ORIGINAL ARTICLE

Prevalence of Osteoporosis in Chronic Liver Disease (CLD) Patients in a Tertiary Care Hospital

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ABSTRACT

Background: Metabolic bone disease complicating chronic liver disease (CLD) has become a major clinical problem.

Methods: Our study was a prospective case control study included 70 cases and 70 controls. Patients with CLD falling in age group of 18 to 65 years constituted cases group. They were thoroughly examined and were subjected to baseline investigations including kidney function test, serum calcium levels, serum phosphorus levels, liver function test, complete blood count, lipid profile. All subjects were subjected to Dual Energy X-ray Absorptiometry (DEXA) Scan (GE Lunar-1 Co. Prototype).

Results: The prevalence of osteoporosis in our study at femur neck in the cases was 45.7% vs. 18% in the control group (p=0.001), while at L1-L2 it was 41.4% in cases vs. 15.7 %(p=0.001) in control group. No difference was found when both sites i.e. femur and L1-L2 were compared with each other (p=0.84, chi square of 0.33 in cases and p=0.58, chi square of 1.07 in case of controls).Prevalence of osteoporosis in our study in female cases and controls was higher than male counterparts both at femur and L1-L2. Peripheral DEXA and central DEXA had no difference in detecting osteoporosis among male and female sex.

Conclusion: CLD is an independent risk factor for osteoporosis, hence patients who are first time diagnosed CLD should be screened for osteoporosis with central or peripheral DEXA, and subsequently managed to prevent complications and morbidity associated with osteoporosis.

Key Words: Chronic liver disease (CLD), Osteoporosis, DEXA

INTRODUCTION

Osteoporosis is defined as a skeletal disorder characterized by compromised bone strength that leads to an increased risk of fracture.[1] It is a systemic disease of the skeleton, characterized by low bone mass and altered micro-architecture of bone tissue, with a consequent increase in bone fragility and susceptibility to fracture. There is a disintegration of the bone matrix with normal ratio of mineral to matrix.[2] Future projections indicate that the number of people with osteoporosis will increase exponentially during the first half of this century. Fractures represent the main clinical manifestation of osteoporosis. Half of all women over the age of 50 years will suffer an osteoporotic fracture during their lifetime. Moreover, the increased prevalence of osteoporosis at the hip is expected to lead to a tripling of the number of hip fractures worldwide by 2050.[3] The global burden of disease has been estimated at 1.75 million years, with approximately one-quarter occurring in China and India, and 50% occurring in Western countries alone.[4]

In 1939 a 69 year old woman with long-standing intrahepatic obstructive jaundice and spinal osteoporosis with vertebral compressions was described.[5] Since then it has been firmly established that chronic cholestasis, and also other forms of CLD, are associated with metabolic bone disease.[6-11]In the era of liver transplantation, metabolic bone disease complicating CLD has become a major clinical problem. Most histomorphometric studies have found osteoporosis in CLD to be of a low bone turnover type with reduced osteoblast function, and measurements of biochemical markers of bone metabolism, such as osteocalcin, have confirmed these findings .[12-15] The pathogenesis of osteoporosis in CLD is unknown. Advanced liver disease and cirrhosis are associated with an increased prevalence of osteoporosis.[16] The way in which liver failure affects osteoblast and contributes to the development of osteoporosis is unclear. Numerous growth factors, some of which affect osteoblast function, such as IGF-l and TGF are synthesized by the liver. Toxic substances, such as aluminum and copper, which accumulate in liver failure might also affect bone metabolism. In haemochromatosis an increased iron burden might impair osteoblastic ac-

tivity.[17-18] Bilirubin has been shown to inhibit osteoblast proliferation in vitro. [19-20] Whether cholestasis per se is a risk factor for osteoporosis in CLD is uncertain. We carried out our study to know the prevalence of osteoporosis in CLD patients and to compare it with age and sex matched controls and to assess the importance of CLD as an independent risk factor for osteoporosis.

METHODS

The present work is a hospital based prospective case control study that was carried out in the Department of Gastroenterology, Sher-i-Kashmir Institute of Medical Sciences, Srinagar INDIA , a 700 bedded tertiary care hospital in North India. Study was carried out from August 2014 to May 2016 our study included 70 cases and 70 controls. patients with Chronic Liver Disease (CLD) falling in age group of 18 to 65 years constituted cases group. Patients <18 years and >65 years of age, patients on steroids, post liver transplant patients, patients on bisphophonates, HRT, OCPs, Calcitonin, females with premature menopause or bilateral oopherectomy and pregnant patients were excluded from the cases group. The inclusion criteria for control group was age group of >18 years to 65 years, Non diabetic, non alcoholic, No evidence of secondary or surgical menopause,No evidence of secondary osteoporosis, No evidence of steroid intake, gonadotrophin use. Of 90 subjects initially taken as controls, only 70 fulfilled the criteria for controls and were enrolled for the study after due consent. Informed consent was taken from all subjects, and assent from the older subjects themselves, for participating in the study. Study was cleared by ethical clearance committee of Sheri Kashmir Institute Of Medical Sciences.

After proper consent, subjects with CLD were enquired about the history of related risk factors (smoking, hypertension, diabetes, steroid intake, surgical menopause) and their medical records were checked. Patients were considered active smokers if they had smoked at all during the last month; ex-smokers if they had ever smoked; and non-smokers if they had never smoked. They were thoroughly examined and were subjected to baseline investigations including kidney function test, serum calcium levels, serum phosphorus levels, liver function test, complete blood count, lipid profile. All subjects with CLD were subjected to Dual Energy X-ray Absorptiometry (DEXA) Scan (GE Lunar-1 Co. Prototype).The same methodology (consent, history, thorough examination) was done for the controls before subjecting them for DEXA scan.The DEXA definition of osteoporosis and the bone mass criteria followed for its diagnosis were adopted from the World Health Organization (WHO) definition of osteoporosis (1994). The WHO definition of osteoporosis has 2 clear and different components: The first is the BMD changes, which does not yield any information related to micro architectural changes. It is likely, though, that in the near future, new, sophisticated techniques such as quantitative micro-computed tomography (micro CT), high-resolution QCT and finite element analysis, so far not available for clinical practice, may help us to study, in the clinical setting, quality and micro architectural changes. The second component of the WHO definition of osteoporosis is the clinical consequence of having low bone mass and micro architectural deterioration, as represented by the bone fragility fracture, also called an osteoporotic fracture. The T-score was used for the evaluation of BMD and for the definition of the different stages of BMD according to the WHO definition of osteoporosis. Each T-score difference in BMD represents 1 SD from the peak bone mass.Osteoporosis was defined as T-Score of equal to or below -2.5 at femoral neck or L1L2 spine or both.

Data obtained were subjected to statistical analysis. The Categorical variables in the study have been shown in terms of frequency and percentages. The Pearson chi square test and Fisher exact test have been used to analyze the data. Continuous variables were analyzed by ANOVA technique. The statistical software SPSS version 20.0 has been used. P values less than 0.05 were considered to be statistically significant. Data obtained from case study were compared with controls.

RESULTS

Comparison of osteoporosis among cases and controls is shown in Table 1 and Table 2. Average BMD at femoral neck in cases stood at 0.88±0.085 g/m², while BMD at L1L2 spine measured at 0.96±0.087 g/m². There was no significant difference between the two sites as for as occurrence of osteoporosis is concerned in CLD patients (45.7% vs. 41.4%, p= 0.84, chi 0.33).The central DEXA at spine had no significant sensitivity in diagnosing osteoporosis in CLD patients over peripheral DEXA at femur neck. Among cases, at femur neck females formed a significant majority with osteoporosis. Prevalence of osteoporosis based on femoral neck T-Score was highest in Child class C.Prevalence of osteopenia was highest in Child class B.Study showed while DM is an important risk factor for CLD, it did not increase the risk for osteporosis. Comparable results were obtained from the study of L1L2 T-Score and diabetes.

There was no significant difference between the two sites as far as occurrence of osteoporosis is concerned in control group (18.6% vs. 15.7%, p= 0.58 chi 1.07).The central DEXA at spine had no significant sensitivity in diagnosing osteoporosis in controls over peripheral DEXA at femur neck.

Table 1: Comparison of prevalence of Osteoporosis in cases and controls

BMD Group	Femoral neck (cases)	Femoral neck (controls)	P value
Normal	11(15.7%)	38(54.3%)	**0.0001**
Osteoporosis	32(45.7%)	13(18.6%)	
Osteopenia	27(38.6%)	19(27.1%)	
	L1-L2 spine (cases)	**L1-L2 (controls)**	
Normal	13(18.6%)	44(62.9%)	
Osteoporosis	29(41.4%)	11(15.7%)	
Osteopenia	28(40.0%)	15(21.4%)	

Table 2: Comparison of sex distribution of osteoporosis among cases and controls

BMD Group	Femur neck (Cases)		P value	Femur neck (Controls)		P value
	Female	Male		Female	Male	
Normal	4(8.3%)	7(33.3%)	0.012	14(35%)	24(80%)	0.001
Osteoporosis	22(44.9%)	10(47.6%)		11(27.5%)	2(6.6%)	
Osteopenia	23(46.9%)	4(19.0%)		15(37.5%)	4(13.3%)	
	L1-L2 spine (cases)			**L1-L2 spine (Controls)**		
	Female	**Male**		**Female**	**Male**	
Normal	2(4.1%)	11(52.4%)	0.0001	18(45%)	26(86.6%	0.001
Osteoporosis	24(49%)	5(23.8%)		8(20%)	3(10%)	
Osteopenia	23(46.9%)	5(23.8%)		14(35%)	1(3.3%)	

The study showed, prevalence of osteoporosis in 45.7% cases in comparison to 18.6% in controls, taking T-Scores at femoral neck into account. While it was seen in 41.4% cases and 15.7% controls when T-scores at L1L2 were taken into consideration. The prevalence of osteoporosis was significantly high (p=0.0001) in CLD patients.Of all osteoporotic (45) subjects, i.e. cases and controls taken together, 32(71.1%) subjects had CLD and only 13(28.8%) subjects who were having osteoporosis were among non-CLD. The statistical significant difference with a p value 0.001, chi 11.82 was found between the two groups. The data showed that CLD is an important and an independent risk factor for osteoporosis. The reverse however is no true, osteoporosis had no impact on CLD.

DISCUSSION

In order to evaluate whether metabolic bone disease is more common in CLD than in the population it is necessary to compare the patient cohort with an age- and gender- matched population. By doing this, it was found that BMD was lower in a group of patients with CLD when compared with the controls.This reduction was statistically significant at the lumbar spine (p=0.001) as well as at femur neck (p=0.001) which is in accordance with previous reports on metabolic bone disease in CLD affecting mainly trabecular bone.[8,11]

The prevalence of osteoporosis in our study at femur neck in the cases was 45.7% vs. 18% at than in the control group (p=0.001), while at L1-L2 prevalence of osteoporosis in cases was 41.4% vs. 15.7 %(p=0.001) than in control group. In our study there was no difference found when both sites i.e. femur and L1-L2 were compared with each other (p=0.84, chi square of 0.33 in cases and p=0.58, chi square of 1.07 in case of controls).Prevalence of osteoporosis in our study in female cases and controls was higher than male counterparts both at femur and L1-L2.Prevalence at femur neck in female cases was 44.9% vs. 47.6% in males (p=0.012, chi 8.91) while as in controls it was 27.5% vs. 6.6 %(p=0.001, chi 14.09).Prevalence at L1-L2 in females case as compared to males was 49% vs. 23.8 % (p=0.0001, chi 22.67) while as in controls it was 20.6% vs. 10 %(p=0.001, chi 13.84).Peripheral DEXA and central DEXA had no difference in detecting osteoporosis among male and female sex. Loria et al did not found any difference in gender as far as prevalence of osteoporosis in CLD patient was concerned.[21] However, Wariaghli et al, Mounach et al and Sif Ormarsdóttir et al [22-24],found increased prevalence of osteoporosis in females with CLD.These differences in reported prevalence can probably be explained by different patient selection factors, different techniques of bone mass measurement and definition of osteoporosis. It was also found that high rate of osteoporosis occurred in patients classified as Child-Pugh B and C compared with the Child-Pugh A group. About 84.3% of patients having osteoporosis at femur belonged to Child-Pugh group C. This is supported by other studies that have found the highest prevalence of metabolic bone disease in patients with advanced liver disease whereas in earlier stages of liver disease no evidence of bone disease has been found. Collier et al found that alcoholics and those with more severe liver disease that is; Child Pugh class C patients

had the lowest BMD.[25] However studies conducted by Loria et al, Chen C-C et al, Ashraf-ul-alam et al and Hernán David et al found no statistically significant co relation between severity of liver disease and osteoporosis.[21,26-28]

Low BMI is a known risk factor for osteoporosis and increased rate of bone loss in the normal population as mentioned in The Framingham study conducted by Felson et al.[29] Sixteen (94.1%) of patients in our study with a low BMI of <18.5 had osteoporosis while as this number was only 3% in patients with BMI in the range of 18.5 to 25. This is supported by other studies as well. Angulo et al found that BMI <24 correlated with presence of osteoporosis in CLD patients. [30] Wariaghli et al revealed that lower weight and height but not BMI seems to play a predominant role in development of osteoporosis in CLD patients. [22] Sif Ormarsdóttir et al concluded that risk factors for osteoporosis in chronic liver disease were low body mass index and corticosteroid therapy, in addition to high age and female sex.[23] Malnutrition is common in CLD but the reported figures range from 15 to 100% in pre-transplant patients.[31-33] Reasons for low BMI in patients with CLD are probably multi-factorial including malnutrition resulting from malabsorption and anorexia, decreased physical activity and increased resting metabolic rate associated with progression of the liver disease. Using only BMI as a measure of nutrition, we probably underestimated the frequency of malnutrition. BMI is frequently used when evaluating nutritional status in patients with CLD, but somewhat imprecise as it is influenced e.g. by fluid retention in these patients.

Although there have been studies involving thousands of patients with osteoporosis, very few of these have included any patients with CLD. The study can be important tool in assessing the impact of CLD on prevalence of osteoporosis as an independent risk factor when compared to controls. All the patients were known cases of CLD admitted or following Gastroenterology OPD at SKIMS.

Majority (65.70%) of cases in this study belonged to Child-Pugh class C. The reason for this may be that patients in this part of the world seek medical attention only when the disease becomes advanced. Further osteoporosis was more prevalent in Child-Pugh class C patients in our study (58.7% at femur neck).This is evident in other observational studies which have also found that prevalence of osteoporosis is more in advanced Liver diseases

CONCLUSION:

Findings in our study imply that CLD is an independent risk factor for osteoporosis, hence patients who are first time diagnosed CLD should be screened for osteoporosis with central or peripheral DXA, and subsequently managed to prevent complications and morbidity associated with osteoporosis.

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Conflict of Interest: None.

REFERENCES

1. NIH Consensus Development Panel on Osteoporosis Prevention, Diagnosis, and Therapy. Osteoporosis prevention, diagnosis, and therapy. JAMA 2001; 285: 785–795.
2. Wilkin TJ.Changing perceptions in osteoporosis.BMJ 1999; 318: 862-65.
3. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. M Lancet 2002; 359: 1761–1767.
4. Johnell O, Kanis JA.An estimate of the worldwide prevalence, mortality and disability associated with hip fracture. Osteoporos Int 2004; 15: 897–902.
5. Loeper M, Lemaire A, Lesobre R. Spondylomalacie dans la cirrhose biliaire. Arch Mal Appar Dig 1939; 6: 577-87.
6. Sherlock S, Dooley J. London: BlackwellDiseases of the Liver and Biliary System, 9th Edn. Oxford; Blackwell Scientific Publications, 1993.
7. Stellon AJ, Davies A, Compston JE, Williams R.Bone loss in autoimmune chronic active hepatitis on maintenance corticosteroid therapy. Gastroenterology 1985; 89: 1078-83.
8. Bonkovsky HL, Hawkins M, Steinberg K, et al. Prevalence and prediction of osteopenia in chronic liver disease.Hepatology 1990; 12: 273-80.
9. Diamond T, Stiel D, Lunzer. Metabolic bone disease in primary biliary cirrhosis.Hepatology1990; 5: 66-81.
10. Diamond T, Stiel D, Lunzer M, et al Osteoporosis and skeletal fractures in chronic liver disease. Gut 1990; 31: 82-87.
11. Rose J, Compston JE, Crawley EO, Evans W, Evans C, Smith P.Osteoporosis associated with chronic liver disease.Eur J Gastroenterol Hepatol 1991; 3 : 63-69.
12. Hodgson SF, Dickson ER, Heinz WW, Johnson KA, Mann KG, Riggs BL (1985).Bone loss and reduced osteoblast function in primary biliary cirrhosis.Ann Intern Med 1985; 103: 855-60.
13. Stellon AJ, Webb A, Compston JE.Bone histomorphometry and structure in corticosteroid treated chronic active hepatitis.Gut 1988; 29: 378-84.
14. Pietschmann P, Resch H, Muller CH, Woloszczuk W .Decreased serum osteocalcin levels in patients with liver cirrhosis.Bone Miner 1990; 8:103-8.
15. Monegal A, Navasa M, Guanabens N, et al Osteoporosis and bone mineral metabolism disorders in cirrhotic patients referred for orthotopic liver transplantation. Calcif Tissue Int 1997; 60:148-54.

16. Tsuneoka K, Tameda Y, Takase K, Nakano T.Osteodystrophy in patients with chronic hepatitis and liver cirrhosis.Gastroenterol 1996; 31: 669-78.

17. De Vernejoul MC, Pointillart A, Golenzer CC, Morieux C, Bielakoff J, Modrowski D, Miravet L. Effects of iron overload on bone remodeling in pigs.Am J pathol 1984; 116: 377-84.

18. Diamond T, Stiel D, Posen S. Effects of testosterone and venesection on spinal and peripheral bone mineral in six hypogonadal men with hemochromatosis. J Bone Miner Res 1991; 6: 39-43.

19. Janes CH,Dickson ER,Okazaki R, Bonde S,McDonagh AF, and Riggs BL. Role of hyperbilirubinemia in the impairment of osteoblast proliferation associated with cholestatic jaundice.J Clin Invest 1995; 95: 2581-86.

20. Ormarsdóttir S, Jonsson KB, Ljunggren Ö, Lööf L.Toxic effects of unconjugated bilirubin on bone cells in culture.Scand J Gastroenterol 1996; 31 (suppl. 217):28.

21. Loria I, Albanese C, Giusto M, Galtieri PA, Giannelli V, Lucidi C,et al .Bone disorders in patients with chronic liver disease awaiting liver transplantation. Transplant Proc. 2010; 42:1191-3.

22. Wariaghli G, Mounach A, Achemlal L, Benbaghdadi I, Aouragh A, Bezza A et al.Osteoporosis in chronic liver disease: a case-control study Rheumatol Int. 2010; 30:893-9.

23. George J,Ganesh HK, Acharya S,Bandgar TR,Shivane V, Karvat A et al.Bone mineral density and disorders of mineral metabolism in chronic liver disease.World J Gastroenterol. 2009; 15:3516-22

24. Ormarsdóttir S, Ljunggren O, Mallmin H, Brahm H, Lööf L. Low body mass index and use of corticosteroids, but not cholestasis, are risk factors for osteoporosis in patients with chronic liver disease Journal of Hepatology 1999; 31: 84-90.

25. Collier JD,Ninkovic M, and Compston JE,.Guidelines on the management of osteoporosis associated with chronic liver disease,Gut 2002; 50: 1-9

26. 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

27. Alam MA, Ahmed N, Alam S,Mahtab MA. Study of correlation of severity of hepatic cirrhosis with severity of bone changes measured by BMD (bone mineral density) Bangladesh j medicine 2011; 22 : 41-46

28. García Botina HD,Ramírez NC.Osteoporosis in patients with chronic liver disease: an unfamiliar late complication Rev col gastroenterol 2011; 26 :286-95

29. Felson DT, Zhang Y, Hannan MT, Anderson JJ. Effects of weight and body mass index on bone mineral density in men and women: The Framingham study. J Bone Miner Res 1993; 8: 567-62.

30. ***Angulo P***, Grandison GA, Fong DG, Keach JC, Lindor KD, Bjornsson E et al.Bone disease in patients with primary sclerosing cholangitis. Gastroenterology. 2011; 140:180-8.

31. Merli M, Romiti A, Riggio O. Optimal nutritional indexes in chronic liver disease. J Parenter Enteral Nutr 1987; 11: 130S-134S.

32. DiCecco SR, Wieners EJ, Wiesner RH, Southorn PA, Plevak DJ, Krom RA. Assessment of nutritional status of patients with end-stage liver disease undergoing liver transplantation. Mayo Clin Proc 1989; 64: 95-102.

33. ***Wicks*** C, Esquivel CO, Van Thiel DH, Demetris AJ ***et al***. Nutritional assessment in primary biliary cirrhosis: The effect of disease severity. Clin Nutr 1995; 14: 29-34.