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Original Research Article

Risk of Osteoporosis Due To Liver Disease- A Case Control Study

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Abstract

Osteoporosis has become an increasingly recognized complication among patients with chronic liver disease (CLD). The aim of the present study was to assess the prevalence and risk factors of osteoporosis in patients with CLD (primary biliary cholangitis and chronic viral hepatitis B or C patients) in comparison with a group of age- and sex-matched controls. Sixty-four patients with CLD (mean age 51.66 ± 11.54 years), 48 females and 16 males were included. Age- and sex-matched individuals from the general population served as controls. Osteoporosis was evaluated by dual energy X-ray absorptiometry (bone mineral density below -2.5 T score) at the lumbar spine (LS) and total hip (TH). Vertebral fractures were established by densitometric morphometry (vertebral fracture assessment). Bone turnover was assessed by intact parathyroid hormone, osteocalcin and C-telopeptides of type I collagen in the serum. Prevalence of osteoporosis in either the LS or the TH was 45.3%, twice as high as in the controls (19.6%) (RR 2.31, 95% CI 1.42–3.75, P\0.001). Age, menopausal status, cirrhosis and advanced histological stage are not determinant factors for developing osteoporosis in patients with CLD. However, female sex, cholestasis, lower weight and height but not body mass index seem to play predominant role. Three (5.3%) patients had dorsal and LS fractures. It was concluded that osteoporosis is effectively a complication of CLD. Cholestasis in addition to female sex and lower weight and height are risk factors of osteoporosis in CLD.

Keywords: Liver Disease, Osteoporosis.

INTRODUCTION

Chronic liver disease (CLD) can be classified into diseases with primarily hepato cellular damage such as chronic viral hepatitis B or C (CVH) and cholestatic diseases [primary biliary cholangitis (PBC), primary sclerosing cholangitis]. Metabolic bone disease occurring in patients with CLD, known as hepatic osteodystrophy, is a common complication among individuals with long-standing hepatic disease. Osteoporosis is the well known major complication in this chronic hepatitis. Its prevalence vary considerably, it ranges from 20 to 100% [1, 2] according to patient selection and diagnostic criteria. Osteoporosis in CLD mainly affects trabecular bone and has been characterized by low bone turnover with reduced osteoblast function and low serum osteocalcin levels [1, 3-5]. The pathogenesis of osteoporosis in CLD is still unknown and it is likely that multiple factors are operating simultaneously. The aims of this study were to assess the prevalence of osteoporosis in CLD especially in PBC and CVH B or C in comparison with a group of age- and sex-matched controls consisting of healthy subjects and to identify the main risk factors for its development.

PATIENTS AND METHODS

Patients and controls A total of 64 patients with CLD (33 PBC and 31 CVH B or C defined by clinical, biochemical, serological, immunological and histopathological investigations with duration up to 6 months) were selected. They were followed at Gastroenterology Department, Ibn Sina or Military Hospital Mohammed V, Rabat, Morocco. None of them was receiving oral calcium or vitamin D supplements, bisphosphonates, estrogens, corticosteroids or any other treatments that could affect bone mass before the study. Body mass index (BMI) was calculated by dividing weight (kg) by squared height (m2). All patients with CLD were treated for their chronic hepatitis, but the effect of these drugs on bone mineral density (BMD) is not recognized. A total of 97 age- and gender-matched controls were selected from the general population (data used in the study of the Moroccan DXA reference database) [6]. Menopausal status, age of menopause and BMI were assessed in this control group. Patients and controls gave their informed consent to participation in the study. Clinical aspects and hepatic status Information about age, sex, menopausal status, age of menopause for women, BMI and duration of CLD were derived from a questionnaire used for patients. Liver

damage and severity of cholestasis for the patients with PBC were assessed by the following measurements: serum concentration of bilirubin, albumin, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase and gammaglutamyl transferase as well as the prothrombin index. The histological stage was recorded according to Ludwig's criteria [7] for patients with PBC and cirrhotic status was determined for patients with CVH B or C. Bone mineral density measurements Bone mineral density was measured in two sites: LS (L1–L4) and TH using dual energy X-ray absorptiometry (Lunar Prodigy vision General Electric). All measurements were realized by two technicians in all patients and controls. The long-term precision error for the DXA equipment was evaluated by the use of a spine phantom and expressed as the coefficient of variance which 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/cm2 for the spine and hips, respectively [8, 9]. BMD and T score were calculated according to the basis of BMD measurements performed in a sample of non-selected women. A Moroccan data reference curve was used to measure T scores [6, 10]. Osteoporosis was defined as a T score below -2.5 SD of the young adult mean value and osteopenia when the T score is between -1 and -2.5 SD according to the World Health Organization criteria [11]. A similar definition was used for men: BMD less than -2.5 SD from the mean of a young adult male population. The prevalence of osteoporosis in patients with CLD was compared to that reported in non-selected Moroccan population. Fracture assessment A morphometric study of dorsal and LS (T4–L4) was used in order to disclose vertebral fracture using DXA (Vertebral Fracture Assessment) [12, 13] only in patients. It was obtained in 58 patients out of 64 and was realized in association with BMD measurement. The diagnosis of vertebral fracture was performed using the Genant index [14]. It was defined as a reduction of 20% or more in the anterior, middle or posterior height of the vertebral body. Biochemical bone metabolism tests Biochemical bone metabolism tests were performed only in the patient group. All blood and urine samples were drawn after an overnight fast. Serum osteocalcin, C-telopeptides of type I collagen (CTX), and intact parathormone 1-84 (iPTH 1-84) were measured by immunoenzymatic assay (IEA) in 55 patients out of 64 using electrochemiluminescence on an ELECSYS 2010 analyser (Roche Diagnostics, Mannheim, Germany). Serum 25 hydroxy vitamin D (25 OH vit D) was determined by radioimmunoassay (RIA). Alkaline phosphatase, serum calcium, phosphorus and urinary calcium were also measured. Statistics The Statistical Package for the Social Sciences (SPSS 13.0 version) was used for statistical calculations. All data were expressed as mean ± standard deviation. The Chi square test was used to analyze differences in non-continuous variables and the Student's t test in continuous variables. A two tailed P value \0.05 was considered to indicate a significant difference. Correlations were performed using the Spearman test.

RESULTS

Demographical and clinical data of the patients and the controls are shown in Table-1. The mean age of our patients was 51.6 ± 11.5 years (range 26–76 years).

Table-1: Demographic and clinical data of patients with chronic liver disease and controls

	Patients (all)	PBC patients	CVH patients	Controls
N	64	33	31	97
Sex (F/M), (n)	48/16	33/0	15/16	81/16
Age (years), mean	51.66	47.33	56.26	50.19
BMI (kg/m^2), mean ± SD	26.13 ± 4.41	25.45 ± 5.18	26.85 ± 3.34	28 ± 4.32
Menopause, n (%)	29 (60.4)	16 (48.5)	13 (86.7)	46 (56.8)
Age of menopause (years), mean	47.9	47.94	47.85	47.89

CLD Chronic liver disease, PBC primary biliary cirrhosis, CVH chronic viral hepatitis, F female, M male, BMI body mass index

There were 48 (75%) females and 16 (25%) males. A total of 60.4% (29/48) of the females were postmenopausal and 12 became menopausal before the age of 45 years. The mean BMD and T score at the LS and at the TH were significantly reduced at both sites in patients with CLD compared with the control group (LS: P\0.001, TH: P = 0.001). Bone mineral density and T score did not differ between male patients and controls at both sites. However, female patients in premenopause or postmenopause showed lower BMD and T score values when comparing with healthy controls (Table-2). When analyzed separately, patients with PBC showed significant lower BMD than the control group (P\0.00) while, CVH patients did not differ from controls at both sites of BMD measurement. The prevalence of osteoporosis in either of LS (L1–L4) or the TH was significantly higher in the patient group (29/64, 45.3%) compared with the control group (19/97, 19.6%) (RR: 2.31, 95% CI: 1.42–3.75, P\0.001). When the prevalence of osteoporosis was evaluated according to ranges of age, all categories showed higher rate of osteoporosis than the control group with a statistically significant difference for patients between 25 and 44 years (P = 0.03) and between 45 and 54 years (P = 0.003) (Fig-1). The prevalence of osteoporosis was significantly higher in female patients regardless of

their menopausal status than their controls (Table-3). When comparing PBC and CVH patients lower BMD and T score in PBC patients than in the other group was observed (Table-4). A total of 43.8% patients were osteoporotic at the LS and only 9.4% at the TH. 50% patients were osteopenic at the TH and 39.1% at the LS. The clinical, histological and laboratory data of CLD patients with and without osteoporosis are summarized in Table 5. No differences between osteoporotic and non-osteoporotic patients were observed except for age of menopause. BMD at either LS or TH correlated with female sex (r = -0.35, P = 0.004; r = -0.35, P = 0.004) respectively. Weight also correlated with BMD at both sites (LS: r = 0.39, P = 0.001; TH: r = 0.38, P = 0.002) and low BMD was associated with a small height (LS: r = 0.42, P\0.001; TH: r = 0.38, P = 0.002). However, no relationship was identified in patient group neither between BMD and BMI nor among controls. A high age of menopause correlated with low BMD at the LS but not at the TH.

Table-2: Bone mineral density (g/cm2) and T score (SD) of patients and controls

	Lumbar spine BMD and T score			Total hip BMD and T score		
	Patients	Controls	P value	Patients	Controls	P value
All	0.931 ± 0.15	1.04 ± 0.16	\0.001	0.877 ± 0.13	0.953 ± 0.14	0.001
	-2.01 ± 1.31	-1.00 ± 1.36	\0.001	-1.17 ± 1.10	-0.53 ± 1.15	0.001
Females	0.900 ± 0.13	1.03 ± 0.16	\0.001	0.849 ± 0.12	0.937 ± 0.14	0.001
	-2.24 ± 1.21	-1.06 ± 1.38	\0.001	-1.36 ± 1.05	-0.62 ± 1.18	\0.001
Males	1.02 ± 0.15	1.09 ± 0.16	NS	0.962 ± 0.14	1.03 ± 0.11	NS
	-1.32 ± 1.40	-0.70 ± 1.28	NS	-0.58 ± 1.07	-0.43 ± 0.85	NS
Menopausal women	0.879 ± 0.13	0.976 ± 0.14	0.005	0.833 ± 0.11	0.916 ± 0.15	0.01
	-2.40 ± 1.27	-1.51 ± 1.22	0.004	-1.53 ± 0.91	-0.81 ± 1.25	0.01
Menopausal women	0.932 ± 0.13	1.10 ± 0.16	\0.001	0.873 ± 0.14	0.966 ± 0.12	0.01
	-2.01 ± 1.09	-0.47 ± 1.37	\0.001	-1.11 ± 1.20	-0.38 ± 1.03	0.02
Non-menopausal women	0.912 ± 0.15	1.011 ± 0.17	NS	0.859 ± 0.14	1.00 ± 0.17	0.03
	-2.04 ± 1.52	-1.20 ± 1.46	NS	-1.31 ± 1.11	-0.10 ± 1.45	0.02
PBC patients	0.837 ± 0.11	1.04 ± 0.17	\0.001	0.830 ± 0.11	0.944 ± 0.13	\0.001
	-2.39 ± 0.93	-0.93 ± 1.51	\0.001	-1.47 ± 0.99	-0.56 ± 1.14	\0.001
CVH patients	0.978 ± 0.17	1.03 ± 1.46	NS	0.928 ± 0.14	0.972 ± 0.14	NS
	-1.61 ± 1.54	-1.11 ± 1.27	NS	-0.84 ± 1.13	-0.46 ± 1.16	NS

Data expressed as mean ± standard deviation
NS Not significant

Table-3: Prevalence of osteoporosis in patients and controls

	Patients		Controls		P
All	29/64	(45.3%)	19/97	(19.6%)	\0.001
Females	24/48	(50%)	18/81	(22.2%)	0.001
Males	5/16	(31.3%)	1/16	(6.3%)	NS
Menopausal women	17/29	(58.6%)	14/46	(30.4%)	0.01
Non-menopausal women	7/19	(36.8%)	4/35	(11.4%)	0.02
PBC patients	17/33	(51.5%)	14/66	(21.2%)	0.002
CVH patients	12/31	(38.7%)	5/31	(16.1%)	0.04

Table-4: Bone mineral density (g/cm2) and T score (SD) of patients with PBC and those with CVH

	PBC patients		CVH patients		P
BMD LS	0.887	± 0.11	0.978	± 0.171	0.01
BMD TH	0.830	± 0.112	0.928	± 0.144	0.003
T score LS	-2.38	± 0.93	-1.61	± 1.54	0.01
T score TH	-1.47	± 0.99	-0.84	± 1.43	0.02

Serum levels of indices of bone mineral metabolism did not show significant difference between osteoporotic and non-osteoporotic patients with CLD. PTH rates were correlated but not significantly (r = -0.25, P = 0.06) with BMD at the TH. Serum 25 OH vit D was lower in patients with CLD even they were osteoporotic or not. Five out of 64 patients had a history of peripheral fractures. In addition, morphometric X-ray densitometry realized in 56 patients revealed vertebral fractures in 3 patients (5.3%), 2 fractures at the thoracic spine and 1 at the LS grades 1 and 2 according to the Genant classification of vertebral fractures [14].

Table-5: Clinical, biological, histological and densitometric data in patients with and without osteoporosis

	Osteoporosis		No osteoporosis		P
	(29/64)		(35/64)		
	(T score B -2.5)		(T score [-2.5)		
Age (years)	52.55	± 12.34	50.91	± 10.96	NS
Females (%)	50		50		NS
Menopause (%)	58.6		41.4		NS
Age of menopause	49.65	± 4.5	45.42	± 3.9	0.01
(years)					
BMI (kg/m^2)	25.31	± 4.77	26.80	± 4.03	NS
Duration of disease	4.36 ± 3.79		3.80 ± 3.93		NS
(years)					
Histological stages	47.6		52.4		NS
III–IV (%)					
Cirrhotic state (%)	42.1		57.9		NS
T score (lumbar spine)	-3.1 ± 0.55		-1.11 ± 1.04		\0.001
T score (total hip)	-1.80 ± 0.91		-0.64 ± 0.97		\0.001
25 OH D3 (*l*g/l)	10.48	± 6.65	9.92 ± 5.4		NS
Parathyroid hormone	40.03	± 16.28	35.34	± 16.07	NS
1-84 (pg/ml)					
Osteocalcin (ng/ml)	13.84	± 7.46	14.39	± 4.97	NS
CTX (ng/ml)	0.259	± 0.227	0.268	± 0.117	NS

(25 OH D3 25-hydroxy vitamin D3, CTX plasma type 1 collagen cross-linked C-telopeptide)

DISCUSSION

Osteoporosis is a well known and frequently reported complication of CLD with a high fracture rate unlike osteomalacia which is rare in the absence of severe malabsorption or advanced liver disease [1, 15]. The present study shows that osteoporosis is more prevalent in patients with CLD than in the general population. The association of such a complication with chronic hepatitis has been extensively reported in previous studies [1, 15-17]. Various reports [16, 18-20] concluded that cirrhosis and noncirrhotic biliary disease (PBC, PSC) have been linked with high prevalence of osteoporosis and increased risk of fracture [21-23]. In contrast, in some of the studies [3, 17], the only independent risk factors for osteoporosis were a lower BMI and increasing age. In PBC patients, a direct relationship with osteoporosis was found in two recent studies [17, 22], they have confirmed a 4-fold increased risk of osteoporosis and a 2-fold increased risk of fractures in this group of patients in comparison with age-matched controls. In spite of the younger age of our patients (51.6 ± 11.6 years), they developed high rates of osteoporosis than the control group with no difference between osteoporotic and non-osteoporotic patients. This result suggests that older age is not a determinant risk factor for osteoporosis in these patients. This finding is not in agreement with other reports where high age is the most relevant determinant of BMD and was observed in osteoporotic CLD patients in comparison with non-osteoporotic ones [3, 15, 17]. This is probably due to other risk factors of osteoporosis and especially calcium and 25 OH vitamin D deficiency in Moroccan patients which was found in 83% (less than 30 ng/ml) and 40% (less than 15 ng/ml) [24]. Moreover, hypogonadism which is the most common risk of osteoporosis in the general population, although associated with this bone disease in women with CLD seem not playing the most important role in the development of such a complication. Indeed, our female patients even if they were post or premenopausal showed higher prevalence of osteoporosis in either LS or TH in comparison with controls. However, male patients did not differ from the control group. In addition, no significant difference was identified between menopausal and non-menopausal patients according to osteoporotic status. Consequently, the contribution of menopausal status as a risk factor in patients with CLD is less essential than the other factors as confirmed in other studies [15, 17, 25]. Results from this study do not confirm the association of low bone mass with low BMI as reported in previous studies [17, 26]. However, low BMD correlated strongly with low weight and small height but not with decreased BMI. This finding suggests that weight may be more practical to use in clinical situations when evaluating patients with regard to metabolic bone disease as pointed out by others [27, 28]. Cholestatic liver disease has been reported to be associated with higher prevalence of osteoporosis and increased fracture rates both greater than and similar to non-cholestatic disorders [1, 21, 29, 30]. Most studies comparing cholestatic and non-cholestatic CLD [3, 31, 32] have not been able to demonstrate the role of this parameter in the pathogenesis of this bone disease. In our cohort, PBC

patients presented lower BMD statistically significant than CVH patients at LS and TH (P = 0.01 and P = 0.02), respectively and comparing with controls too. Nevertheless, no correlation was found between BMD and hyperbilirubinemia. Hence, cholestasis (PBC) can be considered as a risk factor for the development of osteoporosis in chronic biliary cirrhosis. Furthermore, advanced histological stage of the liver disease was identified as a robust independent risk factor for osteoporosis in various studies [17]. In our experience, this result has not been confirmed. Another interesting observation from this study is that biochemical markers of bone remodeling did not show any difference between CLD patients with and without osteoporosis. Nevertheless, subnormal rates of osteocalcin and decreasing mean rate of 25 OH vit D without any difference according to osteoporotic status were observed in our patients. Our results are in agreement with previous studies [1, 3, 17, 33]. However, the fact that 25 OH vit D and osteocalcin were not measured in the controls in the present study is still a significant drawback to analyze the contribution of vitamin D and osteocalcin status to CLD associated with osteoporosis. Several reports suggest that the first abnormality observed in patients with CLD was the reduction of bone formation whereas, others report normal or reduced bone formation coupled with increased resorption (high turnover) [34, 35]. Pathogenesis of osteoporosis in CLD is complex and is poorly understood. There is much controversy about the risk factors for this bone disease which includes the vitamin D receptor, collagen 1 alpha, low density lipoprotein receptor binding protein 5 and estrogen receptor. In PBC patients, polymorphisms in the vitamin D receptor and collagen 1 alpha gene appear not to be associated with a high risk of osteoporosis [2, 18, 36]. The exact role of RANK/RANK ligand, osteoprotegerin in the pathogenesis of abnormal bone turnover in patients with CLD remains unclear with controversial results on the levels of these proteins in serum [37, 38]. Low IGF I rates, hyperbilirubinemia, corticosteroids or immunosuppressive therapy were also incriminated as risk factors [39, 40]. Conclusions Our study confirmed the association between CLD and osteoporosis which is the main form of hepatic osteodystrophy with prevalence significantly higher to that observed in an age- and sex-matched controls from the general population. Increasing age, menopausal status, and cirrhosis were not determinant risk factors of osteoporosis in CLD. However, female sex, low weight and height but not BMI correlated strongly with low BMD. Cholestatic patients are at higher risk of osteoporosis than CVH patients and healthy controls. Thus, patients with CLD are candidates to develop osteoporosis requiring a close screening and potential prophylactic and therapeutic procedures.

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