STUDY OF CORRELATION OF SEVERITY OF HEPATIC CIRRHOSIS WITH SEVERITY OF BONE CHANGES MEASURED BY BMD (BONE MINERAL DENSITY)

MD. ASHRAFUL ALAM[1], NOORUDDIN AHMED[2], SHAHINUL ALAM[2], MAMUN AL MAHTAB[2]

Abstract

Background & Aim *Metabolic bone disease is common among patients with chronic liver disease and still it is underestimated complication in liver cirrhosis. The prevalence and presentation of bone disease in chronic liver diseases have been poorly described except for cholestatic liver diseases.*

This study aims at evaluation of the prevalence and degree of bone changes in patients with cirrhosis and to correlate severity of hepatic cirrhosis with the severity of bone changes.

Patients and Methods *Bone mineral density (BMD) was studied using dual energy X-ray absorptiometry (DEXA) in 60 subjects of 15-45 years old. Of them 30 subjects are patients with liver cirrhosis and rest of the 30 subjects were control group without having liver disease or any other chronic disease. The diagnosis of cirrhosis was based on clinical, biochemical, and ultrasonographic findings. Patients with renal impairment, cholestatic liver disease, chronic lung disease, prolonged bed ridden patients or deformity of spine, pelvis or wrist were excluded from the study. Results of BMD were then correlated with the Child score.*

Results *Eighteen (60%) patients had decreased bone mineral density (BMD). Of which 15 (50%) patients have got osteopenia and 3 (10%) patients have got osteoporosis. No correlation was found between the T-score and Child Paugh score (p =0.236). Significant correlations were found between BMD and serum bilirubin..*

Conclusion *Liver cirrhosis is a risk factor for the development of bone loss and there is a high prevalence of BMD disorders in cirrhotic patients. The severity of bone loss is not related to the severity of liver disease. Hyperbilirubinemia and low albumin is a contributing factor to altered bone mineral density in patients with liver cirrhosis*

Key words *Hepatic osteodystrophy, osteoporosis, DEXA, bone mineral density, cirrhosis*

Introduction

Liver cirrhosis is a debilitating chronic disease associated with severe complications and raised mortality. Hepatic bone disease is common among patients of chronic liver disease. Hepatic osteodystrophy, and consequent osteopenia and osteoporosis and increased risk of bone fracture, represent some of the recently investigated complications. Initial studies focused on osteoporosis in patients with primary biliary cirrhosis; more recently, however, it has been shown that advance liver cirrhosis of any etiology is a risk factor for osteopenia and osteoporosis and bone fractures independent of its aetiology[1].

The term hepatic osteodystrophy refers to the abnormalities of bone metabolism that occur in the presence of advanced liver disease. Ostemalacia and osteoporosis are common complications of chronic liver disease[2]. Osteoporosis accounts for the majority of cases whereas osteomalacia is rare in absence of advanced liver disease and severe malabsorbtion[3].

Prevalence of hepatic osteodystrophy in patients with liver disease varies from 13% to 70%, depending on the population studied and diagnostic criteria used to define bone disease[4].

With the improvement in survival of patients with chronic liver disease and with the development of liver transplantation, the clinical significance of hepatic osteodystrophy has increased. However, in many patients with non-cholestatic liver disease osteodystrophy may remain unrecognized and untreated[5].

Bone density is the best single predictor of future fracture risk. The advances in bone densitometry and the development of newer techniques such as dual

1. Pharmacology Department, Cox's Bazar Medical College,
2. Department of Hepatology, BSMMU

energy X-ray absorptiometry (DEXA) made it possible to rapidly and precisely quantify the amount of bone in the relevant fracture sites [6]. The high level of precision of this technique allows not only for diagnosis, but also for monitoring response to treatment. It is noninvasive, accurate, rapid and safe[7].

In this work we evaluated the prevalence and degree of bony changes in patients with liver cirrhosis and studied its relation to the severity of liver disease.

Patients and Methods

Between January 2008 and December 2009, a total of 60 adult subjects of 15-45 years of age were recruited from the in patient and out patient department of Hepatology Department, Bangabandhu Sheik Mujib Medical University. Thirty patients were of cirrhosis of liver irrespective of etiology. Thirty healthy controls without having liver disease and absence of other disease which may cause osteopenia and osteoporosis.

The diagnosis of liver cirrhosis was made by clinical features suggestive of cirrhosis of liver, Ultrasonographic evidence of small sized liver with coarse echo texture with or without deranged liver function and/or Endoscopic evidence of esophageal varices.

Stage of liver disease was assessed using the Child-Pugh scoring system[8]. Patients without cirrhosis of liver, post menopausal women, chronic renal failure, chronic obstructive pulmonary disease, Patients on steroid, autoimmune hepatitis, rheumatoid and other arthritic disease, prolonged bed ridden patients, and patients of obstructive jaundice were excluded. All patients were subjected to history taking and clinical examination, in addition to laboratory investigations: Serum bilirubin, Serum Albumin, Prothrombin time, Serum Alkaline phosphates, Endoscopy of upper GIT, Liver biopsy (Group-I, Child class A group of patient) and abdominal ultrasound.

The informed patient consent for the study was obtained.

Bone mineral density evaluation in all patients (both case and control) was done by using biphotonic absorbption of X-rays (duel energy X-ray absorptiometry-DEXA) of whole body. BMD was expressed as grams per square centimeter. The World Health Organization (WHO) criteria for osteopenia and osteoporosis were used to define low BMD[9]. The WHO has defined osteopenia as a BMD between -1 and -2.5 standard deviation (SD) and osteoporosis as a BMD below -2.5 SD of the mean peak value in young adults (T-score). BMD was also compared to the mean value in normal subjects of the same age, sex, and ethnic group (Z-score). A Z-score below -1 SD corresponds to a value in the lowest 25 percentile of the reference range, a value at which the risk of fractures is approximately doubled. Z-score could not be evaluated by the equipment.

Bone status	T score
Normal bone density	T score < -1 STD
Osteopenia	T score between -1 and - 2.5 STD
Osteoporosis	T score < - 2.5 STD
Severe osteoporosis	T score < - 2.5 STD and at least one osteoporotic fracture

Exclusion of vertebral deformity was done by X-ray on the LS or by lateral view of the spine during the DEXA procedure.

Statistical Methods

Individual patient had a code number each. All data was collected in the structured questionnaire and entered into a personal computer. Analysis of the data was done by SPSS (version 13) programme. Significance of the test was done by ANOVA. Statistical significance was determined at p-value <0.05 (significant), and p-value <0.01 (highly significant).

Results

Age range of healthy subjects was 15-45 years and mean age was (32.97±7.18) years. Age range of cirrhosis group was 15-45 years and mean age was (34.57±9.45) years (Figure-1). In cirrhotic group 25 were male and 5 were female. In control group 20 were male and 10 were female. Laboratory parameters of included patients are presented in (Table 1).

Among the 30 cirrhotic patients, 12 (40%) patient had normal BMD value, 15 (50%) had osteopenia, and 3 (10%) had osteoporosis. Among 15 osteopenic patients 3(10%) were from Child's B and 12 (40%) patients were from Child's C. All the 3 (10%) ostoporotic patients were form Child's C (Table-2).

There is statistically significant difference in BMD between Cirrhotic group and control group, mean BMD in control group is 1.29±9.62E-02 and in cirrhotic group is 1.14±0.109.

Table-I

Laboratory parameters of normal, osteopenic, and osteoporotic groups of patients.

	Normal BMD (n=12)		Osteopenia (n=15)		Osteoporosis (n=3)		All (n=30)	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
S.Bilirubin (5-20µmol/L)	33.88	24.53	89.59	112.89	40.06	26.10	62.41	84.89
Alk.Phos (50-136U/L)	171.17	97.99	140.4	46.87	95.67	53.78	148.23	73.74
PT (18-22 sec)	24.75	12.09	26.01	10.63	19.60	5.05	24.86	10.73
S.Albumin (30-50 gm/L)	25.00	7.16	25.07	6.87	22.00	2.65	24.73	6.60
S.creatinine (0.6-1.3 mg/dl)	84.63	13.14	89.24	16.55	88.39	15.32	87.31	14.79
ALT (30-65 U/L)	76.2	56.8	60.4	42.8	68.9	76.5	68.9	65.3

Table-II

Distribution of bone mineral density disorders among cirrhotic patients

Patient group	Normal		Osteopenia		Osteoporosis		Total	
	No.	%	No.	%	No.	%	No.	%
Child A	0	0	0	0	0	0	0	0
Child B	4	13.33	3	10	0	0	7	23.33
Child C	8	26.67	12	40	3	10	23	76.67
All Patients	12	40	15	50	3	10	30	100

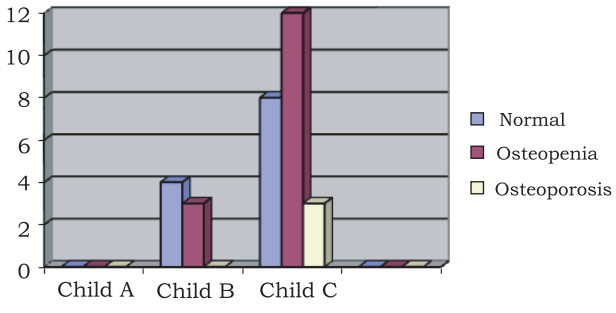

Fig.-1: *Difference of BMD in cirrhotic group of patients*

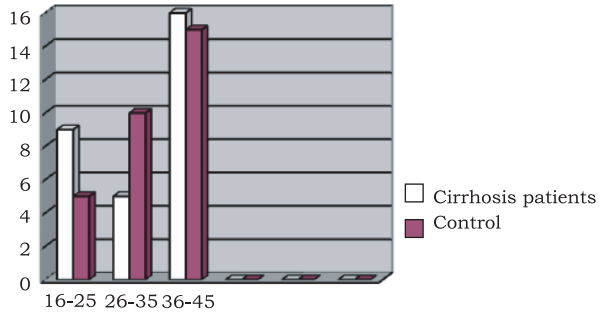

Fig.-2: *Age distribution of patients (n=60)*

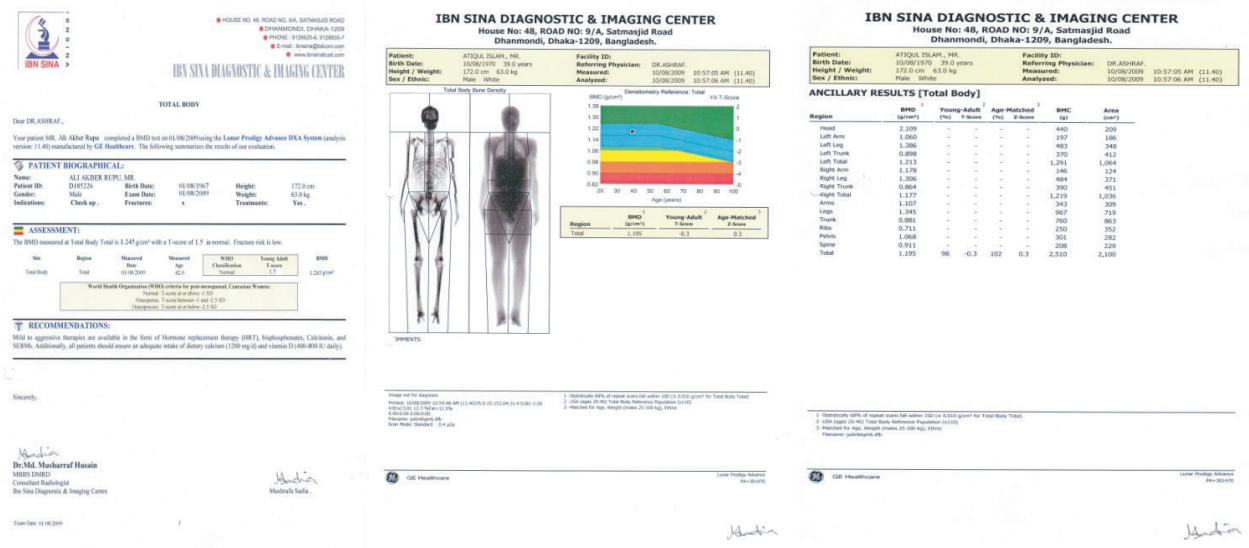

Fig.-3: *DEXA scan*

Table-III

Differences in Child Pugh Score and T score in DEXA scan

Child Pugh Score	T score in DEXA Scan			χ^2 value	df	P value
	Normal	Osteopenia	Osteoporosis			
Child Pugh B	4	3	0	1.677	2	0.432*
Child Pugh C	8	12	3			

Table-IV

Difference in BMD between Child's B and Child's C group of cirrhotic Patients

Child Pugh Score	BMD mean±SD	t	P value
Child Pugh B	1.17±8.87E-02	0.627	0.563
Child Pugh C	1.140±0.115		

Though all three osteoporotic cirrhotic patients were in child's pugh C class proportion of patients with normal, osteopenic and osteoporotic was not different between child's B and C (Table-3).

There is no significant difference in BMD between Child's B and Child's C (Table-4).

Among biochemical tests there is no significant difference in alkaline phosphatase, serum albumin, prothrombin time, serum creatinine among normal, osteopenic and osteoporotic group of cirrhotic patients. But serum bilirubin was found to differ significantly between these groups

The mean Child score of the normal, osteopenic, and osteoporotic groups was 2.67 ± 0.492, 2.80 ± 0.414, and 3.00±0.000, respectively.

Discussion:

Low bone mass and deterioration of bone tissue, leading to increased bone fragility and risk of fracture, are the defining characteristics of osteoporosis as well as osteopenia. In its early asymptomatic stage, osteopenia and osteoporosis can only be detected by measuring bone mineral density (BMD). Early detection of reduced BMD is an important means of prevention, and dual energy x-ray absorptiometry (DEXA) is the most helpful modality[10]. Until relatively recently, bone biopsies were the only way to identify the severity and cause of metabolic bone diseases. Indirect measurement of bone density with DEXA is the most precise technique (1% to 2% error is technician dependent). Dual-energy x-ray absorptiometry (DEXA) remains the gold standard for measurement of bone density. It is simple to perform, non invasive and widely available test[11]. It requires the least exposure to radiation (10 to 30 mSv) of any of the other methods that may be used to measure BMD, such as CT scan[12]. Fracture risk increases 1.5- to 3-fold or more for each standard deviation (SD) decrease in BMD from that of young adult (T score). Osteopenia is considered to be present when BMD is between -1 and -2.5 SD; osteoporosis is defined by the World Health organization (WHO) as BMD more than -2.5 SD below that of a young adult[1].

This study was carried out to see the relation of severity of hepatic cirrhosis with hepatic osteoporosis; we investigated thirty cirrhotic patients irrespective of etiology. The study also included thirty non liver disease persons as control. BMD were done in both groups to asses the bony changes. The cirrhosis patients were included without having any condition like any rheumatoid and other arthritic disease, chronic renal failure, chronic obstructive pulmonary disease, autoimmune hepatitis, obstructive jaundice. Patients on steroid therapy, prolonged bed ridden patients and post menopausal women were also excluded from the study.

Age is recognized as an independent risk factor for low BMD. So in our study the age range of all the patients as well as controls were 15-45 years. Among the patients of cirrhotic group 16 patients were above 36 years of age, 5 patients was in thirties, 9 patients was below 25 years of age. The mean age of cirrhotic group was (34.57±9.45) years. The highest incidence of cirrhosis patients were found at 36-45 age groups. The control patients were included without liver disease or having any condition that may cause osteoporosis. 15 patients were above 36 years of age, 10 patients were in thirties, 5 patients were below 25 years of age. Mean age of control group was (32.97±7.18) years. (Figure 1).

In this study, among cirrhosis patients male were 25 (83.3%) and female were 5 (16.7%). In control patients male were 20 (66.7%) and female were 10 (33.3%). There is male predominance 45 (75%) in the study population.

In this study, among 30 cirrhotic patients 7(23.33%) patients were in Child's group B and 23(76.67%) patients were in child's C. Among the 7 Child's B patients 4(57%) patients had normal BMD and 3(43%) patients had osteopenic BMD, no patient had

osteoporotic BMD. Among the 23 Child's C patients 8(34.8%) patients had normal BMD, 12(52.2%) patients had osteopenic BMD and 3(13%) patients had osteoporotic BMD.

In our study, mean BMD in Control patients was (Mean ± SD), 1.29 ± 9.62E-02 gm/cm^2, minimum BMD was 1.00 gm/cm^2 and maximum 1.38 gm/cm^2. Mean BMD in cirrhotic was (Mean ± SD), 1.14 ± 1.109 gm/cm^2, minimum BMD was 0.976 gm/cm^2 maximum 1.360 gm/cm^2. This difference is highly significant (P<0.05) and correlates with a study conducted by Diamond et al. in 1990, the study demonstrated a significant decrease in osteoblast surface and bone formation rate in chronic liver disease studied compared with that of normal controls[13].

In evaluation of patients according to WHO classification of osteoporosis we found that 60% of cirrhotic patients had decreased bone mineral density (10% had osteoporosis and 50% had osteopenia).Our figure is higher than the study conducted by Cristina Cijevschi et al. (2005), where they found 38% of cirrhotic patients have low BMD[14].

In our study we could demonstrate the increase in prevalence and severity of decreased bone mineral density with the liver dysfunction. In this study we found a significant positive correlation between serum albumin which was similar in previous study done by Alam El Dein R (2003)[15] and significant negative correlation between serum bilirubin level and BMD values which was similar in previous study done by Sevic Uretmen et al. (2005)[16].

In this study, DEXA was used to asses BMD of whole body. As age is recognized as an independent risk factor for low BMD, the use of other criteria rather than T-score can underestimate its prevalence, so the T-score was used in our study for evaluation of BMD disorder. In this study though osteoporosis was found in 3 patients and osteopenia was found in 12 patients in child's C class, and no osteoporosis but 3 patients with osteopenia in child's B, there is no significant differences in child pugh score and T score in DEXA scan (Normal, Osteopenia and osteoporosis) (P=0.432) or T score values (P=0.229).

Mean BMD of Child Pugh B is 11.17±8.87E-02 gm/cm^2 and mean BMD of Child Pugh C is 11.140±0.115 gm/cm^2. There is no significant difference in BMD between Child's B and Child's C. Our finding was similar to the study conducted Francisco J et al. 1998, where they found no significant differences between Child's B and Child's C. In a study conducted by Chen CC et al. 1996, found no differences in BMD of lumber spine in different Child Pugh group of cirrhotic patients[17].

Among the 30 cirrhotic patients 12 (40%) patient have normal T score in DEXA scan, 15 (50%) has got Osteopenia, and 3 (10%) are osteoporotic. (Figure10). There is statistically significant difference in T score between Cirrhotic group and control group. (P=0.000).

In this study no biochemical variables except serum bilirubin was found to differ significantly between the group of cirrhotic patients (normal, Osteopenic or Osteoporotic).Biochemical variables were alkaline phosphatase (P=0.360), prothrombin time (P=0.488), serum albumin (P=0.746), serum creatinine (P= 0.731), serum bilirubin (P= 0.047).

In this study we tried to see the correlation of severity of hepatic cirrhosis with bone changes measured by BMD. We can conclude that liver cirrhosis is a direct risk factor for the development of bone loss and there is a high prevalence of BMD disorders in cirrhotic patients. However no correlation was found between degree of hepatic dysfunction measured by Child Pugh score and severity of bone changes.

References

1. Bikle D. Osteoporosis in gastrointestinal, pancreatic, and hepatic diseases. In: Osteoporosis, Robert M (ed). Acad Press, Washington 2001: 237-258.
2. Rouillard S, Lane NE. Hepatic osteodystrophy. Hepatology. 2001; 33:301–307.
3. Riggs BL, Melton LJ 3rd. Involutional osteoporosis. N Engl J Med. 1986;314:1676–1679.
4. Bernstein CN, Leslie WD, Leboff MS. AGA technical review on osteoporosis in gastrointestinal diseases. Gastroenterology 2003; 124; 795-841.
5. Matloff DS, Kaplan MM, Neer RM, Goldberg MT, Bitman W, Wolfe HJ. Osteoporosis in primary biliary irrhosis: effects of 25-hydroxyvitamin D treatment. Gastroenterology 1982;83:97-102.
6. Brunader R, Shelton DK. Radiologic bone assessment in the evaluation of osteoporosis. Am Fam Physician 2002;65(7):1357-64.
7. Miller PD, Bonnick SL, Rosen C. Guidelines for the clinical utilization of bone mass measurement in the adult population. Society for clinical densitometry. Calcif Tissue Int 1995;57(4):251-2.
8. Pugh RN, Murray Lyon IM, Dawson JL, et al. Transection of the oesophagus for bleeding oesophageal arices. Br J Surg 1973;60(8):646-9.
9. Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. WHO technical report series 843. Geneva: WHO, 1994.
10. Jenny Heathcote. Osteoporosis in Chronic Liver Disease Current Gastroenterology Reports 1999, 1:455–458.
11. John C. Southerland and John F. Valentine Osteopenia and Osteoporosis in Gastrointestinal

Diseases: Diagnosis and Treatment. Current Gastroenterology Reports 2001, 3:399–407.

12. John Damilakis, Thomas G. Maris, Apostolos H. Karantanas. An update on the assessment of osteoporosis causing radiologic techniques. Eur Radiol (2007) 17: 1591–1602.
13. Diamond T, Stiel D, Lunzer M, Wilkinson M, Roche J, Posen S. Osteoporosis and skeletal fractures in chronic liver disease. Gut 1990; 31: 82-87.
14. Cristina Cijesvschi, Catalina Mihai, Eusebiu Zbranca, Petru Gogalniceanu. Osteoporosis in liver cirrhosis. Romanian Journal of Gastroenterology 2005; 14: 337-341.
15. Alam El, Dein R. Evaluation of bone mineral density in cirrhotic patients. Master degree thesis in internal medicine, Faculty of medicine, Ain Shams University, 2003: 75-103.
16. Sevinic Uretmen, Mert Gol, Dilek Cimrin, Esra Irmak. Effects of chronic liver disease on bone mineral density and bone metabolism markers in postmenopausal women. Eur Jour Obs & Gyne and Rep Bio 2005; 123: 67-71.
17. Chen CC, Wang SS, Jeng FS, Lee SD. Metabolic bone disease of liver cirrhosis: Is it parallel to the clinical severity of cirrhosis? J Gastroenterol Hepatol 1996; 11: 417-21.