Osteodystrophy in Hepatitis C virus Related Cirrhosis

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Abstract: Hepatic osteodystrophy is still an underestimated complication of viral liver cirrhosis in spite of the high prevalence of chronic hepatitis C in Egypt. ***Aim:*** To evaluate bone mineral density & to study possible disturbance of vitamin D-Parathyroid hormone- Calcium Axis in a group of HCV cirrhotic patients. ***Patients and methods:*** Bone Mineral density at dorsal & lumbar spine was evaluated using DEXA machine, liver function tests, serum calcium, phosphorus, parathyroid hormone and 25 (OH) vitamin D were measured in fifty HCV cirrhotic patients and twenty age and sex matched adults as a control group. ***Results:*** 90% of patients had decreased bone density (40% in form of osteoprosis & 50% in form of osteopenia). Bone mineral density(BMD) was lower with advancement of cirrhosis (Child- pugh class B and C). BMD was negatively correlated with serum bilirubin and INR and positively correlated with serum albumin and platelet number, however no correlation to Ca, Po4, PTH or 25(OH) vit. D level was found. ***Conclusion:*** Osteoprosis had raised prevalence in patients with HCV related cirrhosis and was correlated to disease severity but disturbance in Calcium- PTH- VitD axis did not seem to play a major role in pathogenesis.

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Intoduction

Patients with chronic parenchymal liver disease often have metabolic bone disorders referred to as hepatic osteodystrophy.[1]

Severe pre-clinical osteoporosis regardless of its cause is a risk factor for development of fracture, which may be a source of morbidity and contribute to mortality in patients already debilitated by chronic liver disease.[2] Therefore the first step toward prevention of morbidity and mortality of hepatic osteodystrophy is to identify those patients with liver cirrhosis who are predisposed to development of osteopenia and osteoporosis.

The pathogenesis of hepatic osteodystrophy is unclear and likely is multifactorial. Histologically, hepatic osteodystrophy is similar to postmenopausal bone loss in that trabecular (cancellous) bone is more rapidly and severely affected than cortical bone.[3] The development of hepatic osteodystrophy may be related to both increase bone resorption & decrease bone formation.[4]

Theoretically; disturbance in endocrine calcium-PTH-vitamin D axis seems to play a role in pathogenesis of osteometabolic disturbance. The liver is an important organ in hydroxylation of vitamin D into its active metabolites. Vitamin D and PTH regulate bone mineral serum levels and bone remodeling. Consequently, chronic liver disease may interfere with vitamin D activation and bone metabolism.[5] However many studies conclude that the clinical relevance of vitamin D- PTH disturbance in hepatic osteodystrophy is unclear.[6,7]Others cannot exclude the participation of secondary hyperparathyroidism in the high turnover and in the bone loss found in these patients. [1,8]

Most studies of bone disease and Ca – PTH – vitamin D disturbances were performed in patients with alcoholic cirrhosis, and primary biliary cirrhosis .In spite of the high prevalence of chronic viral hepatitis, there are relatively few studies of osteometabolic disease and Ca – PTH – vitamin D axis in chronic viral liver disease.

Aim of the Study:

Aim of the Study was to evaluate bone mass and to correlate between severity of liver disease and bone mineral density in a group of Egyptian patients with HCV related cirrhosis in addition to study possible disturbance of vitamin D- PTH- calcium axis in those patients.

Subjects and Methods:

This study was conducted on fifty HCV cirrhotic patients (13 females and 37 males / mean age= 48 ± 8.9 years) referred to Ain-Shams University Hospital from January 2007 to September 2007, and twenty healthy age and sex matched adults as a control group (6 females and 14 males / mean age= 46 ± 8.2 years). A written informed consent was signed by all subjects participating in the study and the study was approved by the local ethical committee.

Diagnosis of HCV related cirrhosis was based on clinical, laboratory and imaging evidence. Patients

were divided according to modified Child-Pugh classification into three groups: class A (score5-6, n= 12) class B (score 7-9, n= 20) and class C (score more than 9, n= 18). Patients in these groups were matched for both age and sex. Patients with liver disease due to other etiologies (eg hepatitis B infection, primary biliary cirrhosis, autoimmune or metabolic causes) were excluded. None of the subjects included in the study had chronic kidney disease, diabetes mellitus**,** history of endocrinal disease, metastatic bone disease or other malignancies. Subjects receiving vitamin D or calcium supplements, hormone replacement therapy, corticosteroids or any drug known to affect bone density were also excluded from the study.

All subjects were subjected for:

1-Full history taking including inquiry about history of previous fractures and bony pains, and thorough clinical examination to ensure that all patients included in the study fulfill the proper criteria for selection.

2- Laboratory investigations including:

a- Liver function tests [total serum proteins, serum albumin, total and direct bilirubin, prothrombin time (P.T), and liver enzymes; aspartate aminotransferase (AST), alanine aminotransferase (ALT)], serum creatinine, complete blood picture, fasting and two hours postprandial blood sugar and alpha fetoprotein, HCV (ab) by ELISA, HCV RNA (qualitative).

b- Serum phosphorus level , serum calcium level and corrected calcium level was calculated according to following equation: Corrected calcium=measured calcium + 0.8 (4-serum albumin)

c- Measurment of serum parathyroid hormone (PTH) by The DSL-10-8000 ACTIVE® I-PTH ELISA (Diagnostic systems Lab Inc., Webster, TX, USA). It is an enzymatically amplified "two-step" sandwich-type immunoassay. Assay was applied according to manufacture instructions

d. Serum 25 hydroxy vitamin D (25(OH) D) by Human 25-Hydroxy Vitamin D EIA Kit from IDS Ltd, Boldon , UK The IDS 25-Hydroxy Vitamin D kit is an enzymeimmunoassay intended for the quantitative determination of 25-hydroxyvitamin D (25-OH D).

3- Abdominal ultrasonography.

4- Measurement of bone mineral density at the dorsal and lumbar spines using dual energy absorptiometry machine (DEXA) bone densitometry was performed using DEXA (DXA QDR 4500^{TM} , Hologic INC, Waltham, USA). Bone mineral density is expressed in milligrams per centimeter squared (mg/ cm^2)

T score and Z score were determined (T-Score: The bone mineral density (BMD) in a patient was reported as a standard deviation in comparison with that of young normal controls, to assess whether there was a decrease in BMD from peak bone mass. Z-Score: The bone mineral density (BMD) in a patient was reported as a standard deviation in comparison with that of age-matched controls, to determine whether the bone density was reduced relative to age - matched controls)
And the subjects were classified according to WHO classification of osteoporosis:

- Normal BMD is represented by a T score of more than -1.
- Osteopenia (low bone mass) is represented by a T score between-1and -2.5.
- Osteoporosis is presented by a T score less than -2.5.
- Established osteoporosis is represented by a T score of less than -2.5 and a previous history of a fragility fracture [(9)].

5- **Statistical Methods:**

Data were collected, revised, verified then edited on P.C. The data were then analyzed statistically using SPSS statistical package version (11).**The following tests were used: calculation of** Mean(X) and standard deviation (SD), Student t- test (t) of independent sample means to compare two quantitative variables, Chi- square test (X2) to compare qualitative variables, analysis of variants (ANOVA test (F)) to compare more than two groups of quantitative variables, Post hoc test [least significance difference test (LSD)] when additional exploration of the differences among means was needed to provide specific information on which means are significantly different from each other.. And Correlation co-efficient test (r-test) to find a linear relation between different values. For level of significance P value > 0.05 was not significant (NS), P< 0.05 was significant (S) and P<0.01 was highly significant (HS).

Results:

74% of patients had bony pains in comparison to 20 % of control group (χ^2 = 16.54, P<0.01). 90% of the fifty patients with posthepatitic cirrhosis enrolled in the study had metabolic bone disorder (osteoporosis in 40% and osteopenia in 50%) according to WHO classification of osteoporosis; while 30% of control group showed decreased BMD in the form of osteopenia, none of them showed osteoporosis, with statistically highly significant difference between both groups (χ^2 = 15.47, P< 0.01) as shown in table 1.

Table (1): Comparison between patients and controls as regards BMD measurement, T and Z score at lumbar spine

Parameters	Patients (n=50)		Control (n=20)		T	P
	X	SD	X	SD		
B.M.D	0.956	1.058	1.179	0.074	4.329	<0.001
T-Score	-2.168	1.487	-0.400	0.655	-3.670	<0.01
Z-Score	-2.276	1.283	-0.490	0.572	-4.294	<0.001

When patients were subdivided according to Child-pough classification; there was statistically highly significant difference in BMD, T- score & Z- score values (table 2). Post hoc tests showed highly statistical difference in comparison Child A patients by Child B and C with no difference between Child B and C as regard these measurement.

Table (2): Comparison between different Child classes as regards BMD, T and Z score.

Parameter	Child A (n=12)		Child B (n=20)		Child C (n=18)		F	P
	X	SD	X	SD	X	SD		
B.M.D	1.09	0.12	0.91	0.18	0.91	0,086	7.62	<0.01
T-Score	-1.14	1.10	-2.37	1.77	-2.27	1.03	4.45	<0.05
Z-Score	-1.20	0.98	-2.52	1.45	-2.73	0.80	7.09	<0.01

BMD had highly significant negative correlation with serum bilirubin and INR & and significant positive correlation with serum albumin and platelet count signifying worsening of BMD with worsening of synthetic liver functions and surrogate markers of fibrosis (table3).

Table (3): Correlation between BMD measurement at lumbar spines and liver function tests

Parameters	B.M.D	
	r	P
S.BIL	-0.433	<0.001
PLT	+0.243	<0.01
Alb	+ 0.54	<0.001
I.N.R.	-0.61	<0.001

On the other hand no significant difference in levels of serum calcium, phosphorus, parathyroid hormone or vitamin D was found between patients and controls (table 4) nor between different child classes (table 5) and no correlation between BMD & Ca, Po4, PTH was found (table 6).

Table (4): Comparison between patients and controls as regard serum calcium and phosphorus, parathyroid hormone, vitamin D

Parameter	Patients (n=50)		Control (n=20)		t	P
	X	SD	X	SD		
s.Ca(mg/dl)	9.096	0.878	9.201	0.945	-1.65	>0.05
s.Po4(mg/dl)	3.05	0.56	3.3	0.25	-1.5	>0.05
S.PTH (pg/ml)	66.094	32.31	49.10	11.03	-1.5	>0.05
25(OH)D (ng/ml)	45.61	17.2	46.66	14.9	-1.7	>0.05

Table (5): Comparison among the three groups of patients as regard serum calcium and phosphorus, parathyroid hormone and vitamin D

Parameter	Child A (n=12)		Child B (n=20)		Child C (n=18)		F	P
	X	SD	X	SD	X	SD		
S.Ca (mg/dl)	9.015	0.782	8.92	0.897	9.09	0.53	1.9	>0.05
S.Po4 (mg/dl)	3.04	0.39	3.28	0.52	2.94	0.7	1.3	>0.05
S.PTH (pg/ml)	56.517	20.97	73.19	42.75	64.51	22.99	1.7	>0.05
25(OH)D (ng/ml)	52.71	18.8	45.3	14.6	44.9	19.2	1.8	>0.05

Table (6): Correlation between BMD measurement at lumbar spines and serum calcium and phosphorus, PTH and vitamin D in patients

Parameters	B.M.D	
	r	P
S.Ca	-0.07	>0.05
S.Po4	-0.02	>0.05
S.PTH	-0.097	>0.05
25(OH)D	-0.04	>0.05

Discussion:

Osteoprosis is not infrequent in chronic liver disease (CLD) as, it occurs in 20% to 100% of patients in some studies[10]. This wide variation in reported prevalence of osteoporosis among patients with chronic liver disease is probably related to patient selection and diagnostic criteria; and although study of bone metabolic abnormality was initially directed to primary biliary cirrhosis patients; recent studies showed no significant difference in presence of osteoprosis between primary biliary cirrhosis patients and HCV related cirrhosis [7].

This study revealed that BMD, T-score and Z-score were significantly lower in patients with child B and C than in child A. ***Gallego-Rojo et al. 1998***[11] found that there was increase in the percentage of osteoporosis with the increase of the severity of cirrhosis. They reported that 37.5% of Child A patients, 60% of Child B patients, 66%of Child C patients were osteoporotic. Also ***Corazza et al., 2000***[12] demonstrated that the progression of the disease from Child A to Child C was accompanied by worsening of BMD measurement. So, this indicated that severity of osteoporosis was increasing with the severity of chronic liver disease; which was also evident in this study by worsening of BMD with worsening of synthetic liver functions and surrogate markers of fibrosis.

Prior studies have shown that bilirubin inhibits osteoblast activity and function in vitro and in animal models of bone mineralization [13]. In the present study there was significant negative correlation between serum bilirubin and BMD at lumber spine. This was in agreement with ***Karan 2001, Uretmen et al ., 2005***[5,14] who found negative correlation between serum bilirubin level and BMD and concluded that elevated bilirubin could depress osteoblastic function which may lead to low turnover osteoporosis. On contradiction to this results ***Smith et al. 2006***[2] found no correlation between serum biliru bin and reduced BMD in patients with end-stage liver disease and bilirubin was not a major contributing factor to hepatic osteodystrophy. In the present study; whether hyperbilirubinemia is involved in the pathogenesis of osteodystrophy or it is just a reflection of lower bone mineral density with deterioration of liver functions was not studied.

This study revealed a highly significant positive correlation between lumbar spines BMD and serum albumin levels and a significant negative correlation between BMD measurements at lumbar spines with prothrombin time in patients with chronic liver disease. This was in agreement ***Corazza et al. 2000***[12] as they found a highly significant positive correlation between BMD measurements and serum albumin levels. ***Duarte et al,. 2001***[8] also reported significant negative correlation between BMD measurements and prothrombin time. This again indicated that BMD values were affected with the deterioration in liver functions.

In this study, the serum calcium, serum phosphorus, parathyroid hormone serum level and 25(OH) vitamin D level showed no statistical difference neither between patients and control nor between patient's subgroups. This study also showed no correlation between serum calcium, serum phosphorus , 25 (OH) vitamin D or parathyroid hormone level and degree of bone loss (BMD).

Duarte et al. 2001[8] also found no significant correlation between serum calcium, phosphorus, PTH, and 25(OH) D and severity of bone loss but they could not exclude the participation of PTH in the high bone turn over and bone loss in the population with chronic viral hepatitis, while ***Gallego-Rojo et al,. 1998*** [11]found reduction in serum 25(OH) D in Child B and Child C cirrhotic patients with viral liver disease.

Although it was previously reported that two different processes, osteomalacia and osteoporosis, seem to coexist in variable proportion in hepatic osteodystrophy patients. This data might indicate that osteoporosis rather than osteomalacia is involved in pathogenesis of hepatic osteodystrophy in chronic liver disease.

Moriera et al. 2004 [15] concluded that the role of calcium-parathyroid hormone-vitamin D axis in hepatic osteodystrophy is controversial. Disturbances in Calcium-PTH-Vitamin D axis are frequently associated with chronic liver diseases (CLD). In patients with CLD, a trend toward decreased serum calcium and vitamin D has already been demonstrated with compensatory increases in PTH levels. Even though reduced vitamin D hydroxylation has been considered the most important mechanism for these alterations, recent studies demonstrates an adequate production of 25(OH) Vitamin D even in end-stage liver disease.

Moreover, recent clinical trials that evaluated treatment with vitamin D and/or 25-hydroxyvitamin D have been largely unsuccessful in reversing or halting the progression of osteoporosis as assessed by histomorphometry, bone mineral density, and fracture incidence. Although vitamin D deficiency per se is likely not implicated in the development of hepatic osteodystrophy, reduced tissue sensitivity to circulating vitamin D due to altered vitamin D receptor genotypes may play a role[13] .

In conclusion liver cirrhosis was a direct and independent risk factor for bone loss which is mainly in the form of osteoporosis rather than osteomalacia and the degree of bone loss was correlated to the severity of the liver disease. So we recommended that BMD should be evaluated in cirrhotic patients. Management and follow up should be done in osteopenic and osteoporotic patients. Other pathological mechanisms should be searched for.

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