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Bone Mineral Density Assessment in Chronic Liver Disease

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Abstract

Aim: The present study was aimed at estimating the prevalence of osteoporosis, symptoms, etiology, factors influencing the osteoporosis in patients with liver complications and to study the association of osteoporosis and severity of liver dysfunction and impact of osteoporosis on quality of life.

Methods: 90 eligible patients tested in Rajiv Gandhi Government General Hospital. Patient's samples were collected, tested and results recorded.

Results: Out of 90 patients (M-84.4%, F-15.6%) and as age progressed, osteopenia and osteoporosis found than the normal patients. Higher percentage of patients had Fatigue symptoms. Common etiology was HBV. As the Child-Pugh-Turcotte (CTP) scoring was increased from A to C the numbers of patients were increased from normal to osteopenia followed by osteoporosis. Statistical significance was found between Normal and Low Bone Marrow Density (BMD) with Model for end-stage liver disease (MELD), Vitamin-D, Para-thyroid hormone and Duration of diseases. Statistical significant found between Normal and Low BMD in the elevation biological markers like T. bilirubin, AST, ALT, SAP (females) and Albumin.

Conclusion: Among the liver diseases patients ¾ of them were with Low BMD. Linear progression of low BMD was found with increased age. With the symptom also we can detect low BMD in liver diseases patients. As the CTP increased low BMD was observed. Alcoholic liver disease had highest proportion of osteoporosis. Routine testing of vitamin D in HBV patients, higher MELD and increased duration of liver diseases will guide us for better and early diagnosis of low BMD among the liver diseases population.

Keywords: Bone mineral density; Chronic liver disease; Cirrhosis, Osteoporosis; Osteopenia

Introduction

Literature database outlines Global Burden of Liver Disease estimates roughly 1.03 million deaths per year in the world wide and over a million deaths in 2010 by cirrhosis [1]. Prevalence in cirrhotic patients varies from 12 to 70% and the liver disease etiology osteoporosis is common among all cirrhotic patients regardless of the liver disease etiology [2].

Among the cirrhotic patients increased prevalence of osteopenia and osteoporosis has been demonstrated in patients with chronic liver disease of different etiologies in the recent times [3]. Osteoporosis is the only complication that persists for years after liver transplantation [4]. Due to osteoporosis most of the fractures are overlooked in non-cirrhotic individuals as they are able to walk than cirrhotic patients who will be hospitalized [5]. Osteoporosis denotes a state in which the bones become porous resulting in increased risk for fractures [6].

These fractures were associated with bone loss due to low osteocalcin levels in patients with chronic liver diseases [7]. Fracture rates are also higher in cholestatic diseases, varying from 13 to 22% according to the degree of liver insufficiency [8]. The percentage of fractures may vary in different studies and up to 40% of patients with chronic liver disease may experience a fracture. Decreased vitamins D, treatment with corticosteroids contribute to worsening bone health. Per 100000 persons there are at least 2000 patients with chronic liver disease, of whom 20-420 have osteoporosis, and 60-880 experienced fractures and a previous fracture increases the risk for later fractures further [9]. There are some relationship between liver diseases and bone marrow density. Direct correlation between extent of liver fibrosis and low bone density has been reported in non-cirrhotic HCV mono-infected patients [10]. Among the bone minerals Vitamin-D deficiency plays an important role in liver diseases patients. Vitamin D (25-hydroxyvitamin D) is a lipo-soluble substance that exerts important effects on bone metabolism. Low levels can be found in about one-third of liver disease patients, but severe deficiency is more common in those stricken by cirrhosis and/or cholestatic diseases, because jaundice can make them more prone to malnutrition, malabsorption, and suppressed skin synthesis [11]. Bone loss in liver diseases patients not only increases the deficiency of vitamin-D but bone loss in liver cirrhosis increases the vertebral damage in the elderly, leading to compression fractures, disability, and spinal deformities

[12]. Vertebral damage in a liver diseases were overlooked which may be due to a reason that vertebral damage can be less symptomatic than hip fractures, which occurs in individuals who are still able to walk [13]. Low osteocalcin levels have been found in patients with chronic liver diseases and are associated with bone loss [7].

In addition to bone loss, liver diseases are complicated diseases. Liver disease is a high morbidity and mortality and 14th most common cause of death all over the world and 4th cause in central Europe [14]. However, in recent years many studies have reported a significant fall in the viral etiology and rise of alcohol induced CLD and this could be due to wider availability of Hepatitis B Vaccination, shifting of professional blood donation to voluntary blood donation, screening of all blood products for HBV. Consequently, with increasing alcohol consumption in the society has led to emergence of alcohol related CLD [15]. Chronic conditions of liver were assessed by two most popular scoring systems named as Child-Pugh-Turcotte (CTP) score and MELD across the globe [16].

Data regarding these rare cases are scarce. Reliable data based on large scale epidemiological studies are missing on true burden of bone disease among chronic liver disease patients [17].

Thus, the potential social and economic burden of the development of osteoporosis and the associated increased in fracture risk in patients with liver disease that tend to be younger than most osteoporotic patients is remarkable. A health problem of this size requires increased awareness, a better understanding of the underlying causes, and development of useful therapeutic concepts.

Based on the above reviews of the highlighted facts and scarcity of data for the cause-specific mortality rate, our present study can bring an estimated globe scenario of Low BMD was the chief cause for the liver dysfunction.

Materials and Methods

A total of 90 patients were studied in Department of Hepatology, Rajiv Gandhi Government General Hospital and Madras Medical College, Chennai.

Inclusion criteria

All Chronic liver disease patients with Child A, Child B, Child C and within age group - Male -21yrs – 70 years and Female -21yrs – till menopause.

Exclusion criteria

All patients with acute exacerbation or flare of disease (billirubin concentration > 5 mg/dL, AST > 2.5 times the upper limit of normal, Leukocytosis > 10 000/mm3), recent gastrointestinal bleeding, renal dysfunction, previous history of chronic disorders associated with changes in mineral metabolism, thyroid, parathyroid disorders, Cushing's syndrome and Diabetes. Patients who received calcium, vitamin D, medications influencing bone metabolism like corticosteroids, hormone replacement therapy, calcitonin, bisphosphonates, cytotoxics, anti-metabolites, anti-coagulants, anti-convulsants, thyroxin and interferon.

Sample size

Considering the prevalence of osteoporosis to be detected as 6%, with a precision of 5% and with an alpha error of 0.05 and an estimated loss to follow up rate of 5%, the required sample size would be 90. Hence it was decided to include about 90 subjects in the study population.

Sampling method

All patients who satisfied the inclusion criteria were included in the study sequentially, hence no sampling was done.

Study tools

A structured Case Report Form (CRF), exclusively developed for the study was used to capture all the relevant socio demographic, clinical, and laboratory parameters.

Study procedure

90, Consecutive chronic liver disease patients were selected after exclusion and inclusion criteria. Patient's history and clinical examination were done. Serum billirubin, urea, creatinine, Aspartate aminotransferase (AST), Alanine aminotransferase (ALT), Serum Alkaline phosphate (SAP) and PT, INR were done. HBsAg [18], HCV-PCR [19], Ascitic fluid analysis, Calcium [20], serum phosphorous [21] were also done. Parathyroid hormone and vitamin D were estimated by chemiluminescence immunoassay (CIA) [22]. Diagnosis of alcoholic cirrhosis was made with a positive answer to more than one question in the CAGE questionnaire and a history of significant alcohol consumption of >30 g/day in men and >20 g/day in women [23].

Severity of liver disease

Severity assessment of the liver disease in patients with cirrhosis was done by Child Pugh Score (CTP) [24] and Model for end-stage liver disease (MELD) [25] scores.

Biological marker analysis

Blood for biological marker analysis was drawn from all the patients enrolled in the study. After an overnight fast for 10 hours, blood for analysis was drawn in the morning.

Bone mineral density measurement

All patients included in the study were subjected to bone mineral density measurement by dual energy x-ray absorptiometry (DEXA).

Dual-energy X-ray absorptiometry technology

A typical DEXA scan machine consists of a padded table on which the patient should lie and movable C-arm with an x-ray tube under the patient and a detector above the patient. The x-ray tube, which is below the patient generate photon beams of two different energy levels, for which is called "dual-energy" source. A collimator below the table controls the scatter of the photons and directs the photons towards the area of interest. The difference in attenuation that is the reduction in intensity of the two photon beams as they go through the body tissue of various composition and distinguishing bone from soft tissue and allows quantification of the bone mineral density. Denser and thicker tissue contains more electrons and will not allow many photons to pass through to the detector. A computer which is specially designed with its proprietary software designed by each manufacturer forms a complete DEXA scan. Radiation exposure to the patient is very minimal, usually of a similar magnitude to daily background radiation. Radiation which is scattered beyond the edge of the DEXA table is negligible. Shielding of the technologist or room is not necessary. But as a safety precaution, the technologist doing the DEXA scan should not sit within three feet of the table edge when the patient is being scanned. DEXA scan measures bone mineral content in grams and bone area in square centimeter, then calculates "areal" BMD in g/cm^2 by dividing bone mineral content and bone area. T-score, the value used for diagnosis of osteoporosis, is calculated by subtracting the mean BMD of a young-adult reference population from the patient's BMD and dividing by the standard deviation (SD) of young adult population. Z-score, used to compare the patient's BMD to a population of peers, is calculated by subtracting the mean BMD of an age, ethnicity and sex matched reference population from the patient's BMD and dividing by the SD of the reference population. DEXA scan should be advised once a year and follow-up of patients on treatment for osteoporosis or osteopenia can be done with DEXA scan every 2 years [26].

According to the World Health Organization (WHO) criteria [27] Normal BMD is represented by a T score of more than -1. Osteopenia (low bone mass) is represented by a T score between-1 and -2.5. Osteoporosis is presented by a T score less than -2.5. Established osteoporosis is represented by a T score of less than -2.5 and a previous history of a fragility fracture.

Patients were divided into three groups on the basis of BMD: Group 1 had normal BMD, Group 2 had osteopenia and Group 3 had osteoporosis.

Site of measurement of bone mineral density

Most common site for measurement of bone mineral density was HIP and SPINE. Other sites of bone mineral density measurement include the peripheral site like calcaneum and wrist. WHO validated is DEXA scanning of the hip or spine.

Ethical issues

Ethics approval obtained from Human Ethics committee, of Rajiv Gandhi Government General Hospital and Madras Medical College, Chennai and patient informed written consent was obtained from all the participants, after explaining the objectives of the study, risks and benefits involved. The personal details of the patients were kept confidential throughout the study.

Statistical methods

Severity of the liver disease as per child Pugh classification was the primary explanatory variable. Age, gender, etiology of liver disease etc were considered as potential confounders. Descriptive analysis of socio demographic, clinical laboratory related parameters was done. Frequencies and percentages were used for categorical variables; quantitative variables were presented as means and standard deviations. Chi square test was used to assess the statistical significance of the association. To facilitate comparison of some of the important laboratory and clinical parameters like duration of disease, 25 (OH) D3 level, PTH levels etc., the outcome is recoded into a binary variable (Normal, Low BMD). The mean values of these parameters were compared between the two groups, using independent sample t-test. IB- SPSS version 21 was used for statistical analysis. Data were expressed as mean ± standard deviation for MELD, PTH, Duration of Diseases and Vitamin-D.

Results

A total of 90 subjects were recruited for the study. 76 male patients (84.4%) and females were 14 (15.6%). Among the study group in the Bone Marrow Density testing 24 patients were normal with the percentage of 26.7%. 40 patients were with osteopenia with the percentage of 44.4% and 26 patients were with osteoporosis with the percentage of 28.9% among the liver CLD patients. 73.3% of total population had osteopenia and osteoporosis. In the recruited patients 42 patients were below the age of 40 and 36 were between the age of 40-60. Only 12 patients were below the age of 40.

We studied association of age and Bone Marrow Density (BMD) and found in age group of below 40 years 52.4% were normal, 38.1% had osteopenia and 9.5% had osteoporosis which were statistically significant (*p-values <0.*05). In the age between 40-60 years higher numbers of patients were found in osteopenia followed by osteoporosis. In the age group above 60 years we found the higher number of patients were in osteoporosis followed by osteopenia. As the age progressed higher number patients were found in both osteopenia and osteoporosis than the normal patients **(Table 1).**

We have studied the symptoms of the patients and found that 37 patients out of 90 had fatigue by which we can detect Low BMD patients among the liver diseases population, 31 had

jaundice, 19 had ascitis and 3 had Joint pain which was statistical significant **(Table 2).**

Table 1 Association of age and gender with BMD among the study population.

Age group (yrs)	Bone Marrow Density (BMD) (n=90)			Chi square value	P-value
	Normal (n=24) 26.7%	Osteopenia (n=40) 44.4%	Osteoporosis (n=26) 28.9%		
<40 (n=42)	22 (52.4%)	16 (38.1%)	4 (9.5%)	18.000	0.000*
40-60 (n=36)	2 (5.6%)	20 (55.6%)	14 (38.9%)	21.000	0.000*
>60 (n=12)	0 (0.0%)	4 (33.3%)	8 (66.7%)	12.000	0.002*
Gender					
Male (n=76)	18 (23.7%)	34 (44.7%)	24 (31.6%)	7.737	0.021*
Female (n=14)	6 (42.9%)	6 (42.9%)	2 (14.3%)	3.429	0.180
* Statistically significant					

Table 2 Symptoms of the patients in the study population.

Symptoms	Number of patients (n=90)	Chi square	P value
Fatigue	37 / 90 (41.1%)	40.000	0.000*
Jaundice	31 / 90 (34.5%)		
Ascitis	19 / 90 (21.1%)		
Joint pain	3 / 90 (3.3%)		
* Statistically significant			

We tried to study the Etiology of the study population and found that chronic HBV was the most common etiology with 48.9%, alcohol with 42.2% and HCV with 8.9%. In the comparison between the etiology and BMD, we found the patients with alcohol has a etiology had a higher number of osetopenia and osteoporosis and HBV had equal number of patients in both osteopenia and normal patients which were statistically significant. In the comparison between the HCV and BMD, higher numbers of patients were found with normal patients. In the bone marrow density based on CTP scoring we found that higher numbers of patients were in the CTP-A scoring followed by CTP-B and CTP-C. As the CTP scoring was increased from A to C the numbers of patients were increased from normal to osteopenia followed by osteoporosis. In the CTP-A, higher number of patients were normal (55%) than osteopenia and osteoporosis. In the CTP-B scoring higher number of patients were found in osteopenia (66.7%) followed by osteoporosis. In the CTP-C scoring higher number of patients were in the osteoporosis (80%). We have studied the abnormal values of biological markers and found T. bilirubin, AST, Albumin, PO_4, and Calcium were elevated with the percentages of 60%, 46.7%, 28.9%, 44.4% and 46.7% respectively. Statistical significance was done by McNemar test and found significant of T. bilirubin, AST, Albumin, PO_4, and Calcium **(Table 3).**

Table 3 Association between bone marrow density and its etiology, CTP scoring and biological marker.

Clinical features			Bone Marrow Density (BMD)			Chi square	P value
			Normal	Osteopenia	Osteoporosis		
Etiology (n=90)	Alcohol (38/90) (42.2%)		2 (5.3%)	20 (52.6%)	16 (42.1%)	21.158	0.000*
	Hepatitis-B (44/90) (48.9%)	18 (40.9%)	18 (40.9%)	8 (18.2%)	6.818	0.033*	
	Hepatitis-C (08/90) (8.9%)	4 (50.0%)	2 (25.0%)	2 (25.0%)	1.500	0.472	

CTP scoring (n=90)	CTP A (40/90) (44.4%)		22 (55.0%)	16 (40.0%)	2 (5.0%)	23.700	0.000*
	CTP B (30/90) (33.3%)	2 (6.7%)	20 (66.7%)	8 (26.7%)	25.200	0.000*	
	CTP C (20/90) (22.2%)	0 (0.0%)	4 (20.0%)	16 (80.0%)	31.200	0.000*	
Biological Marker	T. bilirubin (54/90) (60%)		4 (7.4%)	24 (44.4%)	26 (48.1%)	24.667	0.000*
	AST (42/90) (46.7%)	6 (14.3%)	20 (47.6%)	16 (38.1%)	11.143	0.004*	
	ALT (22/90) (24.4%)	4 (18.2%)	14 (63.6%)	4 (18.1%)	13.636	0.001*	
	SAP (25/90) (27.8%)	Male (19/90) (21.1%)	6 (31.6%)	6 (31.6%)	7 (36.8%)	0.158	0.924
		Female (6/90) (6.7%)	---- (0%)	4 (66.7%)	2 (33.3%)	6.000	0.050*
	T. protein (4/90) (4.4%)	---- (0%)	4 (66.7%)	2 (33.3%)	6.000	0.050*	
	Albumin (26/90) (28.9%)	---- (0%)	10 (38.5%)	16 (61.5%)	22.615	0.000*	
	PO4 (40/90) (44.4%)	12 (30%)	16 (40%)	12 (30%)	1.200	0.549	
	Calcium (42/90) (46.7%)	16 (38.1%)	16 (38.1%)	10 (23.8%)	2.571	0.276	
* Statistically significant							

There was a statistical significant difference between two study groups in MELD (9.08 vs 17.79, P value <0.001). The mean MELD score, duration of disease were significantly higher in LOW BMD group than normal BMD indicating severity of CLD. The Duration of disease was also significantly higher in low BMD group, compared to Normal BMD group (17.21% vs. 30.03 %, P value-0.015). Vitamin D was lesser in LOW BMD group compared to Normal BMD group (16.19 ng/ml vs. 20.00 ng/ml, P value-0.010). There was no statistical significance between the two study groups in Para Thyroid Hormone (PTH) **(Table 4).**

Table 4 Association of MELD, duration of disease, Vitamin D and PTH between normal and low BMD cases.

Parameter	Normal	Low BMD	P value
	Mean ± SD	Mean ± SD	
MELD	9.08 ± 3.30	17.79 ± 6.225	0.001*
Duration of disease (months)	17.21 ± 10.41	30.03 ± 26.40	0.015*
Vitamin D (ng/ml)	20.00 ± 5.71	16.19 ± 6.21	0.010*
PTH (pg/ml)	42.82 ± 10.20	37.54 ± 10.70	0.039*
*Statistically significant			

Discussion

Metabolic disorders are important factor to be concentrated and needs an attention. ¾ of our study subjects were with osteopenia and osteoporosis and ¼ were normal in present study. In a study by Alam et al., 60% of patients were with osteopenia and osteoporosis [28]. Prevalence of hepatic osteodystrophy varies from 13% to 70% in Western countries while it has been reported higher 68% and 95% from India [29]. From the Southern part of India we conducted our current study and found 73.3% of patients had low BMD.

New finding of our present study was below 40 years of age higher numbers of patients were normal and in age 40-60, osteopenia were found followed by osteoporosis.

We tried to study the symptoms to find an early diagnosis of Low BMD in liver diseases and found that fatigue was found in

higher number of patients of Low BMD. Patients with fatigue in liver diseases patients can be tested for BMD testing to find an early diagnosis of Low BMD.

HBV were the most common etiology found among the liver diseases patients with Low BMD. In a study by Rinkesh et al. alcohol was the common etiology among their study subjects. [30]. Gabriela et al. found Hepatitis B and C have been shown to increase the concentration of proinflammatory cytokines and promote reductions in bone mass [31]. It has been shown that the incidence of osteoporotic fractures in patients with hepatitis C is significantly reduced after successful interferon therapy. In our current study there was a statistical significance found between Hepatitis B and low BMD patients and not with HCV.

Ying Peng et al. found that CTP and MELD scores have been widely used to predict the outcomes of cirrhotic patients [32]. In our present study CTP and MELD, not only predicted the liver diseases patients but also showed statistical significance between low BMD and normal patients.

As the CTP scoring increased from A to C, a linear increase from normal to low BMD like osteopenia and osteoporosis was a new finding in our study, hence by CTP scoring also we can have an early diagnosis of Low BMD in liver diseases patients.

High MELD scoring and duration of liver diseases also plays a role in Low BMD in patients with liver diseases. Thus if we check the Bone marrow density in patients with higher MELD and duration of liver diseases will help us to detect more number of patients with Low BMD in liver diseases patients. Early markers are important tool for any therapeutic intervention for any diseases. Vitamin D was also lesser in Low bone marrow density patients.

Conclusion

In conclusion, among the liver diseases patients ¾ of them were with Low BMD. As the age increased, low BMD was observed. With the symptom of fatigue in liver diseases we can detect low BMD. There was linear increase of low BMD with increased CTP scoring. Higher MELD and increased duration of liver diseases and routine vitamin D testing will be a tool to detect low BMD patients among the liver diseases subjects.

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