Renal Failure

ISSN: 0886-022X (Print) 1525-6049 (Online) Journal homepage: informahealthcare.com/journals/irnf20

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To cite this article: A. Eftal Yücel, H. Kart-Köseoglu, I. Isiklar, E. Kuruinci, F. N. Özdemir & H. Arslan (2004) Bone Mineral Density in Patients on Maintenance Hemodialysis and Effect of Chronic Hepatitis C Virus Infection, Renal Failure, 26:2, 159-164, DOI: 10.1081/JDI-120038501

To link to this article: https://doi.org/10.1081/JDI-120038501

Published online: 07 Jul 2009.

RENAL FAILURE
Vol. 26, No. 2, pp. 159–164, 2004

CLINICAL STUDY

Bone Mineral Density in Patients on Maintenance Hemodialysis and Effect of Chronic Hepatitis C Virus Infection

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ABSTRACT

Objective: To determine the prevalence of osteopenia and osteoporosis in HD patients at our center; to investigate whether HCV infection affects BMD in hemodialysis patients; to test for correlations between bone mineral density (BMD) and clinical and laboratory parameters in this population. *Subjects and Methods:* The study involved 76 end-stage renal disease patients. Forty-three (56.6%) patients were tested negative for anti-HCV antibodies and HCV-RNA. Thirty-three (43.4%) of them had positivity of anti-HCV antibodies and permanent or intermittent HCV-RNA positivity at least for two years. Mean HD duration was 86.4 months. Patients completed a standard questionnaire that listed age, sex, occupation, education level; cause of renal failure, smoking history, dialysis duration, and sports activities engaged in during life, and pathologic bone fractures. The women answered additional items about age at menarche, number of pregnancies and menopausal status. Each subject underwent a baseline physical examination, including measurement of body weight and height for calculation of body mass index. The results of laboratory tests that had been done at monthly visits in the previous year were retrospectively evaluated, and mean levels for the year were used for correlation testing. Bone mineral density was measured in the spine, femoral neck and forearm. Relationships between BMD values and chronic

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DOI: 10.1081/JDI-120038501
0886-022X (Print); 1525-6049 (Online)

HCV infection, laboratory results and clinical parameters were analyzed. *Results:* In the 43 patients who were negative for anti-HCV antibodies and HCV-RNA, spine BMD testing showed osteopenia in 16 (37.2%) cases and osteoporosis in 7 (16.3%) cases. The corresponding values for the neck of the femur were 14 (32.6%) and 6 (14.0%), and for the forearm were 19 (44.2%) and 15 (34.9%). In the 33 anti-HCV antibodies and HCV-RNA positive patients; spine BMD testing showed osteopenia in 10 (30.3%) cases and osteoporosis in 7 (21.2%) cases. The corresponding values for the neck of the femur were 17 (51.5%) and 4 (12.1%), and for the forearm were 4 (12.1%) and 25 (75.8%). Bone mineral density decreased as dialysis duration increased ($p<0.05$). There was no statistical difference between BMD measurements of chronic HCV infection positive and negative group. *Conclusion:* However the mean BMD values for all three sites in the 76 HD patients were low HCV infection may not be a risk factor for low BMD in this population.

Key Words: Bone mineral density; Hemodialysis; Hepatitis C virus.

INTRODUCTION

Renal osteodystrophy in patients on maintenance HD is a complex pathology of bone. This condition may occur in the form of high-turnover bone disease, as in osteitis fibrosa, or low-turnover disease, as in hyperparathyroidism, osteomalacia or adynamic bone disease that can cause reduced bone mineral density (BMD).[1–4] Age, female gender, low calcium intake, thin body habitus, cigarette smoking, alcohol abuse, previous glucocorticoid treatment, premature loss of gonadal function, and decreased physical activity are known risk factors for abnormal loss of BMD.[5] Also, dual x-ray absorptiometry (DXA) results have shown that patients on dialysis have lower BMD than age- and sex-matched controls.[6–10] Some authors believe that patients on maintenance HD may have additional risk factors for reduced BMD.[6–14]

Chronic HD patients also have a high rate of hepatitis C virus (HCV) infection,[15] and this virus is known to cause various musculoskeletal symptoms.[16] Recent reports have documented that HCV can cause osteosclerosis in patients with normal renal function.[17–19] However, other investigators have speculated that osteoporosis is the main process involved in hepatic osteodystrophy.[20,21] These authors suggest that chronic hepatitis is associated with decreased 25-hydroxylation of vitamin D, which could lead to osteomalacia and secondary hyperparathyroidism.

The effect of HCV infection on BMD in patients on maintenance HD has not been investigated to date. Our aim in this study was to investigate whether HCV infection affects BMD in hemodialysis patients; to determine the prevalence of osteopenia and osteoporosis in HD patients at our center, to assess for correlations between BMD and clinical and laboratory parameters in these populations.

SUBJECTS AND METHODS

We studied 76 patients with end-stage renal disease (44 [57.9%] men and 32 [42.1%] women) who were receiving regular HD therapy at our center. Forty-three (56.6%) patients were tested negative for anti-HCV antibodies and HCV-RNA. Thirty-three (43.4%) of them had had positivity of anti-HCV antibodies and had permanent or intermittent HCV-RNA positivity at least for two years (mean duration, 5.4±1.9 years; range, 2–8 years). Each patient was undergoing 4-hour sessions three times weekly with cuprophan membranes. The mean age of the group was 44.4 years (range, 25–65 years) and the mean HD duration was 86.4 months (range, 24–231 months). Thirteen (40.6%) of the 32 women were postmenopausal or permanently amenorrheic. The etiologies of renal failure were glomerulonephritis (n=15), hypertensive nephropathy (n=9), chronic pyelonephritis (n=8), nephrolithiasis (n=6), polycystic kidney disease (n=3), obstructive uropathy (n=2), Alport's syndrome (n=2), toxic nephropathy (n=1) and unknown (n=30). Patients with diabetes mellitus, thyroid disease, inflammatory rheumatic disease, psoriasis or malignancy were excluded. Four patients had received corticosteroid therapy. Three of these four had undergone renal transplantation and developed chronic rejection.

At the beginning of the study, all patients completed a standard questionnaire that listed age, sex, occupation, education level, cause of renal failure, smoking history, dialysis duration, duration and frequency of any sports activities engaged in during life, and pathologic bone fractures. The women also answered questions about age at menarche, number of pregnancies and menopausal status. Each subject underwent a baseline physical examination. Weight and height were measured, and body mass index was

Table 1. The patients' clinical and demographic characteristics.

Characteristic	HCV (−) group	HCV (+) group
Sex (male/female)	23/20	21/12
Age (years)	44.0±7.8 (29–58)	44.3±8.6 (25–65)
Height (cm)	162.5±10.2 (130–182)	166.7±9.5 (153–187)
Weight (kg)	61.1±11.5 (33–85)	58.6±9.5 (40–82)
Body mass index (kg/m^2)	24.1±4.9 (17.6–40.8)	24.8±4.3 (19.3–36.9)
Age at menarche (years)	14.1±1.4 (11–16)	14.4±2.2 (12–20)
Age at menopause (years)	45.9±6.0 (40–57)	39.0±9.5 (25–45)
Number of smokers/packages per year	167.3±235.7 (0–810)	168.0±217.9 (0–900)
No. of patients who had engaged in any sports activity	8/43	4/12
Average serum calcium over 1 year (mg/dL)	9.3±0.6 (7.4–10.7)	9.3±0.5 (8.4–10.7)
Average serum phosphorus over 1 year (mg/dL)	4.6±1.0 (3.0–9.2)	4.6±0.9 (3.0–7.3)
Average serum alkaline phosphatase over 1 year (U/L)	217.4±86.2 (103–441)	295.4±143.4 (129–646)
Average serum parathormone over 1 year (mg/dL)	149.9±129.5 (11.7–567.7)	262.6±188.9 (22.3–722.7)
Average erythrocyte sedimentation rate over 1 year (mm/h)	42.0±15.9 (8.7–81.3)	35.6±19.5 (8.0–95)
Average C-reactive protein over 1 year (mg/L)	13.6±14.0 (1.3–73.0)	11.2±10.1(1.0–47.0)

calculated as body weight divided by the square of the individual's height in meters. We also retrospectively reviewed all the patients' medical records for information about pathologic bone fractures and avascular necrosis. The results of laboratory tests that had been done at monthly visits in the year prior to the study were retrospectively evaluated, and the mean levels for the year were used for correlation testing. Table 1 shows the demographic and clinical laboratory data that were collected in HCV positive and negative group.

We measured the BMD of the spine, femoral neck and forearm (radius) by DXA (Hologic, Inc. model QDR 4500, fan beam x-ray bone densitometry, ELITE ACCLAIM series), and used the World Health Organization definitions for osteopenia and osteoporosis. These definitions are based on T-scores, which reflect the number of standard deviations by which a patient's value differs from the mean for a group of young normal controls. Osteopenia was defined as a T-score between -1.0 and -2.5, and osteoporosis was defined as T-score ≤ -2.5.

Serologic testing for HCV antibodies was done using the Abbott AxSYM System HCV version 3.0 assays. Serum samples were investigated for the presence of HCV-RNA using nested reverse transcriptase-polymerase chain reaction (RT-PCR) analysis. The 5′ non-coding region of HCV was amplified using the primer sets 209/940 (external set) and 211/939 (internal set). [Serum HCV-RNA levels were found significantly lower in the hemodialysis patients and sometimes it can be detected negative.[22] Therefore, patients who had had positivity of anti-HCV antibodies and permanent or intermittent HCV-RNA positivity at least for two years were included. Aminotransferase was reported to be insufficient for screening of hepatitis C virus infection in hemodialysis; therefore, this parameter was not used as a criterion of chronic HCV infection in this study.[23] In our center we repeated reverse transcriptase-polymerase chain reaction (RT-PCR) analysis for HCV-RNA in hemodialysis patients with six months interval].

Serum levels of calcium (Ca), phosphorus (P) and alkaline phosphatase were measured by enzymatic calorimetric testing (STANBIO); serum parathormone levels were determined by microparticle enzyme immunoassay (Abott-TDX); serum C-reactive protein levels were measured by nephelometry; and erythrocyte sedimentation rates were determined using the Westergren method.

At the time of the study all the patients were taking alphacalcidol and Ca supplementation, with dosing based on serum Ca, P and parathormone monitoring that had been done since the start of HD therapy. The following were set as ideal levels for Ca supplementation: Ca x *P* product <70, serum Ca between 9.5 and 10.5 mg/dL, and *P* between 4.5 and 5.5 mg/dL. Alphacalcidol treatment was stopped when serum parathormone fell below 120 pg/mL, and was started when the level exceeded 250 pg/mL. None of the postmenopausal females were receiving hormone replacement therapy. Heparin was used in all patients for anticoagulation.

We tested correlations between the BMD measurements and chronic HCV infection, the laboratory and clinical parameters described above.

Table 2. The results of dual x-ray absorptiometry in the 76 maintenance hemodialysis patients.

Bone site	Anti-HCV antibodies	T-score mean±SD (range)	Z-score mean±SD (range)	Osteopenia prevalence[a] (%)	Osteoporosis prevalence[b] (%)
Femoral neck	(−) n=43	−0.8±1.5 (−3.6–3.7)	−0.2±1.2 (−2.8–2.4)	14 (32.6%)	6 (14.0%)
	(+) n=33	−1.2±0.9 (−3.1–0.7)	−0.6±0.9 (−2.2–1.1)	17 (51.5%)	4 (12.1%)
Spine L1–L4	(−) n=43	−0.9±1.7 (−5.0–3.6)	−0.4±1.6 (−3.5–4.3)	16 (37.2%)	7 (16.3%)
	(+) n=33	−1.2±1.4 (−3.9–1.1)	−0.6±0.9 (−2.2±1.1)	10 (30.3%)	7 (21.2%)
Distal third of radius	(−) n=43	−2.1±1.8 (−7.6–1.7)	−1.6±1.8 (−7.0–2.5)	19 (44.2%)	15 (34.9%)
	(+) n=33	−3.5±1.7 [−6.8–(−0.3)]	−3.0±1.7 (−6.5–0.1)	4 (12.1%)	25 (75.8%)

[a]T-score between −1.0 and −2.5.
[b]T-score ≤ −2.5.

Statistical Methods

The software program SPSS for Windows V 11.0 was used to process and statistically analyze all data. Group data are shown as mean±SD. p values <0.05 were considered to indicate statistical significance. Pearson's correlation coefficient was used to test for relationships between BMD values (spine, femur and radius) and clinical findings and laboratory results. Group means were compared using the Student's t-test (parametric variables) or Mann-Whitney U test (non-parametric variables). Proportions were compared using chi-square testing. The effects of HCV and dialysis duration on BMD were assessed using linear regression analysis.

RESULTS

The BMD results for the spines, femurs and radii in the HCV-positive and HCV-negative groups are shown in Table 2. In the 43 HCV-negative patients, spine BMD assessment showed osteopenia in 16 (37.2%), osteoporosis in 7 (16.3%) and normal results in 20 (46.5%) cases. The corresponding values for the neck of the femur were 14 (32.6%), 6 (14.0%) and 23 (53.4%), and the corresponding results for the forearm were 19 (44.2%), 15 (34.9%) and 9 (20.9%). In the 33 HCV-positive patients, spine BMD testing showed osteopenia in 10 (30.3%), osteoporosis in 7 (21.2%) and normal results in 16 (48.5%) cases. The corresponding values for the femoral neck were 17 (51.5%), 4 (12.1%) and 12 (36.4%), and the corresponding results for the forearm were 4 (12.1%), 25 (75.8%) and 4 (12.1%). In both groups, the frequency of osteoporosis of the forearm was higher than the frequencies of osteoporosis of the spine and the femur.

Bone mineral density measurements of femoral neck, spines and radii in the HCV-positive and HCV-negative groups were significantly correlated with HD duration ($p<0.05$). Measurements of the spine, femoral neck and forearm were not correlated with any of the other laboratory or clinical parameters studied. The rate of HCV infection also increased with dialysis duration ($p<0.05$).

DISCUSSION

In line with other reports in the literature, we observed reduced BMD in the HD patients. In our study, the DXA assessments revealed significantly lower density in the forearm than at the other sites evaluated. We also found that BMD decreased with increasing dialysis duration, as supported by literature.[6–14]

Hepatitis C virus remains one of the most important infectious problems in patients on maintenance HD.[15] The prevalence of this infection in all patients at our center is 21%, and 43.4% of the 76 HD patients we studied had chronic HCV infection. Little is known about the effects of HCV on BMD in normal individuals or in patients on maintenance HD. Since 1992, at least eleven case reports have documented diffuse bone pain and osteosclerosis associated with HCV infection.[17–19] Each of these patients presented with elevated serum alkaline phosphatase activity, and all exhibited increased bone density. Their bone biopsies indicated accelerated skeletal remodeling, but the pathogenesis underlying the increased bone density is unknown. It is possible that HCV in the liver or in other tissues induces production of cytokines or growth factors that indirectly increase bone remodeling.[24] Beyer and colleagues reviewed skeletal x-rays of 107 HCV-positive patients and found no radiographic

evidence of osteosclerosis.[25] In contrast, as mentioned above, other studies have suggested that the main process involved in hepatic osteodystrophy is osteoporosis. The mechanisms that cause bone loss in chronic hepatitis are unknown, but some authors have proposed that decreased 25-hydroxylation of vitamin D might lead to osteomalacia and secondary hyperparathyroidism.[20,21] Duarte et al. studied BMD, biochemical markers of bone turnover, and the calcium-parathormone vitamin D axis in 100 patients with chronic hepatitis due to HCV.[20] The authors found that the BMD of these chronic HCV patients' radii, spines and femurs were low compared to findings in an age-matched population. Our study revealed that chronic HCV infection is not a significant risk factor for decreased BMD in patients on maintenance HD.

In conclusion we found that the mean BMD values in HD patients were low and radius seemed to be the most affected part of the skeleton. Bone mineral density decreased as dialysis duration increased. The results suggest that chronic HCV infection may not be a risk factor for low BMD in this population.

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