The spectrum of bone disease in Jordanian hemodialysis patients

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ABSTRACT

Objectives: To evaluate the spectrum of mineral abnormalities and bone disease (BD) in hemodialysis patients at Jordan University Hospital (JUH), Amman, Jordan.

Methods: A cross-sectional study was conducted among 63 patients (38 males and 25 females), mean age 44.19 years (range 17-76 years), with chronic kidney disease (CKD) on regular hemodialysis at JUH between November 2004 and April 2005. All patients have undergone complete blood count, chemistry profile, alkaline phosphatase, serum albumin, intact parathyroid hormone (iPTH) and plain x-rays.

Results: Bone disorders were identified in 45 patients on x-rays (70%). Osteopenia was found in 43 patients (68.3%), subperiosteal resorption in 24 patients (38.3%) and metastatic calcification in 22 patients (35%). Hypocalcemia was found in 28.6% and hypercalcemia in 7.9%. All patients were taking calcium carbonate, and 55.5% of patients were on vitamin D supplements. The calcium levels in 63.5% and the phosphorus levels in 50.8% of patients were within the recommended guidelines of the National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI). Serum i-PTH level was above 300 pg/ml "high turnover" bone disease in 24.6% of patients, 21.3% had iPTH of 150-300 pg/ml "target", and 44.3% had i-PTH levels below 100 pg/mL suggesting "a dynamic" bone disease. Patients with severe bone disease had a statistically significant higher iPTH levels ($p<0.005$).

Conclusion: Bone disease and mineral abnormalities are common in hemodialysis patients at JUH. Earlier detection of bone disease and better overall management strategy may reduce the frequency and severity of bone disease in CKD patients in Jordan.

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Calcium and phosphate homeostasis and parathyroid hormone (PTH) play an important role in the development of bone disease in chronic kidney disease (CKD).[1,2] The spectrum of bone disease in patients with CKD ranges from low-turnover bone disease such as adynamic bone lesions to the high-turnover bone disease such as osteitis fibrosa lesions. The classic form of renal osteodystrophy is osteitis fibrosa cystica (OFC), which is attributed to secondary hyperparathyroidism, Vitamin D ($1,25(OH)_2D_3$) deficiency as well as phosphate retention have been implicated as a major factor in the pathogenesis of hyperparathyroid bone disease in patients with CKD.[3,4] A significant number of patients with CKD with mineral and metabolic disorders may not manifest the symptoms of parathyroid bone disease.[5] However,

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a careful evaluation often discloses subtle or even profound radiological features on skeletal x-rays. The aim of this study is to determine the spectrum of bone disease and the frequency of electrolytes disorders in patients with CKD on regular hemodialysis and to assess the fraction of our patients meeting the targets set by National Kidney Foundation Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines at the largest teaching hospital in Jordan.

Methods. A cross-sectional chart review study was conducted among patients diagnosed to have CKD and on regular hemodialysis. Subjects were all patients who were presented to the Renal Unit at the Jordan University Hospital (JUH) from November 2004 to April 2005. Patients with CKD, aged 17-76 years old who had no history of preexisting conditions or drug treatments known to accelerate bone loss were potential subjects for the study. Inclusion in the study also required availability of the results of a blood chemistry profile (including calcium, phosphorus, alkaline phosphatase, serum creatinine, albumin and globulin, serum i-PTH, and random blood sugar. Exclusion criteria included patients who underwent kidney transplantation or transient hemodialysis, patients with a history of multiple myeloma, rheumatoid arthritis, tuberculosis arthritis, systemic lupus erythematosus arthritis, or patients with bone disease diagnosed prior to CKD. The underlying medical problem in these patients might have direct effect on the severity of bone disease.

Laboratory results outside the reference range of the JUH laboratory were considered abnormal. Patients with i-PTH of 150-300 pg/ml were considered to have "target" bone turnover and i-PTH levels below 100 pg/mL (normal 10-65 pg/mL) suggested "adynamic" bone turnover and patients with i-PTH levels above 300 pg/mL were considered to have "high turnover" bone disease.

Data were collected by chart review by an independent reviewer trained for this study. The following demographic and historical data were extracted for each subject: age, gender, etiology of CKD current dietary and supplemental calcium intake, vitamin D supplementation, and weight were recorded. The identification of bone disorders were established by an independent radiologist by reviewing the radiographs of the hands and forearm for all patients and specific x-rays in some patients whenever it was indicated.

A bone severity scoring system was used to evaluate the severity of bone disease according to the presence of abnormal radiological findings at or during the baseline evaluation (**Table 1**). Six bone abnormalities were evaluated on x-rays and each finding was given one point. Overall, a patient with a score of 1 or less was considered to have a mild bone disease (group A), a patient with a score of 2-3 would have a moderate bone disease (group B) and a score of 4 or more points would have a severe bone disease (group C). The severity of bone disease in these 3 groups was correlated statistically (using the Statistical Package for Social Sciences version 11) with the clinical, demographic features and chemistry profile of these patients. A $p<0.05$ was considered statistically significant.

Table 1 - X-ray score for patients with renal osteodystrophy.

X-ray finding	Severity*
Osteopenia	1 point
Subperiosteal resorption	1 point
Metastatic calcification	1 point
Tuft resorption (acroosteolysis)	1 point
Pathological fractures	1 point
Brown tumor	1 point

*severity score, mild disease score (1), moderate disease score (2-3), severe disease score (≥4)

Table 2 - Kidney disease outcomes quality initiative target ranges.

Parameter	Goal
Phosphorus (PO_4)	3.5-5.5 mg/dL
Calcium (Ca)	8.2-10.2 mg/dL
Ca × PO_4 product	<55 mg^2/dL^2
Parathyroid hormone	150-300 pg/mL

Table 3 - Correlations of the bone severity score in hemodialysis patients with different variables.

Variable	*P*-value
Age	0.198
Gender	0.236
Diabetes mellitus	0.742
Hypertension	0.04
Duration of end stage renal failure	0.166
Pain	0.133
Swelling	0.944
Deformity	0.601
Weakness	0.39
Fractures	0.487
Asymptomatic	0.182
Calcium	0.864
Phosphorus	0.759
Parathyroid hormone	0.005
Alkaline phosphatase	0.24

Results. Sixty three patients, mean age 44.19 years (range 17–76 years), met the inclusion criteria for the study. All blood samples were collected from all patients before hemodialysis (HD) commenced. Serum phosphorus ($PO_{4)}$, calcium (Ca), alkaline phosphatase (alkP)**,** and i-PTH levels were measured. Both PO_4 and Ca levels were measured by using the calorimetric method. The radioimmunoassay using the i-PTH RIA kit was used for the measurement of i-PTH. A high PTH level (>300 pg/ml) was detected in 24.6% and in 4.9% of the patients the level was very high (>500 pg/ml), a low PTH (<100 pg/ml) was detected in 44.3%, and a normal i-PTH level was detected in 21.3%. In the parathyroidectomy group, a lower PTH level was more common. The mean phosphorus level was 4.35 mg/dl (range 1.93-7.10 mg/dl), 28.6% of patients had hypocalcemia, and 7.9% had hypercalcemia. Calcium level (63.5%), phosphorus level (50.8%), and i-PTH levels (21.3%) of patients were within the recommended guidelines of the K/DOQI (**Table 2**). All patients were taking calcium carbonate, 19% of patients were taking regular one-alpha vitamin D, and 36.5% on rocaltrol. None of the patients were on aluminum containing binders. Forty-five patients (70%) had abnormal radiographs on-hand x-rays (**Figure 1**). Osteopenia was the most common radiological finding (68.3%), subperiosteal resorption in 24 patients (38.3%) and metastatic calcification in 22 patients (35%) (**Figure 2**). Analysis of the clinico biochemical characteristics showed that patients with hypertension (p<0.04) and high iPTH (p<0.005) had a statistically significant severe bone disease (**Table 3**).

Discussion. Secondary hyperparathyroidism (sHPT) is a common complication of chronic kidney disease (CKD) that can lead to clinically significant chronic bone disease. Renal osteodystrophy (ROD) refers to a spectrum of bone diseases that range from high-turnover lesions arising predominantly from excessive PTH secretion (high-turnover bone disease) to low-turnover lesions that are most commonly associated with normal or reduced serum PTH levels.[5,6] Hyperparathyroid (high turnover) bone disease is the most common form of bone disease in patients with CKD followed by mixed osteodystrophy, low-turn over bone disease, and osteomalacia.[7,8]

Data on the frequency of bone abnormalities in patients with CKD from Middle Eastern countries is scarce or nonexistent. In Saudi Arabia, Huraib et al[9] reported osteosclerosis as the most common radiological finding in their series. In Jordan, no

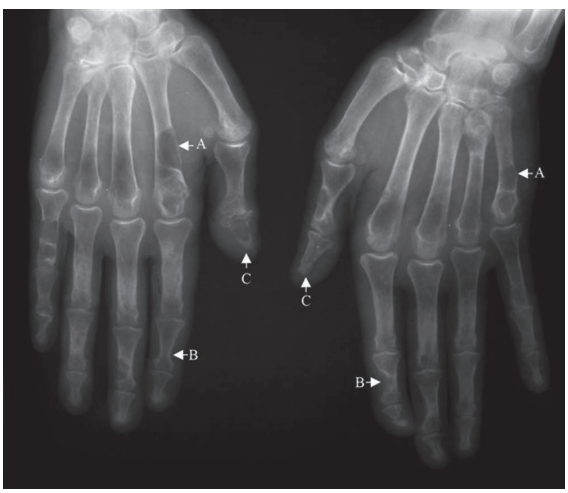

Figure 1 - Radiograph of both hands (frontal view) showing **(A)** multiple and bilateral brown tumors, **(B)** marked subperiosteal resorption and **(C)** distal phalangeal resorption (acroosteolysis). Note also diffuse osteopenia.

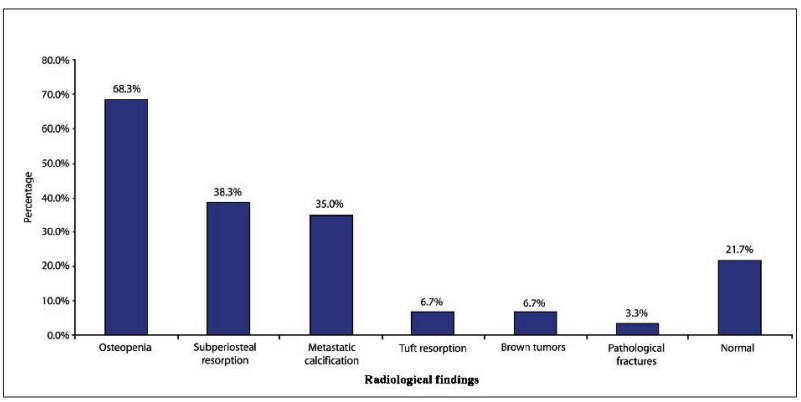

Figure 2 - Distribution of x-ray findings in 63 patients on hemodialysis.

data is available on the frequency and type of bone abnormalities in patients with CKD. We sought to determine the frequency of this problem in patients with CKD at the renal unit at JUH using the clinical features, laboratory data and radiological findings.

The prevalence of the different forms of renal bone disease in patients with CKD may vary depending on several factors such as; severity of hyperparathyroidism, dietary intake, duration of hemodialysis, aluminum exposure, therapy with vitamin D metabolites, and dialysis related factors.[5,6,10] The PTH levels in patients with CKD is an important parameter in predicting bone disease; in one study by Pei and Hercz,[7] 42% of patients with iPTH level <100pg/mL had low turnover or 'aplastic' bone, 23% of patients with iPTH levels 100-200 pg/mL had 'normal' bone turnover, and 35% of patients with iPTH levels >200pg/mL had sHPT.[8] In this study, only 21.3% of HD patients have met the guidelines of Kidney Disease Outcomes Quality Initiative (K/DOQI)[11,12] for the control of serum levels of i-PTH, 73% for calcium and 58.7% for the phosphorus. This is probably due to the routine use of calcium carbonate supplements and the non-compliance with vitamin D supplements.

The frequency of bone disease in our study was 70% based on skeletal x-rays evaluation, osteopenia was the most common form (68.3%), subperiosteal resorption 38.3%, metastatic calcification 35% and brown tumors were seen in 6.7% (**Figure 2**). These results are similar to other regional studies from Israel, which showed a 66.7% prevalence rate of renal osteodystrophy,[13] Egypt 33.3%,[14] and 57% in the Czech Republic.[15] Studies from Singapore, reported renal bone disease in 24.4% of patients,[16] and in Turkey, a high turnover renal osteodystrophy was the most common bone disease 47% seen among children with chronic renal failure undergoing continuous ambulatory peritoneal dialysis.[17] The high frequency of bone disease seen in our patients possibly related to the frequency of dialysis, non-compliance with diet and medications and malnutrition.

In the present study, adynamic bone disorder (patients with PTH levels <100 ng/l) is present in 44.3% presumably related to either surgical parathyroidectomy or due to over treatment with vitamin D in the predialysis stage. Parathyroidectomy has been reported to ameliorate the symptoms of hyperparathyroidism in HD and transplant patients.[18,19] In the present study, subtotal/total parathyroidectomy was considered as the treatment of choice in 17 patients (27%) with advanced secondary hyperparathyroidism.

Aluminum accumulation in the bones of patients undergoing maintenance dialysis is a well established entity.[20] This may be due to the use of large amounts of aluminum-containing phosphate binding agents for prolonged periods or parenteral exposure to inadequately treated water for dialysis solutions.[21] However, highly purified dialysis solutions are being used in our unit and none of our patients was using aluminum-containing binders for the control of hyperphosphatemia so the possibility of aluminum-related bone disease is unlikely in our patients.

One limitation of our study is that the small number of patients and the lack of bone biopsy for pathologic confirmation. However, many studies have shown that the frequency of bone disease in HD patients is positively correlated with the iPTH levels[22-24] and this obviates the need for bone biopsy in our patients.

Our data on the bone disease in HD patients is the first from Jordan and is based on the study of patients attending the renal unit at JUH. The personal, and financial burden of the long-term complications of bone disease in patients with CKD emphasize the need for better screening to detect ROD earlier in these patients, and the need for better overall management of HD patients. Further studies from additional centers, especially from the Ministry of Health and the Royal Army Hospitals are needed.

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