A cross-sectional study of chronic liver disease patients complicating to hepatic osteodystrophy

Mohammed Jaleel P.¹, S. Bhagyabati Devi¹, Ningthoukhongjam Reema¹*, Thangjam Gautam Singh², Dhileeban Maharajan P.¹

¹Department of Medicine, RIMS, Imphal, Manipur, India
²Department of Radiodiagnosis, Shija Hospital, Imphal, Manipur, India

Received: 20 April 2020
Accepted: 20 May 2020

*Correspondence:
Dr. Ningthoukhongjam Reema,
E-mail: thangjamreema@gmail.com

ABSTRACT

Background: Hepatic osteodystrophy encompasses the spectrum of metabolic bone diseases in chronic liver disease (CLD) patients. CLD causing changes in BMD is well known. Although BMD evaluation in CLD cirrhosis are recommended by societies of British and American gastroenterology, very less number of literature exist from India and none from the North-eastern region of India. Aim of the study to determine the association and severity of bone mineral density changes in patients with CLD and to correlate it with different aetiologies and severity of CLD.

Methods: This cross-sectional study which included 79 patients with CLD was conducted in RIMS, Manipur from September 2017 to August 2019. All CLD patients of age 18-60 years were included. DEXA scan and other related blood investigations were performed.

Results: Chronic alcohol intake (56.9%), viral infection (20.3%) and mixed (17.7%) were the main aetiology of CLD in our study. Seventy three (92.4%) of the total 79 patients had low BMD (Osteopenia in 29 (36.7%) and osteoporosis in 44 (55.7%) patients). Osteoporosis was detected in 53.4% of alcohol related Cirrhosis, 25% of viral liver disease. Majority of the severe CLD patients (Child class C) had osteoporosis (70.6%) as compared to less severe groups (23.5% and 36.4% in class B and A respectively).

Conclusions: CLD patients have high prevalence of osteoporosis. Severity of liver disease, alcoholic liver disease, serum calcium and vitamin D deficiency predisposes to osteoporosis in these patients. Hence early screening of BMD is necessary in CLD patients.

Keywords: Bone mineral density, Chronic liver disease, Hepatic osteodystrophy, Osteoporosis

INTRODUCTION

Liver disease is one of the major diseases affecting the Indian population. The mortality death rate in India population is 22 per 1 lakh according to WHO data.¹ Amongst the liver disease, Chronic liver diseases (CLD) shares the main burden of the disease. Chronic liver disease is characterised by ongoing inflammation in the liver for at least 6 months from any cause which may progress to cirrhosis and end-stage liver disease. Chronicity of liver disease is determined either by duration of liver disease for more than 6 months or by evidence of either severe liver disease or physical stigmata of Chronic liver disease.² ³ The etiologies of CLD are alcoholism, chronic viral hepatitis (hepatitis B and hepatitis C), autoimmune hepatitis, non-alcoholic steatohepatitis, biliary cirrhosis (primary biliary cirrhosis, primary sclerosing cholangitis, autoimmune cholangiopathy and cardiac cirrhosis), inherited metabolic liver disease (hemochromatosis, Wilson’s disease, α-1 antitrypsin deficiency and cystic fibrosis) and cryptogenic cirrhosis.⁴
Chronic liver disease may result in complications including portal hypertension, variceal bleeding, ascites, spontaneous bacterial peritonitis, hepatic encephalopathy, hepato-pulmonary syndrome and hepato-renal syndrome. Alteration in bone metabolism is a less recognized chronic complication of liver disease which is defined under the generic term hepatic osteodystrophy.³ Hepatic osteodystrophy (HO) manifest as osteopenia, osteoporosis and osteomalacia.⁴ In west, prevalence rate of HO ranges from 13-70% and in India 68 and 95%.⁷,⁸ Stronger association between cirrhosis and osteoporosis than between cirrhosis and osteomalacia is found. Decreased Bone mineral density (BMD) in form of osteopenia and osteoporosis is significantly associated with CLD in many of the western literature. Moreover, subsequent fracture rate of 3% to 44% is also reported.¹¹ Early screening of osteoporosis in patients with CLD is essential as advanced hepatic osteodystrophy adversely affect both the quality of life and long-term prognosis of CLD patients. As HO remains under diagnosed and undertreated complication, establishing this intricate relationship will help to improve outcome with timely intervention for HO. This association has not been studied extensively in the Indian population.¹⁰ Therefore, this study was performed to see the correlation of hepatic osteodystrophy with the risk factors of CLD in this part of the country.

Aims and objectives of the study is to determine the association and severity of reduced BMD in patients with Chronic liver disease and to determine the correlation of hepatic osteodystrophy with different etiologies and severity of Chronic liver disease

METHODS

This cross sectional study was conducted over a period of 2 years from September 2017 to August 2019. Seventy nine patients diagnosed with Chronic Liver Disease with ages upto 60 years were included in the study. Cases included patients with chronic liver disease admitted to medicine ward and attended Medicine OPD, RIMS Imphal. Ultrasound whole abdomen to confirm the diagnosis was performed. DEXA scan of lumbar spine (L1-L4) and bilateral femur were taken using “Lunar Prodigy advance Direct-Digital Densitometry”. Patients with thyroid or parathyroid disorders, renal failure or malignancy were not included. Those who were on medications like corticosteroids; oestrogens, calcitonin, bisphosphonates, anticonvulsants, anticoagulants and sodium fluoride were also excluded. Ethical clearance for the study was taken from the Research Ethics Board, RIMS Imphal.

Bone mineral density was expressed in terms of T-score. The World Health Organization has defined reduced BMD in to two categories. Osteoporosis is characterised by BMD less than -2.5 standard deviations of the mean BMD of a sex matched, young healthy population, i.e, a T score less than <-2.5. Osteopenia is defined as bone loss with a T score between -1 and -2.5.¹² Serum vitamin D- ELISA reader (Multiskan) at wave length 450nm using ELISA Kit was used for vitamin D level estimation. For the purpose of analysis, 25 (OH) vitamin D concentrations were categorized based on K/DOQI. Vitamin D level above 30ng/ml was taken as optimal level. Levels between 20 and 30 ng/ml was considered as insufficient and a value less than 20ng/ml as vitamin D deficiency.¹³

Statistical analysis

Statistical analysis was done by IBM SPSS Statistics Data Editor 21.0. Descriptive statistics such as Mean±SD, frequency and percentages were used for analysis. Analysis of variance (ANOVA), student t test (two tailed, independent and Chi-square/ Fisher Exact test have been used to find the significance of study parameters. A p-value of <0.05 was considered statistically significant.

RESULTS

The present cross-sectional study conducted in RIMS for 2 years duration consisted of 79 patients diagnosed to have Chronic Liver Disease with age 18 years - 60 years. The mean age of the participants was 45.77±7.77 years with majority of them over 41-50 years (40.5%). Majority of the subjects were males (87.3%) while the female constituted 12.7%. More than two-third of the patients were having significant alcohol intake (75.9%) followed by smokers (26.6%). Diabetes (13.9%) and Hypertension (15.2%). Pedal edema was the most common complaint (77.2%) followed by jaundice (64.6%), altered sleep pattern (57%) and malena (50.6%) (Table 1). Majority had Ascitis (in 75.9% patients) followed by Acute hepatitis (in 70.9%), Hepatic encephalopathy (in 62%) and Upper gastrointestinal bleed (in 50.6%), shown in Figure 1.

All the CLD patients were anemic (mean haemoglobin 8.78(g/dl) with low serum albumin level (2.57±0.58) and higher Mean serum bilirubin level (was 5.63 mg/dl with standard deviation 5.89), (T-score values.

| June 2020 | Vol 7 | Issue 6 | Page 1014 |

International Journal of Advances in Medicine |
significant (p-value <0.001). All the 3 patients with non-alcoholic steatohepatitis (NASH) had osteoporosis and there was only one autoimmune hepatitis patient in the study group who was non-osteoporotic (Table 3). Majority of the patients (64.6%) were brought to hospital with Child Pugh class C, rest others are class B (21.5%) and class A (13.9%). More than two-third from severe liver disease patients were having osteoporosis (70.6%) compared to less than half in less severe groups and is statistically significant (p-value = 0.001), (Table 4). Vitamin D deficiency was present in 95.5% of the patients with osteoporosis and its association is statistically significant (Table 5).

Table 1: Distribution of Clinical symptoms of patients studied (N=79).

| Presenting complaints       | Frequency* | Percentage |
|-----------------------------|------------|------------|
| Pedal edema                 | 61         | 77.2       |
| Jaundice                    | 51         | 64.6       |
| Altered sleep pattern       | 45         | 57.0       |
| Malena                      | 40         | 50.6       |
| Constipation                | 34         | 43.0       |
| Hematemesis                 | 29         | 36.7       |
| Altered behavior            | 22         | 27.8       |
| Abdominal discomfort         | 18         | 22.8       |
| Breathlessness              | 12         | 15.2       |
| Decreased urine output      | 11         | 13.9       |
| Fever                       | 10         | 12.7       |
*Multiple answers were allowed

Pedal edema was the most common complaint (77.2%) in this study population followed by jaundice (64.6%), altered sleep pattern (57%) and malena (50.6%).

![Figure 1: Presenting symptoms of CLD Subjects.](image)

Majority had ascitis (in 75.9% patients) followed by acute hepatitis (in 70.9%), Hepatic encephalopathy (in 62%) and Upper gastrointestinal bleed (in 50.6%).

Table 2: Comparison of hematological parameters in relation to Osteoporosis (N=79).

| Hematological parameters (unit) | Bone mineral density, mean±sd | No osteoporosis group | Osteoporosis group | p value |
|---------------------------------|--------------------------------|-----------------------|--------------------|---------|
|                                 | Mean ±sd                        |                       |                    |         |
| Hemoglobin (g/dl)               | 8.78±1.96                       | 8.90±1.89             | 8.69±2.03          | 0.644   |
| Leucocyte count (per mm$^3$)    | 8504.81±2725.53                 | 7885.43±4016.38       | 8997.50±4449.40    | 0.253   |
| Platelet count (lakhs/ mm$^3$)  | 1.58±0.76                       | 1.67±0.67             | 1.51±0.82          | 0.364   |
| Random blood sugar (mg/dl)      | 128.28±40.07                    | 124.66±33.66          | 131.16±44.69       | 0.477   |
| Serum albumin (mg/dl)           | 2.57±0.58                       | 2.77±0.60             | 2.41±0.52          | 0.005*  |
| Total bilirubin (mg/dl)         | 5.63±5.89                       | 5.22±5.58             | 5.96±6.17          | 0.584   |
| Aspartate aminotransferase (IU/l)| 127.04±105.30                  | 105.60±58.58          | 144.09±129.34      | 0.107   |
| Alanine aminotransferase (IU/l) | 94.46±78.68                     | 95.49±93.04           | 93.64±66.21        | 0.918   |
| Alkaline phosphatase (IU/l)     | 278.87±134.4                    | 239.94±115.71         | 309.84±141.29      | 0.021*  |
| γ glutamyl tranpeptidase (IU/l) | 194.05±243.7                    | 188.69±271.62         | 198.32±222.14      | 0.863   |
| Urea (mg/dl)                    | 32.39±21.13                     | 28.66±15.80           | 35.36±24.34        | 0.163   |
| Creatinine (mg/dl)              | 1.23±0.62                       | 1.16±0.43             | 1.29±0.74          | 0.373   |
| Sodium (meq/l)                  | 133.70±4.15                     | 134±3.71              | 133.45±4.5         | 0.565   |
| Potassium (meq/l)               | 4.14±0.60                       | 4.23±0.51             | 4.06±0.66          | 0.222   |
| Calcium (mg/dl)                 | 8.35±0.58                       | 8.69±0.57             | 8.08±0.43          | <0.001* |
| Prothrombin time (sec)          | 18.88±3.90                      | 19.34±4.17            | 18.51±3.67         | 0.352   |
| International normalized ratio  | 1.59±0.31                       | 1.55±0.26             | 1.62±0.34          | 0.304   |
| Vitamin d level (ng/ml)         | 19.82±7.47                      | 26.26±6.13            | 14.69±3.28         | <0.001* |

Asterix* indicates Statistically significant
All the CLD patients were anemic (mean hemoglobin 8.78g/dl) with low serum albumin level (2.57±0.58) and higher Mean serum bilirubin level (was 5.63mg/dl with standard deviation 5.89).

Most of them had low serum vitamin D level (19.82±7.47).

Figure 2: Distribution of patients by categories of Bone Mineral Density (N=79).

73 (92.4%) of the total 79 patients were having low Bone Mineral Density (osteopenia (36.7%) and osteoporosis (55.7%).)

More than two-third of severe (child class C) liver disease patients had osteoporosis (70.6%) (Statistically significant, p-value = 0.001).

In Table 5 distribution of Vitamin D categories in relation to Osteoporosis (N=79): 95.5% of the patients with osteoporosis had deficient Vitamin D.

Table 5: Distribution of vitamin D categories in relation to Osteoporosis (N=79).

| Vitamin D levels | Bone Mineral Density, n (%) | P-value |
|------------------|-----------------------------|---------|
| Deficiency       | 2 (5.7)                     | 42 (95.5) | <0.001 |
| Insufficient     | 25 (71.4)                   | 2 (4.5)  |         |
| Sufficient       | 8 (22.9)                    | 0 (0)    |         |

DISCUSSION

Hepatic Osteodystrophy (HO) is the generic term representing alterations in bone mineral metabolism in chronic liver disease patients. Multiple pathophysiological basis are being suggested. Chronic inflammation and decompensated liver or cirrhosis in CLD induced by different etiological agents may be the potential mechanism. Firstly, OPG/RANKL ratio is high in CLD induced by different etiological agents may be the potential mechanism. Secondly, Increased tumour necrosis factor -alpha (TNF-α) and Interlukin (IL-6) levels and decreased Insulin-like growing factor -1 (IGF-1) level in patients with cirrhosis may contribute to the development of hepatic osteodystrophy. Chronic liver disease leads to hyperbilirubinemia, hypogonadism, deficient 25 hydroxy -vitD3, and deficient Vit K. In advanced liver disease, 25-hydroxylation in the liver tissue is impaired leading to Vitamin D deficiency .This deficiency causes secondary hyperparathyroidism which in turn increases bone turnover and bone mineral lost. Vitamin k helps in formation of osteocalcin which is the main bone matrix protein. Its deficiency leads to osteopenia. Most common type of CLD in Northeastern India is Alcoholic liver disease. Alcohol inhibit changes in carboxy-terminal propeptide of type I procollagen,a protein representing synthesis of type-I collagen which is required in bone metabolism. Osteocalcin formation is also decreased by alcohol.

In this study, chronic alcohol intake was the main cause of liver disease (56.9%) followed by viral infection (20.3%), and mixed etiology - Alcoholic and viral (17.7 %). Similar findings were reported from various other study parts of India also. Sharma et al, reported 62.9% as alcohol related from 178 CLD patients from North India. Seventy percentage were alcohol related in entire liver diseases in a study conducted by Perme et al, in North-East India which was followed by viral etiology in 29%. Similar alcohol predominance is reported by Ray in Eastern India.
Seventy three (92.4%) of the total 79 patients were having low bone mineral density in which 36.7% were having osteopenia and remaining 55.7% were having osteoporosis. Similar findings of increased frequency of osteoporosis were found in case control study by Arora et al, with 42% had osteoporosis as compared to 20% in control. Four patients (5.1%) from osteoporotic group had skeletal fractures and were regrouped into severe osteoporosis. Even though frequency of osteoporosis was more in the age group of 51-60 years this observation was not statistically significant. There was no statistically significant gender association with frequency of osteoporosis.

Osteoporosis occurrence was more in alcohol related cirrhosis as compared with viral liver disease with p-value <0.001. Number of patient detected to have osteoporosis were 24 of alcoholic etiology and 13 from combined alcoholism with viral hepatitis etiology.

But further association with etiology of liver disease could not be studied as patients with NASH and autoimmune hepatitis were less in number.

Nearly two third of patients (64.6%) were in severe group as per Child Pugh score. Only 13.9% were from Child class A. More than two-third from severe liver disease (Child Pugh score C) patients were having osteoporosis (70.6%) compared to less than half in less severe groups and is statistically significant (p-value=0.001). These findings were correlating with the study of Monegal et al, where they established association of low BMD with severity and etiology of the CLD. Further they reported that alcoholic and Child Pugh score C patients were having lowest BMD values. Nicoll et al, reported only 19% with osteoporosis in 252 cirrhotic patients. This may be because majority of patients were in good prognostic group (87.4% in Child Pugh class A) and alcohol related cirrhosis was only 33.3% in that study. Patil et al, and Diamond et al, reported association between osteoporosis and severity of Liver disease in their studies. Both of these studies failed to find out the association with etiology of liver disease. Arora et al, also reported this association with severity of Liver diseases. On the irony, Loria et al, reported that there is no association between osteoporosis and severity of liver disease. This may be because of the smaller sample size (35) of the study.

Vitamin D deficiency also was common and was there in 95.5% of the patients with osteoporosis and had statistically significant association with BMD. Only 22.9% of the entire sample population had sufficient serum vitamin D level. Karoli et al, also had reported the significant association between osteoporosis and vitamin D level. Low levels of vitamin D in cirrhotic patients as compared to control group were reported by Monegal et al, also in his study. Serum calcium level was generally low (8.35±0.58) in the study population. Statistically significant association was there between calcium level and osteoporosis.

Limitation of the study is first, small sample size of the study may not show exact scenario of the community. Second, cross sectional design of the study limited extension of interpretation to the causality of associations. Third, all the patient included were from same centre and hence selection bias could not be excluded. Despite these limitations, this study had the advantage of being the first study evaluating bone health in cirrhotic patients in North East India where there is high prevalence of liver cirrhosis.

CONCLUSION

Chronic liver disease is associated with decreased BMD, more so with alcohol etiology. Severity of liver disease was statistically associated with BMD reduction. Other contributing factors include smoking, hypertension, hypoalbuminemia, vitamin D and calcium deficiencies. Hepatic Osteodystrophy is one of the important complications of CLD, hence screening for BMD is highly recommended in all cirrhotic patients.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: The study was approved by the Institutional Ethics Committee

REFERENCES

1. World Health Rankings. World Health Organization 2017. Available at: http://www.worldlifeexpectancy.com/india-liver-disease. Accessed on 10 July 2018.
2. Tahir A, Malik RF, Ahmad I, Krishin J, Akhtar P. Aetiological factors of chronic liver disease in children. J Ayub Med Coll Abbottabad. 2011;23(2):12-4.
3. Angulo P, Machado MV, Diehl AM. Fibrosis in nonalcoholic fatty liver disease: Mechanisms and clinical implications. Semin Liver Dis. 2015;2(1):132-45.
4. Sudeshana M, Kunukum S, Mehebub R, Soumendra NH. Clinical and etiological study on chronic liver diseases. Int J Contemp Medi Surg Radiol. 2018;3(2):77-80.
5. Nakchbandi IA, van der Merwe SW. Current understanding of osteoporosis associated with liver disease. Nat Rev Gastroenteral Hepatol. 2009;6(11):660-70.
6. Dempster DW, Lindsay R. Pathogenesis of osteoporosis. Lancet. 1993;341(1):797-801.
7. Hay JE. Osteoporosis in liver diseases and after liver transplantation. J Hepatol. 2003;38:856-65.
8. Rouillard S, Lane NE. Hepatic osteodystrophy. Hepatology. 2001;33:301-07.
9. 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(28):3516-22.
10. Sachdev S, Bhasin RC, Kumari CK, Reys M. A study of metabolic bone disorder in cirrhosis liver. J Assoc Physic Ind. 1976;24:5-11.
11. Hay JE, Guichelaar MM. Evaluation and management of osteoporosis in liver disease. Clin Liver Dis. 2005;9(1):747-66.
12. Guarino M, Loperto I, Camera S, Cossiga V, Di Somma C, Colao A, et al. Osteoporosis across chronic liver disease. Osteopor Int. 2016;27(6):1967-77.
13. Ringe JD, Kipshoven C. Vitamin D-insufficiency: An estimate of the situation in Germany. Dermatoendocrinol. 2012;4(1):72-80.
14. Huang Z, Wei H, Cheng C, Yang S, Wang J, Liu X. Low bone mineral density in chronic hepatitis B virus infection: A case-control study. Pak J Med Sci. 2017;33(2):457-61.
15. Moschen AR, Kaser A, Stadlmann S, Millonig G, Kaser S, Mühlechner P, et al. The RANKL/OPG system and bone mineral density in patients with chronic liver disease. J Hepatol. 2005;43:973-83.
16. Szalay F, Hegedus D, Lakatos PL, Tornai I, Bajnok E, Dunkel K, et al. High serum osteoprotegerin and low RANKL in primary biliary cirrhosis. J Hepatol. 2003;38:395-400.
17. González-Calvin JL, Mundi JL, Casado-Caballero FJ, Abadía AC, Martín-ibañez JJ. Bone mineral density and serum levels of soluble tumor necrosis factors, estradiol, and osteoprotegerin in postmenopausal women with cirrhosis after viral hepatitis. J Clin Endocrinol Metab. 2009;94:4844-50.
18. López-Larramona G, Lucendo AJ, González-Castillo S, Tenias JM. Hepatic osteodystrophy: An important matter for consideration in chronic liver disease. World J Hepatol. 2011;3(12):300-07.
19. Mukherjee PS, Vishnubhatla S, Amarapurkar DN. Etiology and mode of presentation of chronic liver diseases in India: A multi centric study. PLoS One. 2017;12(10):e0187033.
20. Berg KM, Kunins HV, Jackson JL, et al. Association between alcohol consumption and both osteoporotic fracture and bone density. Am J Med. 2008;121:406-18.
21. Sharma B, Marwaha R, Raina S, Sharma N. Etiological profile of cirrhosis in a hilly state of North India. J Clin Exp Hepatol. 2015;5(1):46-9.
22. Perme O, Singh YI, Singh KR, Devi BS, Rao A, Singh SK. Prevalence of diabetes in chronic liver disease patient admitted in medicine ward in RIMS Hospital, Imphal. J Med Soc. 2016;30(2):84-8.
23. Ray G. Trends of chronic liver disease in a tertiary care referral hospital in Eastern India. Ind J Pub Health. 2014;58(3):186-9.
24. Arora AC, Manocha RG, Prasad S. Hepatic osteodystrophy: A study of the prevalence of osteoporosis in cirrhosis of liver and its correlation with severity of liver disease. Ind Assoc Clin Medi. 2017;18(1):36-9.
25. Monegal A, Navasa M, Guanabens N, Peris P, Pons F, Martinez OMJ, et al. Osteoporosis and bone mineral metabolism disorders in cirrhotic patients referred for orthotopic liver transplantation. Calcif Tissue Int. 1997;60(2):148-54.
26. Nicoll R, Black A, Bailey L, Dundas P, McMellan L, Vijayan B, et al. Fracture risk calculation tool enhances dual-energy X-ray absorptiometry scan referral pathway in cirrhosis patients. Eur J Gastroenterol Hepatol. 2016;28(7):757-61.
27. Patil S, Nagarajan K, Vadukot M, Nair H. Hepatic Osteodystrophy: Prevalence and correlation with aetiology and functional class. Clin Exp Hepatol. 2015;5(2):40-5.
28. Diamond TH, Stiel D, Lunzer M, McDowall D, Eckstein RP, Posen S. Hepatic osteodystrophy: static and dynamic bone histomorphometry and serum bone Gla-protein in 80 patients with chronic liver disease. Gastroenterology. 1989;96(1):213-21.
29. Loria I, Albanese C, Giusto M, Galtieri PA. Bone disorders in patients with chronic liver disease awaiting liver transplantation. Transplant Proc 2010;42(4):1191-3.
30. Karoli Y, Karoli R, Fatima J, Manhar M. Study of Hepatic osteodystrophy in Patients with Chronic liver disease. J Clin Diagn Res. 2016;10(8):31-4.