PAPERS AND SHORT REPORTS

Who gets renal bone disease before beginning dialysis?

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Abstract

To identify patients at risk from renal bone disease we compared the demographic characteristics of 243 patients with end stage renal failure grouped according to the presence (97 (40%)) or absence of severe renal bone disease as judged by histological criteria. Youth, female sex, tubulointerstitial types of nephropathy, and a long duration of uraemia were all identified as significant independent risk factors for the development of bone disease. The relative risks from being female and having tubulointerstitial renal disease were separately identifiable when the estimated observation of renal failure was short (less than four years).

The identification of patients at high risk from bone disease may clarify the pathogenesis and treatment strategies of renal osteodystrophy.

Introduction

The prevalence of renal osteodystrophy in patients with end stage chronic renal failure depends on the criteria used for diagnosis. Nevertheless, it is apparent that a minority have severe bone disease whether this is judged by bone histology,^{1,2} radiographic findings,^{3,4} or symptoms.⁴ Surprisingly little is

known about the factors that determine which patients will develop severe bone disease, although such knowledge might be of value in understanding the pathogenesis of the disorder, predicting which patients are at risk, and planning prophylaxis. Factors considered have included the age and sex of patients⁵⁻⁷ and the duration and nature of their renal disease,^{3,4,8,9} but the interrelations between these putative risk factors are not clear. To define the characteristics of the population susceptible to bone disease we examined the interrelations between renal bone disease and various demographic features of a large, unselected series of patients with end stage uraemia.

Patients and methods

PATIENTS

Two hundred and thirty six patients (aged 12-66 years) with end stage chronic renal failure were studied within six months after beginning regular haemodialysis treatment. All patients entering the haemodialysis-transplantation programme at the Oxford Renal Unit between 1970 and 1979 were included in the study, and the population was not otherwise selected. These patients had received no previous treatment for bone disease apart from aluminium hydroxide for control of hyperphosphataemia, but none was hypophosphataemic. In particular, vitamin D analogues or metabolites and anticonvulsant drugs were not given.

We also studied seven patients (aged 14-49) with chronic progressive renal failure who had developed symptomatic bone disease requiring treatment before end stage was reached. These patients were assessed at the time of their bone biopsy and before the start of specific treatment. Plasma creatinine concentrations at the time of assessment ranged from 480 to 640 $\mu\text{mol/l}$ (5.3-7.1 mg/100 ml), and all seven eventually required dialysis treatment. In including these patients we assumed that their bone disease would not have improved spontaneously by the time dialysis was required.

METHODS

Transiliac bone biopsy specimens were obtained from all 243 patients. Undecalcified sections of trabecular bone were stained and examined according to methods previously described.^{9,10} Osteomalacia was diagnosed if five or more osteoid lamellae were visible under polarised light in any osteoid seam.¹¹ Osteitis fibrosa was diagnosed if marrow fibrosis extending beyond resorption cavities was present.¹⁰ Patients without osteomalacia or osteitis fibrosa

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according to these criteria were classified as having no bone disease or mild disease, as the appearance of bone in these patients was not invariably normal. Radiographic skeletal surveys were performed in 239 patients (incomplete in four patients). The radiographs were examined by two of us for the presence of subperiosteal erosions of the phalanges, clavicles, or elsewhere and for osteosclerosis of the spine or elsewhere. Activity of alkaline phosphatase was measured in plasma by Vickers multiple channel analyser (*p*-nitrophenylphosphate substrate) in 239 patients. The age and sex of all patients were noted, and, as far as possible, the cause and duration of renal failure were also established. The duration of renal failure was defined as the interval (to the nearest year) between the first recorded finding of a raised serum concentration of urea or creatinine and the initiation of regular haemodialysis treatment. This information was available in 235 patients. The causes of renal failure were established by clinical, biochemical, radiographic, or histological means in 239 patients and divided according to whether the renal lesion affected principally the glomeruli or renal vasculature or whether tubulointerstitial disease was a predominant feature (table I).

TABLE I—Prevalence of bone disease as judged by differing criteria according to nature of renal disease

Nature of renal disease	n	No (%) of patients with:			
		Histological bone disease	Erosions	Osteosclerosis	Hyperphosphatasia
Glomerulovascular disease:					
Glomerulonephritis	108	35 (32)	23 (21)	11 (10)	14 (13)
Hypertension	21	5 (24)	2 (10)	0	4 (20)
Other causes*	6	0	0	0	0
Total	135	40 (30)	25 (19)	11 (8)	18 (14)
Tubulointerstitial disease:					
Reflux nephropathy	60	29 (48)	20 (34)	11 (19)	32 (53)
Polycystic disease	25	16 (64)	5 (21)	2 (8)	5 (20)
Analgesic nephropathy	9	2 (22)	2 (22)	0	1 (11)
Other causes†	10	8 (80)	6 (60)	3 (38)	7 (70)
Total	104	55 (53)	33 (33)	16 (16)	45 (43)
Unknown	4	2 (50)	0	0	0
Total	243	97 (40)	58 (24)	27 (11)	63 (26)

*Includes diabetes, amyloid, trauma, cortical necrosis, and arterial disease.

†Includes obstructive uropathy, tuberculosis, and medullary cystic disease.

Because renal bone disease is profoundly modified by haemodialysis and transplantation, and because we wished to determine the factors influencing the prevalence of bone disease at end stage renal failure before these procedures, survival analysis was not considered to be appropriate. We therefore examined the association between the demographic features of the population and the presence of histological and radiographic findings by the χ^2 test. The effect of multiple categorised factors on the probability of developing bone disease was assessed using the technique of relative risk analysis.^{12 13} Student's *t* test for unpaired observations was used to compare mean activities of alkaline phosphatase and the estimated duration of renal failure in various subgroups. Alkaline phosphatase activities were $\log_{10}$ transformed before analysis as the distribution of values was skewed to the right. Values shown are given as the antilog of the mean (SEM) unless otherwise indicated. Values for the estimated duration of renal failure were also skewed but were not $\log_{10}$ transformed as the sample size was sufficient (by the central limit theorem) to enable the use of Student's *t* test.

Results

BIOCHEMICAL, RADIOGRAPHIC, AND HISTOLOGICAL CORRELATES

Histological evidence of bone disease was present in 97 (40%) of the 243 patients. This disease was classified in 49 (50%) as osteitis fibrosa, in 19 (20%) as osteomalacia, and in 29 (30%) as a combination of the two.

As expected, there was a highly significant association between the presence of osteitis fibrosa on bone biopsy and subperiosteal erosions on radiographs ($\chi^2=46.7$; $p<0.001$). Osteosclerosis was observed less often than subperiosteal erosion but was also associated with histological evidence of bone disease ($\chi^2=17.1$; $p<0.001$), noted more often when both osteomalacia and osteitis fibrosa were present than with either disorder alone (table II). Mean plasma alkaline phosphatase activity was significantly greater in patients with subperiosteal erosions than those without (131 (120-144) *v* 75 (73-77) IU/l; $p<0.001$) and was also greater in patients with osteosclerosis (125 (106-147) *v* 81 (78-84) IU/l; $p<0.001$). Plasma alkaline phos-

phatase activities were significantly higher in patients with histological bone disease than in those without (115 (108-123) *v* 72 (65-74) IU/l; $p<0.001$), and differences were also noted between various histological subtypes (table II).

AGE

The prevalence of bone disease was greater in patients aged below 21 but did not differ between any other age decades. The increased prevalence in those aged under 21, compared with older patients, was apparent whether bone disease was assessed histologically ($\chi^2=5.7$; $p<0.02$), radiographically ($\chi^2=20.1$; $p<0.01$), or by mean plasma alkaline phosphatase activities (148 (120-182) *v* 83 (80-85) IU/l; $p<0.02$) (table III). Five of the seven patients requiring treatment for bone disease before reaching end stage renal failure also came from this young age group ($\chi^2=28.3$; $p<0.001$), and young patients had a threefold greater risk of developing renal bone

TABLE II—Mean plasma alkaline phosphatase activity (95% confidence limits in parentheses) and prevalence of radiographic bone disease in patients with end stage renal failure grouped according to results of histological bone biopsies

Histological findings	n	Plasma alkaline phosphatase* (IU/l)	No (%) of patients with:	
			Subperiosteal erosions	Osteosclerosis
Mild bone disease	146	72 (67-77)	13/143 (9)	6/145 (4)
Osteomalacia	19	81 (66-99)	5/19 (26)	2/18 (11)
Osteitis fibrosa and osteomalacia	29	137 (109-220)	13/28 (46)	10/27 (37)
Osteitis fibrosa	49	119 (98-145)	27/49 (55)	9/49 (18)

*Log₁₀ transformed before analysis as distribution of values was skewed to the right.

disease (table IV). The distribution of sex, the type of renal disease, and the duration of renal failure did not differ significantly in this group compared with the rest of the population.

SEX

Women had a significantly greater prevalence of bone disease as judged by histology ($\chi^2=13.0$; $p<0.001$) and radiography (subperiosteal erosions; $\chi^2=6.6$; $p<0.02$). Plasma alkaline phosphatase activities differed less between the sexes (95 (89-100) *v* 83 (79-89) IU/l; $p=0.06$) (table V). The increased risk of renal bone disease in women was 2.6 greater than that in men (table IV).

ESTIMATED DURATION OF RENAL FAILURE

The prevalence of both histological and radiographic bone disease increased with the estimated duration of renal failure, although a similar trend was not seen with plasma alkaline phosphatase activities. The mean (SEM) duration of renal failure was significantly greater in those with bone disease than those without as judged by bone

TABLE III—Effect of age on prevalence of renal bone disease as judged by mean serum alkaline phosphatase activity (95% confidence limits in parentheses), skeletal radiographic findings, and bone histology

Age (years)	n	Plasma alkaline phosphatase* (IU/l)	No (%) of patients with radiographic:		No (%) of patients with histological bone disease
			Subperiosteal erosions	Osteosclerosis	
≤20	20	148 (98-223)	14/21 (67)	9/19 (47)	14/21 (67)
21-30	47	75 (66-86)	9/47 (19)	8/48 (77)	16/48 (33)
31-40	56	80 (70-90)	11/56 (20)	5/56 (9)	23/56 (41)
41-50	71	88 (77-100)	14/71 (20)	2/72 (3)	27/73 (37)
≥51	45	87 (77-97)	10/44 (23)	3/44 (7)	17/45 (38)

*Log₁₀ transformed before analysis as distribution of values was skewed to the right.

TABLE IV—Risk factors identified and risk of developing histological bone disease relative to remainder of population studied (risk of 1)

Risk factor	Relative risk	
	Mean	95% Confidence limits
Young age (<21 years)	2.94	1.81-4.78
Female	2.59	2.21-3.04
Long duration of uraemia (>4 years)	2.01	1.66-2.42
Interstitial types of renal disease	2.09	1.79-2.43

TABLE V—Effect of sex and type of renal disease on prevalence of bone disease

Type of nephropathy	No of observations	Plasma alkaline phosphatase* (IU/l)	No (%) of patients with:		
			Radiographic bone disease		Histological bone disease
			Osteosclerosis	Periosteal erosions	
Males (n = 154)					
Glomerular	103	75 (69-82)	8/102 (8)	18/101 (18)	28/103(27)
Tubulointerstitial	51	99 (81-120)	9/55 (16)	12/52 (23)	21/51 (41)
Females (n = 85)					
Glomerular	32	89 (73-107)	3/33 (9)	12/32 (38)	12/32 (38)
Tubulointerstitial	53	99 (85-114)	7/45 (16)	34/53 (64)	34/53 (64)

*Mean with 95% confidence limits in parentheses. Log₁₀ transformed as distribution of values was skewed to the right. Type of nephropathy was not determined in 4 patients.

histology (2.6 (0.2) v 1.8 (0.2) years; $p < 0.005$) or subperiosteal erosions (2.7 (0.3) v 1.9 (0.2) years; $p < 0.025$). The relative risk of developing renal bone disease in patients who had had renal failure for more than four years was twice as great as that in patients with a shorter duration of uraemia (table IV).

TYPE OF RENAL DISEASE

Patients with tubulointerstitial forms of renal disease showed a significantly higher prevalence of histological bone disease ($\chi^2 = 12.3$; $p < 0.001$) and subperiosteal erosions ($\chi^2 = 6.1$; $p < 0.02$) than those with glomerulovascular forms of renal disease. Mean plasma alkaline phosphatase activities were also higher (99 (93-105) v 78 (75-82) IU/l; $p < 0.002$) (table V) and the relative risk of bone disease twice that for the remaining patients (table IV).

INTERRELATIONS BETWEEN RISK FACTORS

Age, sex, estimated duration of renal failure, and type of renal disease all appeared to affect the relative risk of developing bone disease (table IV). The possibility that these risk factors were not independent of each other was considered. The sample distribution across sex, type of renal disease, and duration of renal failure was the same for those aged under 21 as for the remainder of the population, suggesting that young age was a genuinely independent factor.

Interrelations were more complex in the case of sex and type and duration of renal disease as correlations were observed between these factors. Women had a similar mean (SEM) duration of renal failure to men (2.4 (0.2) v 1.9 (0.2) years) but a greater prevalence of tubulointerstitial forms of renal disease ($\chi^2 = 17.9$; $p < 0.001$). Also, the mean duration of renal failure was longer in patients with tubulointerstitial than glomerulovascular disease (2.5 (0.2) v 1.8 (0.2) years;

$p < 0.01$). We therefore studied the relative risks in each subgroup of the population categorised by sex and type and duration of renal disease. The duration of renal failure was classified as either short (less than four years; 179 (76%) of all patients) or long (four or more years).

The results (figure and table VI) showed that, for patients with a short history of renal failure, both interstitial nephropathy and being female had an adverse effect on the risk of developing bone disease and that these effects could not be accounted for by inter-correlations between the factors. In patients with a long history of renal failure, however, neither being female nor the presence of interstitial renal disease was a significant risk factor. A long duration of renal failure was a particularly significant risk factor in men with glomerular or vascular forms of renal disease (relative risk 4.0 (table VI)).

Discussion

Each of the demographic features studied—age, sex, type of renal disease, and estimated duration of renal failure—appeared independently to influence the prevalence of bone disease in patients reaching end stage uraemia using our criteria for the presence and absence of bone disease. The classification of the presence or absence of bone disease by the radiographic or

histological appearances of bone is somewhat arbitrary as most patients reaching end stage renal failure show histological abnormalities. There is, however, an appreciable variation in histological appearances, with some patients having overt abnormalities and others minor changes of hyperparathyroidism such as increased osteoclastic and osteoblastic surfaces.¹⁴ We and others have therefore found it helpful to categorise histological findings according to the severity as well as the type of bone disease.^{9,15} The striking correlations observed between plasma alkaline phosphatase activities, radiographic findings, and bone histology suggest that such a classification was appropriate (table II).

Using these criteria, appreciable bone disease was present in only 97 (40%) of patients, and disease necessitating treatment before the onset of haemodialysis occurred in only seven (3%) of the 243 patients. The prevalence of osteitis fibrosa (78 patients (80%)) was significantly greater than that of osteomalacia (48 patients (50%)), in agreement with the view that hyperparathyroid bone disease arises earlier than osteomalacia in the course of renal failure.¹⁶

Bone disease in children and adolescents may be more obvious in the sense that patients often present with deformity or growth failure.¹⁷ Using more objective criteria we have confirmed that the prevalence of bone disease is higher in children and adolescents than in adults, whether assessed radiographically, biochemically, or histologically.^{8,5-7} In contrast, there was no relation between age and bone disease among the adult population. The susceptibility of the young may be related to the higher rate of bone remodelling¹⁸ and greater requirements for vitamin D and calcium.¹⁹ The normal adolescent growth spurt is accompanied by increased serum

concentrations of 1,25-dihydroxyvitamin D ($1,25(\text{OH})_2\text{D}$),²⁰ but in uraemia production of this hormone is impaired²¹ and both the retardation of growth and the severity of hyperparathyroid bone disease may be aggravated by impaired production of 1,25-dihydroxyvitamin D.²²⁻²³ It would perhaps not be surprising therefore if the effects of 1,25-dihydroxyvitamin D deficiency were more pronounced in adolescents.

Top: Effect of type of renal disease and short (●—●) or long (○—○) duration of uraemia on relative risk of women developing histological evidence of bone disease. Bottom: Effect of sex and short (●—●) or long (○—○) duration of uraemia on the risk of developing bone disease in the presence of interstitial kidney disease. The dotted horizontal line refers to the risk in the remaining population. Vertical bars indicate 95% confidence intervals. Note the logarithmic coordinates.

of renal failure seen in these patients. Our analysis suggests, however, that the nature of the renal disease and the duration of renal failure are independent risk factors.

The effect of sex on the prevalence of bone disease was not spurious despite the unequal distribution of sex between the two categories of renal disease. This unexpected finding has recently been independently reported in patients receiving haemodialysis⁷ but is contrary to an earlier study using fewer patients and radiographic criteria alone.³

Precedents for such a sex difference in metabolic bone disease include the more appreciable age related bone loss in women than men²⁴ and the greater incidence of primary hyperparathyroidism.²⁷ These differences are probably due to diminished production of gonadal steroids, a phenomenon also observed in chronic uraemia.²⁸⁻²⁹ Gonadal steroids may play a more critical part than hitherto recognised in the skeletal metabolism of women with chronic renal failure.

Other factors, not considered in this study, are undoubtedly important. Examples include privational deficiency of vitamin D,²³⁻³⁰ hypocalcaemia,⁴⁻³¹⁻³² systemic acidosis,⁴⁻³² hyperphosphataemia,⁴ and dietary deficiency of calcium,³³ which might additionally influence the severity of bone disease. Some of these biochemical factors may, however, be related to the nature of the renal disease. For example, patients with tubulointerstitial forms of renal disease have lower serum concentrations of calcium, phosphate, and bicarbonate than others.⁴⁻³²

The interrelations between the factors studied indicated that among patients with uraemia of short duration (reflecting a rapid progression of renal failure) both interstitial renal disease and female sex conferred a high risk of developing bone disease. A long history of uraemia, reflecting a slower rate of decline in renal function, was a risk factor, particularly in men with glomerulovascular forms of disease. A long history of uraemia did not appear to confer a significant additive risk in women with tubulointerstitial disease, possibly because of the hetero-

TABLE VI—Interrelation of identified risk factors. The risk of having bone disease was compared in patients categorised as shown in the first column but subdivided according to the additional features shown in columns 2-4

Risk factor	Long duration	Interstitial nephropathy	Female	Relative risk		
				Mean	95% Confidence interval	
Female	Yes	Yes		1.00	0.32	3.13
	Yes	No		1.13	0.31	4.11
	No	Yes		4.36*	2.63	7.23
	No	No		1.66	0.96	2.87
Interstitial nephropathy	Yes		No	0.90	0.31	2.61
	No		No	1.78*	1.21	2.61
	Yes		Yes	0.80	0.20	3.16
	No		Yes	4.67*	2.39	9.17
Long duration of uraemia		Yes	No	2.00	0.81	4.90
		No	No	3.95*	2.27	6.85
		Yes	Yes	0.46*	0.22	0.97
		No	Yes	2.68	0.74	9.80

*Significant ($p < 0.05$) differences.

The effect of the type of renal disease on the prevalence of bone disease may also be due to differences in the capacity of renal tubules to synthesise 1,25-dihydroxyvitamin D.²⁴ In addition, patients with prominent tubulointerstitial disease have other defects of tubular function such as polyuria and renal loss of phosphate, bicarbonate, and calcium, all of which might also contribute to bone disease. The differing incidence of bone disease in the various types of renal tubular acidosis has also been attributed to the associated renal tubular defects.²⁵ The nature of the renal disorders may also influence the type of bone disease that develops. For example, patients with interstitial and obstructive forms of renal disease have a high incidence of osteomalacia.⁴ We have not been able to confirm a previous report that patients with polycystic disease have a lower prevalence of hyperparathyroid bone disease (table I).³ The increased prevalence of bone disease in patients with tubulointerstitial disease has been noted by others in selected populations⁷⁻⁸ but has generally been attributed to the longer duration

geneity of this class of disorder. Indeed, this subgroup (female, interstitial nephropathy, long history) seemed marginally protected from bone disease, but the clinical importance of this finding was not clear.

Attention has recently focused on the possibility of preventing renal osteodystrophy by the prophylactic use of 1α -hydroxylated vitamin D derivatives.³⁴ Prophylaxis is more likely to be effective if given early, and this may therefore entail giving these preparations to patients before they need dialysis treatment. This may be hazardous as the subsequent increase in serum calcium and phosphate concentrations may accelerate the rate at which renal function deteriorates.³⁵⁻³⁶ Our data suggest that certain groups of patients—those aged under 21, those with interstitial renal disease, and those with a long history of renal failure—are more at risk than others. Restricting prophylaxis to patients at high risk will spare those at low risk from the hazards of such treatment and also make it easier to evaluate its efficacy.

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A prospective randomised controlled clinical trial comparing somatostatin and vasopressin in controlling acute variceal haemorrhage

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Abstract

Twenty two patients were entered into a randomised controlled clinical trial comparing the efficacy of somatostatin and vasopressin in controlling acute variceal haemorrhage. Somatostatin was significantly more successful in controlling acute variceal haemorrhage than vasopressin ($p=0.003$). Furthermore, no complications were observed during treatment with somatostatin.

Introduction

The main objective of vasoactive drug treatment of portal hypertension is to control variceal haemorrhage until definitive treatment can be undertaken. Although vasopressin has been used for several years for the emergency control of bleeding oesophageal varices,¹ it is successful in only about half of all patients.² Moreover, treatment with vasopressin may have undesirable side effects such as coronary vasoconstriction, pulmonary oedema, and abdominal colic.³

Somatostatin, first isolated from the hypothalamus in 1972,⁴ is widely distributed throughout the body, particularly high concentrations being found in the central nervous system, gastrointestinal tract, and pancreas. In addition to inhibiting the release of many gastrointestinal hormones,⁵⁻⁷ somatostatin is also a potent inhibitor of gastric and pancreatic secretions.^{8,9} Furthermore, studies of the effects of somatostatin on hepatic haemodynamics in animals and on wedged hepatic venous pressure in man have suggested that somatostatin may be effective in controlling acute variceal haemorrhage.^{10,11} The aim of this study was to compare the efficacy of somatostatin and vasopressin in controlling acute variceal haemorrhage in a prospective randomised controlled clinical trial.

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