Original Article

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Bone Mineral Density in Thai Patients with Chronic Hepatitis C, before and after Treatment with Pegylated Interferon/Ribavirin Combination

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ABSTRACT

Background: Loss of bone mineral density (BMD) frequently occurs in patients with cirrhosis secondary to chronic hepatitis C virus infection. However, little is known about the occurrence of bone disease in chronic hepatitis C patients without cirrhosis and the effect of pegylated interferon/ribavirin therapy on BMD. This study is aimed to evaluate the prevalence of osteopenia and osteoporosis in Thai patients with chronic hepatitis C both before and after pegylated interferon/ribavirin treatment.

Methods: Fifty-seven consecutive patients with chronic hepatitis C underwent a BMD measurement by dual x-ray absorptiometry in the lumbar spine (LS) and the femoral neck (FN). In addition, some bone metabolism markers were also measured.

Results: BMD was lower than age-matched population in most of our patients with mean Z-scores of -0.444 (-3.3 - 1.6) at LS and 0.56 (-1.8 - 3.4) at FN region. The prevalence of osteoporosis and osteopenia were 3.5% (95% CI: 0.97-11.92) and 22.8% (95%CI: 13.8-38.98), respectively. BMD was correlated with the patient's weight and serum phosphate, but not with other liver function tests. Ten patients who had a followed-up BMD assessment after 6 months of treatment with pegylated interferon/ribavirin had a significant increase in post-treatment BMD by a mean of 0.02 gm/cm2 (95%CI: 0.008-0.03, p = 0.006) at LS and 0.01 gm/cm^2 (95%CI: 0.001-0.02, p = 0.036) at FN.

Conclusion: There was a significantly reduced BMD in chronic hepatitis C patients compared with age-matched population. According to our preliminary result, the treatment with pegylated interferon plus ribavirin had a positive effect on BMD and should be further investigated.

Key words : Bone mineral density, chronic hepatitis C, pegylated interferon, ribavirin

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INTRODUCTION

Bone abnormalities both osteopenia and osteoporosis are well-known extrahepatic complications of chronic liver disease. Reduced bone formation and low bone turnover are the factors contributing to the increased bone loss observed in chronic liver disease. The prevalence of osteopenia and osteoporosis among patients with cirrhosis ranges from 23-60% and 7-44%, respectively. The highest prevalence is observed in cholestatic and alcoholic liver disease[1-4]. A recent study revealed that the prevalence of osteoporosis in patients with cirrhosis secondary to hepatitis C or B viruses was nearly 50%[15]. Reduction in bone mineral density (BMD) leads to increased bone fragility. There were many studies demonstrating that osteopenia and osteoporosis resulted in a 2-fold and 4 to 5-fold increased risk for fracture, respectively[16,17].

There are many risk factors that predispose individuals to development of osteoporosis but no particular risk factors have cause bone abnormality in chronic liver diseases. However, there are many factors that may contribute to the pathogenesis of osteoporosis including cirrhosis, particularly chronic cholestasis[5], corticosteroid use[6], smoking[7], physical inactivity[8], alcohol abuse[9], malnutrition and vitamin D deficiency[10,11]. All of these risk factors are contributing factors for the deterioration of bone metabolism in chronic liver disease. However, the results of the studies investigating the relative impact of these factors have not been consistent.

Most studies of bone disease were performed in patients with cirrhosis. Only a few studies on of prevalence of osteoporosis have been performed in patients suffering from chronic hepatitis B or C, without overt cirrhosis. A small recent study from Germany showed that patients with non-cirrhotic chronic viral hepatitis B and/or C displayed a prevalence of osteoporosis of 15% and 20%, respectively. This study also demonstrated a correlation between a decrease in BMD and an elevation in bone turnover markers in the more advanced stages of fibrosis without cirrhosis.[12]

In addition, combination therapy with interferon and ribavirin for chronic hepatitis C may affect bone turnover. Data from pediatric chronic hepatitis B patients suggested that treatment with interferon could contribute indirectly to prevent hip osteoporosis.[13] However, data in adult patients revealed that a treatment of chronic hepatitis C with interferon plus ribavirin may induce bone loss.[14] Up to date, there are no prospective studies to evaluate bone mass in chronic hepatitis C patients, before and after the treatment with interferon plus ribavirin.

Since most of these studies were from Western countries and there might be some differences in Western and Asian populations, such as races, dietary intake, sun exposure, or hepatitis C genotype, which may affect BMD. Therefore, in the present study we evaluated BMD and some biochemical bone turnover markers in Thai patients with non-cirrhotic, chronic hepatitis C.

MATERIAL AND METHODS

Patients

Fifty-seven patients with chronic hepatitis C of Siriraj hospital's hepatitis clinic participated in this study. All patients were positive for HCV seromarker (anti-HCV) and HCV RNA by polymerase chain reaction (PCR). Liver biopsy specimens were obtained within 1 year prior to study entry and analyzed according to the Knodell Histological Activity Index (HAI) for both necroinflammatory activity and fibrosis stage.

The relevant demographic- and disease-related data at the time of enrollment are listed in Table 1. Patients were excluded if they had one of the following conditions: decompensated cirrhosis (defined as Child Pugh score >6), history of bleeding gastroesophageal varices, receiving hormone or any medications related to bone metabolism (including estrogen, vitamin D >400 IU/day, calcium >1 gm/day and corticosteroid), co-infection with chronic hepatitis B, co-infection with human deficiency virus (HIV), pregnancy or lactation, ongoing alcohol consumption >30 gm/day, prior treatment with interferon and/or ribavirin or having other significant medical conditions associated with an alteration in bone metabolism.

Data were recorded by both personal and extensive chart review. These data included body weight, height, smoking habit, menstrual status, amount of alcohol and coffee intake.

All patients signed informed consent and the protocol was approved by the local human ethics committee.

Bone mineral density measurements

Bone mineral/mass density (BMD in gm/cm^2) was assessed in all patients at lumbar spine (LS; L2-L4) and femoral neck (FN) region using dual X-ray

Table 1 Baseline characteristics and biochemical markers in chronic hepatitis C patients

Parameters	Patients (N = 57)
Age (yr)	46 (29-64)
Male (%)	33 (57.9%)
BMI (Kg/m^2)	24.9 (17.1-37.7)
Smoking >10 cigarettes/D, (%)	6 (10.5%)
Alcohol >20g/D, (%)	9 (15.8%)
HCV	
genotype 1, (%)	36 (63.2%)
genotype 3, (%)	21 (36.8%)
HCV-RNA viral load (IU/ml)	4,712,605 (2,061-21,700,000)
HAI score	9.5 (2-16)
Fibrosis	
score 0-1, (%)	29 (51.8%)
score 3-4, (%)	27 (48.2%)
Lumbar BMD (gm/cm^2)	1.109 (0.784-1.409)
Lumbar T score	-0.386 (-2.8 - 2.1)
Lumbar Z score	-0.444 (-3.3 - 1.6)
Femur BMD (gm/cm^2)	0.975 (0.73 - 1.365)
Femur T score	0.293 (-1.7 - 3.3)
Femur Z score	0.56 (-1.8 - 3.4)
Osteopenia, (%)	13 (22.8%)
Osteoporosis, (%)	2 (3.5%)
Calcium (mg/dl)	8.915 (7.9-9.7)
Phosphate (mg/dl)	3.121 (1.7-4.9)
Intact PTH level (pg/ml)	37.859 (16.12-82.92)
ALT (U/L)	108.14 (14-276)
Albumin (g/dl)	4.3 (3.5-5)
ALP (U/L)	78.87 (31-137)

absorptiometry (DEXA). All scans were carried out on the same machine by the same operator. The results of BMD were compared with mean BMDs from age- and sex- matched controls from a large population database (Hologic) and expressed as standard deviation of the mean (Z-score) to avoid bias of age and sex. Definitions of osteopenia and osteoporosis were based on T-scores according to WHO criteria. The BMD measurements between 1 and 2.5 standard deviations below the mean for young adults (-2.5 < T-score ≤ -1) were defined as osteopenia, whereas T-score ≤2.5 were defined as osteoporosis.

Statistical analysis

Data for continuous variables were summarized by median or mean and range, while data for categorical variables were summarized by frequency counts and percentage. Correlations between variables were assessed by Spearman rank correlation test. D ifferences between groups were assessed using Fisher's exact test for binary variables, and paired t-test for continuous variables. A p-value of <0.05 was considered statistically significant.

Results

The demographic and disease-related data at the time of enrollment are listed in Table 1. The mean T-scores were -0.386 (-2.8 - 2.1) at LS and 0.293 (-1.7 - 3.3) at FN region. At the time of enrollment, the prevalence of osteoporosis and osteopenia were 3.5% (95% CI: 0.97-11.92) and 22.8% (95%CI: 13.8-38.98), respectively.

Compared to an age-matched population, we found a moderately decreased bone mass at lumbar region. The mean Z-scores were -0.444 (-3.3 - 1.6) at LS and 0.56 (-1.8 - 3.4) at FN region. There were 31.6% of the patients with BMD more than 1 standard deviation below mean BMD of age-matched population (Z-score < -1) (Table 1)

BMD was found to be significantly correlated with body weight (p = 0.009) and BMI (p = 0.047). This study did not demonstrate any correlation between BMD and disease-related parameters, including HCV-RNA levels, HCV genotype, serum ALT, degrees of necroinflammation, fibrosis or steatosis on liver histology (Figure 1 and 2)

In most cases, serum phosphate, calcium and PTH

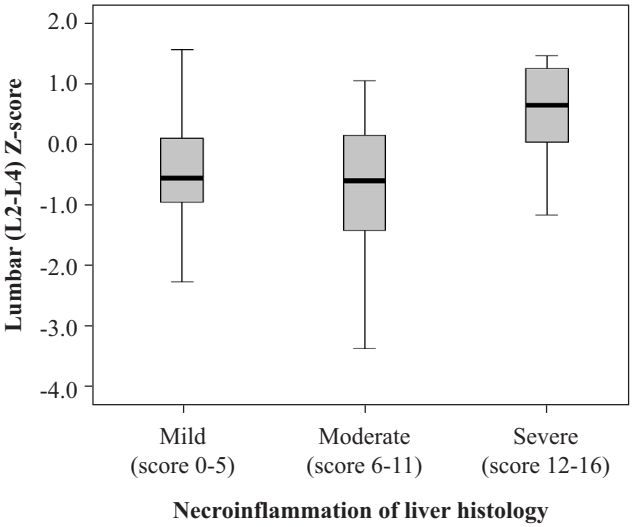

Figure 1 Liver necroinflammation and lumbar Z-score

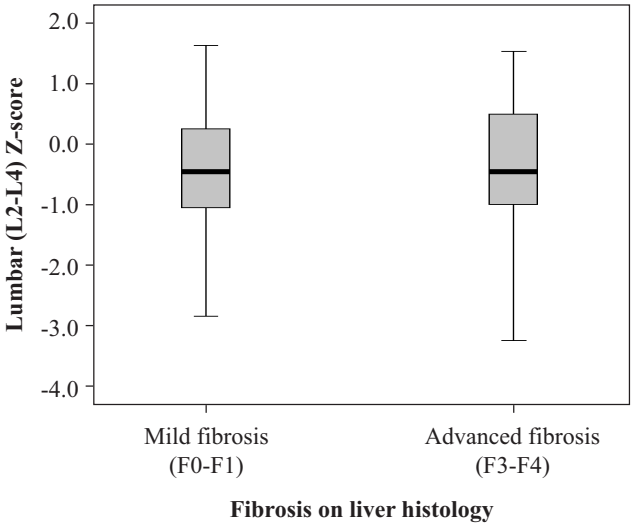

Figure 2 Degree of liver fibrosis and lumbar Z-score

Table 2 Correlation of lumbar BMD with demographic and disease-related data in patients with chronic hepatitis C

Parameters	r	p-value
Age	-0.208	0.37
Height	0.21	0.118
Weight	0.344	0.009
BMI	0.264	0.047
HCV-RNA	-0.208	0.121
HAI score	-0.106	0.437
Serum ALT	0.98	0.47
Serum ALP	0.085	0.54
Serum calcium	0.065	0.645
Serum phosphate	-0.368	0.007
Intact PTH level	-0.15	0.287

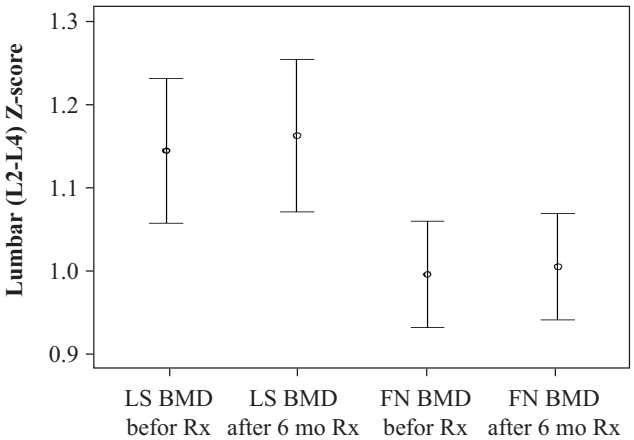

Figure 3 Lumbar BMD and femoral neck BMD before and after 6 months of treatment with pegylated interferon combined with ribavrin

level were in the normal range. Serum phosphate was negatively correlated with BMD (p = 0.007). (Table 2)

Of 10 patients who had a follow-up BMD assessment after 6 months of treatment with pegylated interferon plus ribavirin, nine patients had increased BMD after the treatment. As compared to the pre-treatment BMD, there was a statistically significant increase in LS-BMD by 0.02 gm/cm2 (95%CI : 0.008-0.03, p = 0.006) and FN-BMD by 0.01 gm/cm^2 (95%CI : 0.001-0.02, P = 0.036). (Figure 3)

Discussion

Our study revealed a lower BMD in 57 chronic hepatitis C patients when compared with general Thai population. The prevalence of osteoporosis and osteopenia were 3.5% and 22.8%, respectively, which were lower than a previous study by Schiefke, *et al*.[12] This may be contributed to that our patients were younger of age, having greater BMI, male predominated and probably having a difference in races and lifestyle compared to Caucasians.

More BMD reduction in patient with chronic hepatitis C was observed in lumbar region, which represents a trabecular bone, than in femoral neck region, which represents a cortical bone. This finding suggested that a reduction of BMD in chronic hepatitis C patients was more prominently affecting the trabecular bone than cortical bone.

We found that BMD had a significant correlation with weight and BMI in this group of patients, as previously described in post-menopausal women. We could not find any correlation between BMD or any predictors for osteopenia and the liver-related parameters, such as HCV-RNA, HCV genotype, serum ALT and degrees of necroinflammation, fibrosis or steatosis on liver histology.

According to the previous hypothesis stating that an increase in bone turnover is a cause of osteopenia in patients with chronic liver disease. In this study, we found a correlation between a higher in serum phosphate and a lower in BMD (p = 0.007), which supported this hypothesis. But we could not demonstrate any correlations between BMD and intact PTH level, serum calcium or serum ALP.

Nine out of 10 patients who had obtained a 6-month follow-up after treatment with pegylated interferon plus ribavirin had increased BMD. This suggested that pegylated interferon and/or ribavirin had a

positive effect on bone density. This finding was contradicted to previous finding from Solis-Herruzo, *et al*.[14] Who reported that bone density decreased after treatment with alpha interferon and ribavirin. To confirm this finding, we have designed further study to collect more number of patients and extend a follow up period to measure BMD at 6 months after completion of treatment.

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