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Risk factors for reduced bone density in haemodialysis patients

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Abstract

Background. Renal osteodystrophy may result in considerable morbidity for patients with end-stage renal disease. Secondary hyperparathyroidism, adynamic bone disease and osteomalacia, the main bony problems in chronic renal failure, may all be responsible for a reduction in bone mineral density (BMD). This can result in an increased fracture risk. By virtue of their age, post-menopausal status (in women), sedentary life-style and treatment (including previous corticosteroids), haemodialysis patients may be expected also to be at risk for developing osteoporosis, but little is known about the relative importance of these factors.

Methods. We report a prospective study examining the prevalence of reduced bone mineral density (BMD) and its association with a wide range of factors, in a heterogenous group of 88 chronic haemodialysis patients. Femoral neck and lumbar BMD were measured by dual-energy X-ray absorptiometry (DXA). Stepwise multiple linear regression analysis was used to identify risk factors associated with low bone mass.

Results. Forty three patients (48.9%) had reduced BMD, and in 17 (19.3%) BMD was below the fracture threshold as defined on DXA measurements by the World Health Organization (WHO). The BMD had significant negative associations with age, serum parathyroid hormone (PTH) levels, current gastric acid suppression therapy, female gender, age at menarche and history of previous fracture. Positive associations were found with weight, haemoglobin concentration, average serum phosphate, weekly heparin dose, oral calcium supplementation and history of parathyroidectomy.

Conclusions. We have confirmed the importance of PTH-related bone disease in affecting BMD in haemodialysis patients, but have found that some other factors, which are known to be risk factors for osteoporosis, are also important.

Key words: DXA; haemodialysis; osteoporosis; parathyroid hormone; renal osteodystrophy; risk factors

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Introduction

Osteoporosis is associated with considerable morbidity and mortality in the general population, and large epidemiological studies have identified several risk factors for increased loss of bone mineral including advancing age, female gender, premature loss of gonadal function, thin body habitus, decreased physical activity, low calcium intake, cigarette smoking, alcohol abuse and excess glucocorticoid exposure [1]. In patients on haemodialysis, bone mineral density (BMD) may be adversely affected by a number of additional factors, but these have not been studied extensively.

Fracturing bone disease in the past was associated with aluminium overload [2] but, since this problem has been addressed, largely through water purification and avoidance of aluminium-containing phosphate binders, few studies have reported fracture prevalence specifically in haemodialysis patients [3–5]. These studies have reported an increased prevalence of fractures; the risk for hip fracture is increased 3- to 4-fold in patients with end-stage renal disease [3]. Though the relative risk was highest in the third decade, the absolute risk of fracture was highest in those above 70 years. There is a similar exponential increase in hip fracture associated with ageing in the general population. In addition to the fracture risk posed by an increasingly older population accepting long-term dialysis, many patients have reduced bone mineral content which may be attributable to other factors. Thinning of the bony cortex, which is responsible for the largest contribution towards reduced bone mineral content in chronic renal failure [6], results in increased fracture risk. In recent years, emphasis has been placed on the importance of disorders of vitamin D metabolism and parathyroid hormone (PTH) secretion [7]. However, several studies have been unable to demonstrate an association between reduced bone density and PTH levels [8–11], suggesting that other factors may be involved. Adynamic bone disease, increasingly identified as a significant form of renal osteodystrophy, is likely to be associated with reduced BMD, though concrete data are lacking. By virtue of their age, post-menopausal status (in women), sedentary life-style and

treatment including previous corticosteroids, haemodialysis patients may be expected to be at risk for developing osteoporosis, but little is known about the relative importance of these factors.

Currently, dual-energy X-ray absorptiometry (DXA) is the preferred method of measuring BMD due to its high precision and accuracy, short scan time and low radiation dose [12]. BMD measurements are important in the investigation of bone disease because they have been shown to predict fracture risk and currently are used to define osteoporosis [13]. The definitions advocated by the World Health Organization (WHO) are based on *T*-scores (*T*-score = measured BMD − young adult BMD/young adult standard deviation). From this, patients may be divided into normal ($T > -1.0$), osteopaenic ($T \leqslant -1.0$ and > -2.5) and osteoporotic ($T \leqslant -2.5$).

We report here the results of a study to determine the BMD and to investigate the relative importance of a wide range of factors in causing loss of bone mineral content in haemodialysis patients.

Subjects and methods

Patients

Patients were recruited from the dialysis unit at City Hospital, Nottingham and a satellite unit at King's Mill Centre, Mansfield, UK. All patients with end-stage chronic renal failure who had been on haemodialysis for longer than 1 month and who were able to complete an interview were considered eligible. Of the 106 patients who gave their consent, four died, two received renal transplants and one moved to another city before completing the study. Five patients withdrew their consent for the DXA scan due to concern about exposure to radiation, and four failed to attend for the DXA scan. One DXA scan failed due to technical problems. Eighty eight patients completed the study and their demographic data and biochemistry are summarized in Table 1. There were 48 males (54.5%) and 40 females (45.5%), of whom 32 were post-menopausal or permanently amenorrhoeic. The racial composition of the group was: nine Asian (10.2%), seven black (8.0%) and 72 white (81.8%). Chronic renal failure was of unknown aetiology in 34 patients (38.6%) and due to glomerulonephritis in 14 (15.9%), adult polycystic kidney disease in eight (9.1%), diabetic nephropathy in seven (8.0%), hypertension in six (6.8%), obstructive uropathy in five (5.7%), reflux nephropathy in four (4.5%), renovascular disease in three (3.4%), amyloidosis in three (3.4%) and non-recovery of acute renal failure in three (3.4%). The mean duration of dialysis in the group was 41.5 months (range 1–266 months) and the hours of dialysis per week ranged from 7–15 with a mean of 11.2. The dialysate calcium concentration was 1.0 mmol/l in 24 patients, 1.25 mmol/l in three patients and 1.5 mmol/l in 61 patients. Six patients (6.8%) had suffered fractures of long bones (excluding phalanges) since commencement of renal replacement therapy, and seven (8.0%) had undergone partial parathyroidectomy for severe secondary hyperparathyroidism. Gastric acid suppression therapy (either H_2 receptor antagonists or proton pump inhibitors) was being taken by 32 patients (36.4%), and 12 (13.6%) were taking warfarin. None of the post-menopausal females were receiving hormone replacement therapy (HRT). Dietary calcium intake was <500 mg/day in all but two patients, whose intake was 500–1000 mg/day.

Table 1. Patient characteristics

Characteristic	Value (mean ± SD)	Range
Age (years)	58.2 ± 17.3	18.7–87.0
Height (m)	1.66 ± 0.1	1.440–1.894
Weight (kg)	66.3 ± 14.3	35.4–104.9
Body mass index (kg/m^2)	23.9 ± 4.4	14.9–39.4
Smoking history (pack years)	12.4 ± 18.4	0–80
Alcohol intake (g/day)	2.0 ± 6.6	0–50
Current activity score (METs/day)	32.4 ± 4.1	24.0–51.0
Heparin dose (U/week)	14 726.8 ± 5994.7	0–33 750
Cumulative steroid dose (mg)	4680.9 ± 11 908.9	0–70 433
Alphacalcidol dose (μg/week)	1.1 ± 1.7	0–10.5
Calcium supplementation (mg/day)	1305.9 ± 1137.4	0–6000
Erythropoietin dose (U/week)	4720.5 ± 4331.0	0–16 000
Average serum calcium over 1 year (mmol/l)	2.52 ± 0.16	2.03–2.94
Average serum phosphate over 1 year (mmol/l)	1.87 ± 0.40	0.69–3.03
Average alkaline phosphatase over 1 year (IU/l)	268.1 ± 248.8	80–2194
PTH (ng/l)	238.8 ± 222.1	4–989
Serum ferritin (μg/l)	407.6 ± 309.6	21–2056
Urea reduction ratio (%)	64.9 ± 8.1	45.2–82.6
Haemoglobin (g/dl)	9.8 ± 1.5	5.6–13.7

Data collection

Collection of demographic data and treatment details was performed by means of a structured interview and review of patient folders and treatment records. Current physical activity levels were assessed using a questionnaire developed by Sallis *et al.* [14] and are expressed in metabolic equivalents (METs). Dietary calcium intake was documented with a questionnaire developed and validated by the Dietetics Department at City Hospital. Weight is measured before and after dialysis in all patients. The weight used in this study was the average of three post-dialysis weights recorded in the week prior to entry.

Biochemistry

Serum urea, creatinine, albumin, calcium, phosphate and alkaline phosphatase are measured every 2 months using standard autoanalyser techniques. Calcium levels were corrected for albumin concentration. The urea reduction ratio (URR) was calculated using urea levels before and after dialysis. Intact PTH levels were measured within 6 months of entry into the study using a radioimmunoassay ('Incstar' Atlantic Antibodies). From 24 January 1997, this was changed to a chemiluminescent enzyme immunometric assay performed with an automated analyser ('Immulite', Diagnostic Products Corp.). Results from the latter assay were converted to make them comparable with the results from the previous assay using a formula developed and

validated by the Clinical Chemistry Laboratory at City Hospital.

Bone densitometry

DXA studies of the lumbar spine and left hip (or right hip if this was not possible for technical reasons) were performed by the Radiology Department at City Hospital using a 'Lunar Expert-XL' densitometer (Lunar Corp.). Both systems report actual values obtained and *T*- and *Z*-scores which reflect the number of standard deviations by which a patient's value differs from the mean of a group of young normal or age-matched controls, respectively. Thus a *T*-score of -2.5 represents a BMD value 2.5 standard deviations below the mean of a young normal population. The WHO has defined osteoporosis in terms of T-score criteria. Osteopaenia is defined as a *T*-score of between -1.0 and -2.5, and osteoporosis as $\leqslant -2.5$ [13].

The study was approved by the Nottingham City Hospital Research Ethics Committee and all patients gave informed consent prior to entry into the study.

Analysis

Group data are shown as mean $\pm$ SD. Correlations between different bone measurements were assessed using Pearson's correlation coefficients. A stepwise multiple regression analysis was used to investigate relationships between bone measurements and risk factors for, or biochemical markers of, bone disease. Potential differences between the means of multiple subgroups were assessed with a Kruskal–Wallis test. Analyses were performed using SPSS for Windows 6.1 and Statview 4.01.

Results

Bone densitometry

The results of bone densitometry measurements in the 88 patients who completed the study are shown in Table 2. A high degree of correlation was found between DXA measurements at the two different sites in the femur ($r=0.92$; $P<0.001$); correlation coefficients between DXA lumbar spine values and femoral neck ($r=0.53$; $P<0.001$) or total hip ($r=0.60$; $P<0.001$), though lower, were still statistically significant.

Factors associated with reduced bone mineral density

Possible risk factors for and biochemical markers of bone disease were entered as independent variables in a stepwise linear multiple regression analysis. These included all the factors listed in Table 1 and, in addition, gender, history of long bone fracture, current smoking, previous parathyroidectomy, cumulative duration of previous transplant function, treatment with gastric acid suppression therapy and treatment with warfarin. The analysis was repeated for femoral neck BMD and total hip BMD. Independent variables which entered the equation for different analyses and reached statistical significance (*P*-values <0.05) are shown in Table 3. To examine associations within subgroups, the process was repeated using the data for female patients and for patients over 60 years. In the former analysis, age at menarche and menopausal status were added as independent variables; results are shown in Table 4.

Discussion

We have found a moderate reduction in mean BMD in this unselected population of chronic haemodialysis patients. The mean *Z*-score of -0.4 for the DXA measurement of the femoral neck implies that these patients are only moderately worse off than age-matched controls. This is similar to the results of several other studies using different methods of bone density measurement [8,10,11,15–17]. In our study, the prevalence of femoral neck BMD below the fracture threshold was 19.3%. Thus, although the mean BMD was only moderately reduced, a significant proportion of patients were at increased risk for fractures. Little is known about the fracture risk of haemodialysis patients with reduced BMD. In the only comprehensive epidemiological study reported by Gupta and colleagues, hip fracture risk among US Medicare end-stage renal failure patients was increased 3- to 4-fold [3]. In the general population, the risk of fracture increases 1.5–3 times for each standard deviation of decrease in BMD [13]. Six of our patients had a history of long-bone fracture, and there was a negative association between a history of fracture since the commencement of renal replacement therapy and femoral neck BMD in patients over 60 years, confirming that the risk is increased.

The relatively weak correlation between lumbar and femoral DXA measurements ($r=0.60$ and 0.53) is probably related to the effects of spinal osteophytes and aortic calcification which may spuriously elevate lumbar BMD measurements [18].

Table 2. Results of DXA in 88 chronic haemodialysis patients

	Measurement mean $\pm$ SD	*T*-score mean $\pm$ SD	*Z*-score mean $\pm$ SD	Osteoporosis[a] prevalence (%)	Osteopaenia[b] prevalence (%)
DXA femoral neck density (g/cm^2)	0.850 ± 0.170	-1.51 ± 1.38	-0.40 ± 1.22	19.3	48.9
DXA total hip density (g/cm^2)	0.890 ± 0.190	-1.25 ± 1.37	-0.48 ± 1.21	13.6	40.9
DXA lumbar (L2–L4) density (g/cm^2)	1.180 ± 0.280	-0.31 ± 2.25	0.56 ± 2.22	15.9	19.3

[a] *T*-score $\leqslant -2.5$; [b] *T*-score < -1.0 but > -2.5.

Table 3. Independent variables reaching significance from stepwise linear multiple regression analyses using femoral neck BMD and total hip BMD as dependent variables (all patients)

	Femoral neck BMD ($R^2=0.51$)		Total hip BMD ($R^2=0.59$)	
	Coefficient (B)	Standard Coefficient (β)	Coefficient (B)	Standard Coefficient (β)
Age	−0.003	−0.32	−0.002	−0.18
Weight	0.004	0.33	0.006	0.44
PTH	−0.0002	−0.27	−0.0003	−0.34
Gastric acid suppression therapy	−0.10	−0.30	−0.09	−0.24
Haemoglobin	–	–	0.02	0.16
Female sex	–	–	−0.09	−0.23
Average phosphate (1 year)	–	–	0.08	0.18
Weekly heparin dose	0.000005	0.19	–	–

Table 4. Independent variables entering the equation in repeated stepwise linear multiple regression analyses using femoral neck BMD and total hip BMD as dependent variables in (i) female patients and (ii) patients older than 60 years

	Female patients ($n=40$)				Patients >60 years ($n=49$)			
	Femoral neck BMD ($R^2=0.53$)		Total hip BMD ($R^2=0.67$)		Femoral neck BMD ($R^2=0.61$)		Total hip BMD ($R^2=0.64$)	
	B	β	B	β	B	β	B	β
Age	−0.004	−0.39	−0.005	−0.44	–	–	–	–
Weight	–	–	0.006	0.44	0.004	0.31	–	–
Height	–	–	−0.64	−0.26	–	–	–	–
PTH	–	–	–	–	−0.0002	−0.23	−0.0002	−0.25
Acid supp[a]	−0.12	−0.32	−0.12	−0.33	−0.13	−0.40	−0.11	−0.29
Female sex	–	–	–	–	–	–	−0.18	−0.46
Menarche[b]	−0.04	−0.37	−0.04	−0.38	–	–	–	–
Ca suppl[c]	–	–	–	–	0.00005	0.30	0.00006	0.27
PT surgery[d]	0.13	0.25	0.15	0.28	–	–	–	–
Fracture[e]	–	–	–	–	−0.17	−0.29	–	–
Heparin[f]	–	–	–	–	–	–	0.000007	0.21

[a]Gastric acid suppression therapy; [b]age at menarche; [c]oral calcium supplementation; [d]parathyroidectomy; [e]fracture since commencing renal replacement; [f]weekly heparin dose (units).

Cortical porosity is increased in hyperparathyroidism [19] and it is therefore not surprising that serum PTH is an important determinant of BMD. As can be seen from Tables 3 and 4, serum PTH was negatively associated with BMD measurements. Secondary hyperparathyroidism remains the most common type of renal bone disease found in haemodialysis patients. Either in isolation or as part of a mixed renal osteodystrophy picture, it has been reported on bone biopsy in 57 of 117 (49%) haemodialysis patients [7] and in 61 of 73 (84%) in a mixed group of haemo- and peritoneal dialysis patients [17]. Several studies have reported a similar negative association between PTH levels using a variety of measurements of BMD [20–22]. Other studies, however, have been unable to show a negative association between PTH levels and BMD [8–11,23]. While this may be explained by the small number of patients or the use of C-terminal PTH assays in some of the studies, it suggests that other factors affect BMD in haemodialysis patients. In female patients, previous parathyroidectomy was positively associated with femoral BMD (Table 4), suggesting recovery of the skeleton after correction of secondary hyperparathyroidism. This is supported by a similar finding in another cross-sectional study [16] and by longitudinal studies following parathyroidectomy [24].

Adynamic bone disease and osteomalacia may both be associated with reduced BMD but, as this study did not include bone histology, we are unable to comment on the prevalence in this population. Aluminium overload may be responsible for both conditions, and the definitive diagnosis of this rests with the discovery of aluminium deposits at the mineralization front on bone histology. In both our units, dialysate water aluminium content is measured routinely 6 monthly and is consistently below the recommended standard of 10 μg/l. Serum aluminium levels are measured routinely in only a small number of patients prescribed aluminium hydroxide as a phosphate binder, and this parameter was therefore not included in the multi-variant analysis.

Age and weight have emerged as important determinants of BMD in our study. Age-related bone loss plays an important role in the pathogenesis of osteoporosis and has been shown to occur in normal adults at a rate of 1–2% per year after age 40 years, increasing to 2–4% for 5–8 years following menopause in women

[1]. Several studies in dialysis patients have reported a negative association between age and BMD in female but not in male patients with end-stage renal disease [20,25]. Two studies found no association between age and BMD [11,21]. However, the mean age of patients in these studies was 43 and 50.5 years, respectively, while in our study patients were older with a mean age of 58.2 years. As dialysis programmes are accepting more and more elderly patients who are also experiencing markedly improved survival rates, age-related bone loss can be expected to become an increasingly important factor affecting bone disease in these patients. In the normal population, there is a positive correlation between weight and BMD [26]. This has been attributed to stimulation of bone formation by weight bearing and to increased peripheral conversion of adrenal androgens to oestrogens by adipose tissue. We have shown a similar association in our patients; though most studies in haemodialysis patients have not assessed patient weight, two studies have reported a positive association between body mass index and measures of BMD [16,21].

The finding of a negative association between gastric acid suppression therapy and BMD was unexpected and, to our knowledge, has not been reported previously. However, a case–control study of risk factors for hip fracture in men found an increased risk of fracture (odds ratio = 1.8) in those who had been treated previously with cimetidine, an effect attributed to its hormonal side effects (blocking of androgen receptors and inhibition of oestradiol 2-hydroxylation) [27]. Hormonal effects would, however, not explain the association in our patients as the majority were receiving omeprazole and not cimetidine. Although gastric acid previously was thought to be necessary to mobilize insoluble calcium complexes in food, calcium absorption has been shown to be normal after inhibition of gastric acid secretion by cimetidine [28]. An alternative explanation is suggested by animal experiments which have shown that the hypergastrinaemia resulting from omeprazole therapy is associated with hypertrophy of the parathyroid glands and a decrease in femoral BMD [29]. There was, however, no difference in PTH levels between our patients receiving gastric acid suppression therapy and those not receiving it (mean 250 ng/l *vs* 232 ng/l; $P = 0.7$). These findings require confirmation and further investigation, as dyspepsia and peptic ulcer disease are common in haemodialysis patients and many receive gastric acid suppression therapy (36% in our study).

Our results suggest that hormonal factors also affect bone density in haemodialysis patients. Female sex was negatively associated with total hip BMD in the group as a whole and in the subgroup of patients over 60 years. In female patients, there was a negative association with age at menarche. We were unable to show any effect of menopause or amenorrhoea, but this may have been due to the fact that 32 of the 40 female patients (80%) fell into this category. Hormonal factors are major determinants of BMD in patients without renal failure. Following menopause, bone loss increases for 5–8 years, and this contributes to the higher prevalence of osteoporosis in women than in men [1]. Peak bone mass has also been shown to be reduced in women with later menarche [30]. Many studies of BMD in dialysis patients have not examined the effect of gender and one has found no difference between the rate of bone loss in men and women [15]. However, Foldes *et al.* using tibial ultrasound reported reduced BMD in female patients [21], and Luisetto *et al.* found lower femoral and lumbar spine BMD in females [31]. One study found that total and pelvic BMD were lower in females over 50 years compared with those under 50 [20], and another reported a lower femoral neck BMD in women with secondary amenorrhoea [16]. There is evidence both from animal and human studies that oestrogen deficiency increases the sensitivity of bone to PTH [32]. These findings have important practical implications as oestrogen deficiency following menopause can be corrected with HRT. None of the patients in this study was receiving HRT.

The relationship between calcium intake, vitamin D supplementation and osteoporosis remains controversial. A review of 37 studies showed that calcium supplements had a consistent effect in preventing bone loss in 12 interventional studies in post-menopausal women and that the effect was greatest in studies in which the baseline calcium intake was low [33]. Few studies have addressed the issue of calcium supplementation in haemodialysis patients, although oral 1α-hydroxycalciferol treatment has been shown to prevent the loss of BMD at the lumbar spine in 165 male patients [34]. Many of our patients were receiving calcium-containing phosphate binders and we found a positive association between calcium supplementation and both measures of femoral BMD in patients over 60 years (Table 4). There was no association with dietary calcium intake but this was probably due to the fact that 86 of 88 patients were taking in <500 mg of calcium per day in their diets. We were unable to demonstrate any association between 1α-hydroxycalciferol therapy and BMD.

The positive association between weekly heparin dose, femoral neck BMD in the whole group and total hip BMD in patients over 60 years was unexpected as high dose heparin therapy has been associated with a decrease in BMD [35]. However, the dose of heparin in our patients (mean = 14 727 U/week) was much lower than the $>10\,000$ U/day in these reports. There was a positive correlation between heparin dose and patient weight ($r = 0.39$; $P < 0.001$), and this probably explains the above observations.

We were surprised that the cumulative dose of corticosteroids did not enter the regression equation in any of the analyses, as osteoporosis is a well documented complication of long-term steroid therapy. However, there is evidence to suggest that steroid-induced osteoporosis is reversible, at least in young patients [36]. As the use of steroids in our patients was mostly historical (as part of the immunosuppression for previous renal transplants), this may explain the lack of association.

Weight-bearing physical activity is associated with higher bone mass in cross-sectional studies of patients without renal failure. Prolonged bed rest causes a decrease in BMD while increased physical activity can lead to a small increase in BMD in formerly sedentary individuals [37]. We were unable to identify any association between current activity levels and BMD in haemodialysis patients. The very low current levels of activity (mean = 32.4 METs/day where 24 METs/day represents continuous rest or sleep) may account for this. The finding of a positive association between haemoglobin and total hip BMD may be an indirect indicator of an association with physical activity, as patients with a higher haemoglobin are likely to be more physically active.

In conclusion, while we have confirmed the importance of PTH-related bone disease in affecting BMD in haemodialysis patients, we have found that other factors which are known to be risk factors for osteoporosis, are also important. Age, weight, hormonal factors and calcium supplementation were all found to be determinants of BMD. In addition, we have reported a negative association between gastric acid suppression therapy and BMD as a new observation. These findings suggest that in future, increased attention should be paid to factors associated with osteoporosis and that efforts should be made to identify patients at increased risk for fractures for intervention. Prospective studies are required in order to quantitate the fracture risk and to determine thresholds for intervention.

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