Assessment of Bone Mineral Density in Nonalcoholic Steatohepatitis Cirrhosis

[1]Afroza Begum, [2]Sadia Sultana, [3]Shahnaz Begum and [2]Pupree Mutsuddy

[1]Hepatology Deparment, Bangabandhu Sheikh Mujib Medical University, Dhaka

[2]National Institute of Nuclear Medicine & Allied Sciences, Dhaka

[3]Physiology Department, Uttara Adhunik Medical Colloege, Uttara, Dhaka

Correspondence Address: Afroza Begum, M. Phil (Nuclear Medicine), Hepatology Department, Block-D, BSMMU, Dhaka.
Email: afrozazarif@yahoo.com

ABSTRACT

Objective: **Cirrhosis is characterized by diffused hepatic fibrosis and nodule formation that can occur at any age. It has significant morbidity and mortality. Worldwide common causes of cirrhosis are viral hepatitis (hepatitis B virus and hepatitis C virus), prolonged excessive alcohol intake and nonalcoholic fatty liver disease (NAFLD). Progression of chronic liver disease (CLD) and deterioration of liver function are associated with various hepatic complications. Hepatic osteodystrophy is an important extrahepatic manifestation of advanced liver disease with features of classical osteoporosis and an increased risk for fractures. The objective of the study to assess the bone mineral density (BMD) by duel energy x-ray absorptiometry (DEXA) in patients with nonalcoholic steatohepatitis (NASH) cirrhosis of liver.**

Patients and Methods: **A cross sectional observational study was carried out at National Institute of Nuclear Medicine and Allied Sciences (NINMAS), Bangabandhu Sheikh Mujib Medical University (BSMMU) campus, Dhaka, from July, 2016 to June, 2017. This study included the diagnosed cases of NASH cirrhosis patients presented at outpatient or inpatient department of Hepatology of BSMMU. For measurement of the BMD dual energy x-ray absorptiometry (DEXA) scan was performed by DMS Strator DR Bone densitometer at NINMAS. BMD were measured at lumbar vertebrae L1-L4 and both the femoral neck. Analysis of data from DEXA was computerized and completely automated (software 3DXA, Medix DR.)**

Results: **A total of 54 participants was included and among them 27 were cirrhotic patients (cirrhotic group) & 27 were non-cirrhotic patients with healthy liver (non-cirrhotic group). The age range of the patients was 40-70 years in both groups. Male to female ratio was 1:1.45. The mean age was 56.3 ± 6.7 years in cirrhotic group and 55.0 ± 6.3 years in non cirrhotic group. In cirrhotic group, 22 (66.7%) patients had low BMD and five (23.8%) patients had normal BMD. In non-cirrhotic group, 11 (33.3%) patients had low BMD and 16 (76.2%) patients had normal BMD. The difference was statistically significant ($p < 0.05$) between two groups. Multivariate logistic regression analysis was done to see the effect of multiple independent variables (age, menopause and cirrhosis) on dependent variable (low BMD). In cirrhotic patients odds ratio (OR) was 1.961 (95% CI 0.110 to 25.893) which implies cirrhotic patients had 1.961 times greater chance to develop low BMD than non cirrhotic patients keeping all other factors in fixed level.**

Conclusion: **Hepatic osteodystrophy is an important extrahepatic complication of cirrhosis. NASH cirrhosis is found among elderly people and female. Osteoporosis is common in aged people and menopausal female. But in this study it was observed that a NASH cirrhotic patient is highly significant risk factor for low BMD (osteopenia and osteoporosis) other than aged persons and menopausal females. So, special measures and monitoring should be taken regarding osteoporosis in NASH cirrhotic patient to reduce subsequent morbidity.**

Keywords: **Nonalcoholic steatohepatitis (NASH) cirrhosis, Bone mineral density (BMD) and Duel energy x-ray absorptiometry (DEXA).**

INTRODUCTION

Cirrhosis is defined anatomically as a diffuse with fibrosis and nodule formation in liver. Other than various hepatic complications, progression of chronic liver disease (CLD) and deterioration of liver function are also associated with hepatic osteodytrophy and features of classical osteoporosis which is an important extrahepatic manifestation of advanced liver disease (1,2).

NAFLD was the third most common liver disease after chronic HCV infection and alcoholic liver disease in United States of America (3). NAFLD is a broad term consisting of patient with simple hepatic steatosis, nonalcoholic steatohepatitis (NASH), NASH-related cirrhosis and NASH related hepatocellular carcinoma (HCC). It is strongly associated with insulin resistance and other component of the metabolic syndrome like type-2 diabetes mellitus (DM), central obesity, dyslipidemia and hypertension (4).

Chronic hepatitis B infection and its complications were the predominant liver disease in Asian region. But now-a-days, with the increasing prevalence of obesity, diabetes and metabolic syndrome in the general population, NAFLD has become the most common cause of chronic liver disease in regions of Asia (5). The estimated prevalence of NAFLD is 20-30% and NASH is 3.5-5% (6). Average age for development NASH is 40-50 years and NASH related cirrhosis is 50-60 years. Recently in a study it has been revealed that NAFLD is more prevalent in female among Bangladeshi population and prevalence of NASH in Bangladesh was 42.4% in NAFLD which is much higher (4).

Osteoporosis in CLD mainly affects trabecular bone and has been characterized by low bone turnover with reduced osteoblast function and low serum osteocalcin levels (7). According to Choudhury et al. the prevalence of hepatic osteodystrophy was 97% in alcoholic cirrhosis and 93.7% in viral cirrhosis (8). Bone mineral densitometry (BMD) is the single best approach for establishing the diagnosis of osteoporosis, detecting low bone mass before the disease develops (osteopenia) and for predicting risk for future fracture, compared to the conventional plain x-rays which can reveal osteoporosis only after 30% bone has been lost (9). There are various techniques for determining BMD but the areal bone mineral density (a BMD in gram per square centimeter) from proximal femur obtained by dual energy x-ray absorptiometry (DEXA) still remains the gold standard and this is also promulgated by the World Health Organization (WHO) guidelines for diagnosis of bone fragility. DEXA is a non-invasive, short scan time, low radiation dose (1-10 μSv), high precision and stable calibration technique (10).

Since 1994, WHO study group recommended a definition of osteoporosis and osteopenia that was based on a BMD measurement of spine, hip or forearm expressed as T-scores. The T-scores is defined as the number of standard deviation (SD) above or below the mean bone mineral density of young healthy adult of 25-35 years of age, matched for gender and ethnic group. According to them, a T-score -1 or greater is regarded as healthy bone, a T-score between -2.5 and -1 is classified as osteopenia and a T-score -2.5 or less as osteoporosis. A forth category of 'established osteoporosis' was proposed to denote osteoporosis associated with presence of one or more documented fragility fractures usually of wrist, spine or hip (11). A decreased in T-scores by 1 unit increased fractures risk by a factor of 2.5 (10).

Recently prevalence of NASH has increased in Bangladesh which may turn into cirrhosis. Patients with NASH cirrhosis are relatively older in comparison to other cirrhosis. NASH cirrhosis is usually associated with diabetes mellitus, dyslipidemia, central obesity and hypertension. This has now changed with increasing obesity and diabetes mellitus due to economic prosperity, socio-demographics and life style changes. For this reason NASH cirrhosis patients are more prone to developed hepatic bone disease. This study is expected to be beneficial to find out the extent of bone loss in NASH cirrhosis so that appropriate measures can be taken to avoid risk of fracture.

PATIENTS AND METHODS

The observational study was carried out in NINMAS, Dhaka from July 2016 to June 2017. The population was the diagnosed cases of cirrhosis of liver due to NASH attending outpatient or inpatient department of Hepatology, BSMMU. Similar number of age and sex matched patients without cirrhosis of liver was also selected i.e. 27 patients had cirrhosis (cirrhotic group) and 27 participants had healthy liver (non cirrhotic group). All the patients and the participants were informed about the procedure, benefit and written consent had been taken. The exclusion criteria included: a) cirrhosis of liver due to other etiologies e.g., viral cirrhosis, alcoholic cirrhosis etc. b) CLD with co-existing HCC, patients having chronic kidney disease (CKD), chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, hyperthyroidism, hyperparathyroidism and malignancy c) Patients receiving drugs e.g. steroid, methotrexate or any drugs known to affect bone density and d) prolonged bed ridden patients.

BMD of NASH cirrhosis patients (cirrhotic group) and without cirrhosis patients (non cirrhotic group) was performed by Stratos DR Bone densitometer. BMD was measured at lumbar vertebrae L1-L4 and femoral neck. Analysis of data from DEXA was computerized and completely automated (software 3DXA, Medix DR.) After getting the BMD report, enrolled subjects had been divided into 2 groups: normal BMD and low BMD.

Statistical analyses were carried out by using the Statistical Package for Social Sciences version 23.0 for Windows (SPSS Inc., Chicago, Illinois, USA). The mean values were calculated for continuous variables. The quantitative observations were indicated by frequencies and percentages. Chi-square test was used to analyze the categorical variables, shown with cross tabulation. Multivariate logistic regression analysis was done to analyze the effect of independent variable (age, menopause and cirrhosis) on dependent variable (low BMD). p values <0.05 was considered as statistically significant.

RESULTS

In both cirrhotic and non cirrhotic groups, majority (63.0%) of the patients belonged to age 51 to 60 years. The mean age was found 56.3 ± 6.7 years in cirrhotic group and 55.0 ± 6.3 years in non cirrhotic group. In both groups, female preponderance was seen i.e. 59.3% of the patients were female in study population and male to female ratio was 1:1.45.

Table 1 shows distribution of BMD in cirrhotic and non cirrhotic groups. It was observed that 66.7% patients had low BMD in cirrhotic group and 33.3% patients had low BMD in non cirrhotic group. The difference was statistically significant (p <0.05) between two groups.

Table 1: Distribution of BMD in cirrhotic and non cirrhotic group (n=54)

	BMD				*p* value
	Low BMD (n=33)		Normal (n=21)		
	n	%	n	%	
Cirrhotic	22	66.7	5	23.8	0.002[s]
Non cirrhotic	11	33.3	16	76.2	

s= significant
p value reached from chi square test

In cirrhotic group (n=27), at lumbar vertebrae, right and left femoral neck, normal BMD was found in 21 sites, osteopenia was found in 29 sites and osteoporosis was found in 31 sites. In non cirrhotic group (n=27), at lumbar vertebra, right and left femoral neck, normal BMD was found in 56 sites, osteopenia was found in 20 sites and osteoporosis was found in five sites.

Multivariate logistic regression analysis was done to see the effect of age, menopause and cirrhosis on BMD at lumbar vertebrae, right and left femoral neck. It was observed that at lumbar vertebrae; age and menopause had no significant effect on low BMD (p value were 0.748 and 0.104 respectively). Whereas, the effect of cirrhosis on low BMD was statistically significant (p value was 0.001) (Table-2).

Table 2: Multivariate logistic regression analysis for low BMD at lumbar vertebrae

	OR	95% CI		*p* value
		Lower	Upper	
Age (>50 years)	0.291	0.226	7.919	0.748[ns]
Menopause	1.279	0.060	1.299	0.104[ns]
Cirrhotic	2.951	4.440	82.387	0.001[s]

s= significant
ns= not significant

Similarly at right femoral neck; age and menopause had no significant effect on low BMD (p value were 0.193 and 0.855 respectively). Whereas, the effect of cirrhosis on low BMD was statistically significant (p value was 0.001) (table-3). The effect of cirrhosis on low BMD was same for the left femoral neck (table-4).

Table 3: Multivariate logistic regression analysis for low BMD at right femoral neck

	OR	95% CI		*p* value
		Lower	Upper	
Age (>50 years)	1.148	0.560	17.740	0.193[ns]
Menopause	0.157	0.230	3.177	0.855[ns]
Cirrhotic	2.198	2.536	31.98	0.001[s]

s= significant
ns= not significant

Table 4: Multivariate logistic regression analysis for low BMD at left femoral neck

	OR	95% CI		*p* value
		Lower	Upper	
Age (>50 years)	0.699	0.384	10.523	0.408^{ns}
Menopause	0.152	0.235	3.146	0.819^{ns}
Cirrhotic	2.132	2.453	28.957	0.001^{s}

s= significant
ns= not significant

Table 5: Multivariate logistic regression analysis for low BMD

	OR	95% CI		*p* value
		Lower	Upper	
Age (>50 year)	1.039	0.541	14.758	0.218^{ns}
Menopause	0.898	0.104	1.602	0.199^{ns}
Cirrhotic	1.961	0.110	25.893	0.003^{s}

s= significant
ns= non significant

Table 5 shows effect of different independent variables on low BMD. It was observed that age and menopause had no significant effect on low BMD (p value were 0.218 and 0.199 respectively). Whereas, the effect of cirrhosis on low BMD is statistically significant (p value was 0.003).

DISCUSSION

In recent decades, the management of complication of cirrhosis is improved, increasing the quality of life of cirrhotic patients. Osteopenia and osteoporosis (low BMD) is one of the important extrahepatic complications of cirrhosis. It increases the risk of facture and compromises the quality of life due to pain and deformities. Luxon (2011) reported that cirrhotic patients had two fold higher risk of fracture than the non cirrhotic patients (12). Osteoporosis is the only complication that persists for years after liver transplantation due to use of immunosuppressive drugs like steroids (13, 14).

In this study, it was observed that majority (63%) of the patients belonged to age group 51-60 years in both groups. The mean age was found 56.3 ± 6.7 years in cirrhotic group and 55.0 ± 6.3 years in non cirrhotic group which is similar to studies conducted by Bansalet et al. (2016) and Figueiredo et al. (2003) where mean ± SD age of cirrhotic patients were 50.9 ± 11.0 years and 52 ± 11 years, respectively (15,16).

In present study, in 27 patients in cirrhotic group, normal BMD was found in 21 sites, osteopenia was found in 29 sites and osteoporosis was found in 31 sites. Prem kumar et al. (2017) observed normal BMD in 24 (26.7%) patients, osteopenia in 40 (44.4%) patients and osteoporosis in 26 (28.9%) patients of liver cirrhosis (17). In both the studies, cirrhotic patients had more osteopenia and osteoporosis than normal BMD. Alam et al. (2011) also reported more low BMD (50% had osteopenia and 10% had osteoporosis) than patients had normal BMD value (40%) among 30 cirrhotic patients (18).

Independent risk factors for low BMD were age, menopause and cirrhosis. In this present study, the effect of independent variables (age, menopause and cirrhosis) on dependent variable (low BMD) was analyzed by multivariate logistic regression analysis. It was found that, age and menopause had no significant effect on low BMD (p value were 0.218 and 0.199 respectively). Whereas, the effect of cirrhosis on low BMD is statistically significant (p value was 0.003). In cirrhotic patients odds ratio (OR) was 1.961 (95% CI 0.110 to 25.893) which implies cirrhotic patients had 1.961 times greater chance to develop low BMD than non cirrhotic patients keeping all other factors in fixed level. Atay et al. (2016) reported that in multivariate logistic regression analysis (r2 of the model was 0.18) female sex [OR (95% CI): 2.8 (1.096-7.15), p=0.03], older age [OR (95% CI): 1.039 (1.003-1.076), p=0.03] and lower BMI [OR (95% CI): 0.91(0.836-1.008), p=0.06] tended to have an independent association with osteoporosis (19). In this study, age and menopausal status showed no significant effect on low BMD. In cirrhotic patients odds

ratio (OR) was 1.961 (95% CI 0.110 to 25.893) which implies cirrhotic patients had independent association with low BMD.

CONCLUSION

Low BMD (osteopenia and osteoporosis) is an important extrahepatic complication of cirrhosis. Now-a-days, there is an increase in the number of NASH cirrhotic patients. Generally NASH cirrhosis is found in older age and female patients. Osteoporosis is common in case of old age and menopausal female. In this study it was observed that cirrhosis is a highly significant risk factor for low BMD other than old age and menopausal patients.

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