially in premenopausal women. Osteoporosis has been shown to be significantly associated with postmenopausal status in several studies [5,38].

Cholestatic disease has been reported to be associated with fracture rates both greater than and similar to noncholestatic disorders [39,40]. Interestingly, the highest rate of prevalent fractures (44%) was seen in patients with autoimmune hepatitis, and this was much greater than in patients with PBC (7%) [39]. Incident fracture rates have been even less well characterized. In our series, 9% of the patients had a vertebral fracture. A study of women with PBC found 5% with new radiographic vertebral fractures over 2 years of follow-up [41]. In the control arm of a treatment study in patients with PBC with established osteoporosis, 9% had prevalent vertebral fractures and 13% experienced new radiographic vertebral deformities over the next 1–2 years (similar to the rate of 14% in the etidronate-treated arm) [42]. Reduced lumbar spine BMD (below the fourth percentile) appeared to be a marker for increased risk of vertebral fracture.

In summary, our study indicates that osteoporosis is a common complication in patients with PBC, with prevalence significantly higher to that observed in an age-matched group of healthy women. These data suggest that vitamin D deficiency may be linked to the PBC-associated bone loss and that duration of the liver disease and low BMI are the most important risk factors associated to this osteoporosis.

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