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Changes in Skeletal Mineral in Patients on Prolonged Maintenance Dialysis

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Summary

The measurement of bone loss in patients undergoing maintenance dialysis over a period of two and a half years is reported. The tendency to lose bone is a likely event in renal failure, but depends more on the individual patient than on the type of dialysis used, provided that steps are taken to prevent avoidable calcium loss during dialysis. Vitamin D therapy was an important factor in preventing bone loss in some cases. The tendency to lose bone more readily when both kidneys were absent may have reflected a deficiency of 1-25 dihydrocholecalciferol. On the other hand, bone loss was also observed in transplanted patients. The need to measure bone loss at regular intervals once renal failure has been diagnosed is stressed.

Introduction

Calcium metabolism is always disturbed in chronic renal failure. Absorption of dietary calcium is reduced as a result of

abnormal vitamin D metabolism (Genuth *et al.*, 1969), and increased parathyroid activity commonly leads to excessive bone resorption (Kleeman *et al.*, 1970). Thus, both osteomalacic and fibrocystic bone changes are found. Such disturbed calcium metabolism almost invariably leads to an increased rate of bone resorption which is often associated with the deposition of calcium salts in soft tissues. The difficulty of assessing metabolic balance studies under these circumstances is formidable, but a better understanding about the state of the bone mineral in chronic renal failure can be achieved by measuring the loss of bone.

A previous paper reported a scanning technique which uses the 60 keV emission from the isotope ^{241}Am to measure the bone mineral in the femoral shaft of patients on maintenance dialysis (Atkinson *et al.*, 1970). Measurements made at monthly intervals over 40 weeks showed that 13 patients had a tendency to lose bone mineral. The present paper reports changes in the bone mineral in 15 patients during a much longer period (two and a half years) which includes the time covered by the initial report.

Method

Measurements of bone mineral have been made on a control group of subjects and on 15 patients receiving maintenance dialysis for chronic renal failure. At the beginning of this study six patients were being treated by peritoneal dialysis and seven by haemodialysis. This therapy was maintained during the first 40 weeks (table I). After two and a half years two remained on peritoneal dialysis; six, together with two new patients, were on haemodialysis; and two had received transplants (three had discontinued bone measurements). Only in the two transplanted patients was there any significant renal excretion; of the dialysed

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TABLE 1—Comparison of Rate of Change of Bone Index During First 40 Weeks and During Two and a half Years. Figures in Parentheses are S.D.

Case No.	Age	Sex	Rate of Change of Bone Index* (% per 10 Weeks)	
			1st Study (40 Weeks†)	During 2½ Years
1 (a)	18	F.	-4.7 (± 1.50)	N.S.
2 (c)	35	F.	-1.8 (± 0.77)	N.S.
3 (c)	39	F.	-2.0 (± 1.04)	-0.82 (± 0.27)
4 (c)	41	F.	N.S.	—
5 (c)	44	F.	-4.4 (± 0.92)	-1.58 (± 0.20)
6 (a)	55	F.	-5.5 (± 1.33)	-1.25 (± 0.23)
7 (b)	24	M.	-1.9 (± 0.65)	-1.36 (± 0.15)
8 (d)	39	F.	N.S.	-0.49 (± 0.27)
9 (b)	41	M.	-1.2 (± 0.46)	—
10 (b)	42	M.	N.S.	N.S.
11 (d)	42	M.	N.S.	-0.59 (± 0.21)
12 (b)	47	F.	N.S.	—
13 (b)	49	F.	-2.4 (± 0.90)	-0.87 (± 0.16)
14 (b)	35	F.	—	+2.65 (± 0.42)
15 (b)	30	F.	—	-1.32 (± 0.19)

*Bone index is expressed as g/cm.

†Atkinson *et al.* (1970).

(a) Remained on peritoneal dialysis.

(b) Remained on haemodialysis.

(c) Changed from peritoneal dialysis to haemodialysis.

(d) Received renal transplant.

N.S. = Not significant.

patients five produced negligible amounts of urine and five had had bilateral nephrectomy.

During this prolonged study, apart from changing peritoneal dialysis to haemodialysis, other types of treatment were initiated. These included vitamin D, calcium carbonate, and phosphate therapy, while steroid and immunosuppressive therapy was given to the transplanted patients.

The method used for the measurement of bone mineral has already been described (West and Reed, 1970). The bone index measurements, which have a reproducibility of about 2%, were made at monthly intervals, as were plasma levels of sodium, potassium, chloride, CO₂ combining power, urea, creatinine, calcium, phosphorus, and alkaline phosphatase. Serial creatinine clearance values were obtained on the transplanted patients.

PERITONEAL DIALYSIS

Peritoneal dialysis was repeated at weekly intervals, 2 litres of dialysis fluid being used for each hourly exchange over a period of 36 hours.

The concentration of calcium in the peritoneal dialysis fluid was 7.2 mg/100 ml, but this was reduced during the dehydrating period of each dialysis when a variable quantity of 5% dextrose was added to correct sodium retention (Moriarty and Parsons, 1966). This occasional reduction in calcium concentration of the dialysis fluid did not necessarily cause a negative calcium dialysis balance. On investigation most patients retained calcium from the dialysis fluid, presumably because of its high calcium content (average 260 mg/dialysis, range 88-740 mg). However, when the patient required considerable dehydration the quantity of 5% dextrose used was increased and the calcium balance became less positive. In order to correct this the sodium and chloride concentration of the dialysate was reduced to 120 and 85.7 mEq/l. respectively and the dextrose concentration adjusted to 2.25 g/100 ml. The calcium balance between patient and dialysate then became consistently positive (average 247 mg/dialysis, range 115-337 mg). This change in composition is advocated during the dehydrating phase of long-term intermittent peritoneal dialysis.

HAEMODIALYSIS

Haemodialysis was undertaken three times a week, each session being of 10 hours' duration.

After our original observation of a progressive loss of bone mineral during dialysis (Atkinson *et al.*, 1970) and the reassessment of an earlier finding that the correction of acidosis by

dialysis was incomplete (Morrell and Parsons, 1967), the composition of haemodialysis fluid was changed in an attempt to reduce acidosis still further and thereby increase absorption of dietary calcium (Makoff *et al.*, 1969). The sodium/chloride ratio of the haemodialysis fluid was increased from 1.3:1 to 1.4:1. After this change the average arterial pH and PCO₂ values at the start of dialysis rose during dialysis from 7.408 (range 7.391-7.462) to 7.433 (range 7.400-7.470) and 25.7 (range 24.0-27.9) to 34.9 mm Hg (range 32.0-38.1) respectively. The alteration of sodium/chloride ratio of the dialysis fluid to 1.4:1 changed the ratio in the plasma from 1.35 to 1.5, a larger rise than expected and probably an effect of the Donnan equilibrium across the dialysis membrane and of the Hamburger (chloride) shift.

At the same time as the sodium/chloride ratio was altered the calcium concentration of the dialysate was increased from 6.0 to 6.2 mg/100 ml to counter an estimated loss of 9-18 g calcium/year (1% total body calcium) occurring during routine ultrafiltration. Similarly, since a loss of 5.5-6.2 g calcium/year was possible, an attempt to avoid this was made by adding 6.0 mg/100 ml of calcium to the routine wash-through fluid used in the blood compartment of the dialyser.

Results

The mean bone index for a control group of males (range 4.47-9.78 g/cm, mean 6.79) was indistinguishable from the patient group (range 4.87-7.31, mean 6.47); the mean age was 33 and 36 years respectively. The mean bone index for female patients (range 3.07-6.68, mean 4.39) was lower than their control group (range 4.53-6.62, mean 5.47); the mean age was greater for patients (38 years) than for controls (29 years). This gives an indication of the deviation from normal for female patients, but does not preclude the possibility that both controls and patients may be undergoing bone resorption at the time of measurement. Such bone changes were observed when both rate and extent of the change in bone index were calculated for each subject.

The rates of change in bone index observed during two and a half years, together with those of the earlier study (Atkinson *et al.*, 1970), are shown in table I (patients having the same case numbers for both studies). Values lying more than 3 S.D. from the regression lines fitted to the data for each subject were excluded. Only those regressions having a slope with a significance of $P < 0.1$ were accepted as showing any change, the others being regarded as not significant. The slope of the regression line and the estimated initial bone index were used to calculate the mean percentage change in bone index per 10 weeks.

Measurements of bone index made during a period of 12 months for each of 24 control subjects showed no change, and in only one, a 55-year-old man, was a loss recorded (-1.63 ± 0.74). During the first 40 weeks measurements on patients showed that all but one on peritoneal dialysis (cases 1 to 6) and three out of seven on haemodialysis (cases 7 to 13) lost bone (table I). In the longer period this loss had been reduced in two patients remaining on peritoneal dialysis, but five out of seven patients on haemodialysis showed a loss.

In five patients treatment was changed during the investigation—two receiving transplants (cases 8 and 11) and three being changed from peritoneal dialysis to haemodialysis (cases 2, 3, and 5) (table II). Both "transplant" patients showed a greater fall in bone index after transplantation than before, one (case 8, average creatinine clearance 26.4 mg/min) directly after, the other (case 11, average creatinine clearance 65 ml/min) a year after transplantation. In the post-transplantation year the patient with the lower creatinine clearance (case 8) rejected her kidney. In three patients (cases 2, 3, and 5) the change from peritoneal dialysis to haemodialysis led to an improvement in the uraemia, but in only one (case 5) was a fall in bone index halted. An increase in bone index occurred in another (case 2) before but not after the change in dialysis.

In three instances (cases 1, 3, and 14) dialysis was supplemented by other therapeutic measures (table II). One suffering

TABLE II—Comparison of Rate of Loss before and after Specific Changes in Treatment for Selected Patients. Figures in Parentheses are S.D.

Case No.	Observation Period (Weeks)	No. of Measurements	Rate of Change of Bone Index (% per 10 weeks)	Treatment
1	17	11	-6.50 ($\pm$ 3.57)	Peritoneal dialysis, vitamin D (10,000 IU)
	98	21	+1.22 ($\pm$ 0.60)	Peritoneal dialysis, vitamin D and calcium carbonate (7.5 g/day)
2	79	17	+0.84 ($\pm$ 0.37)	Peritoneal dialysis
	18	5	N.S.	Haemodialysis
3	42	9	N.S.	Peritoneal dialysis
	66	16	N.S.	Haemodialysis and calcium carbonate (7.5 g/day)
5	101	23	-1.41 ($\pm$ 0.48)	Peritoneal dialysis
	14	4	N.S.	Haemodialysis dihydrotachysterol (0.5 mg/day)
8	59	15	+0.95 ($\pm$ 0.46)	Haemodialysis
	48	10	-3.53 ($\pm$ 0.37)	Renal transplant
	28	7	N.S.	Haemodialysis
11	52	12	N.S.	Renal transplant
	28	6	-3.48 ($\pm$ 0.51)	Renal transplant
14	57	10	-0.73 ($\pm$ 0.37)	Haemodialysis, vitamin D (10,000 IU/day)
	43	8	+4.93 ($\pm$ 0.53)	Haemodialysis, vitamin D (40,000 IU/day) calcium carbonate (7.5 g/day)

N.S. = Not significant.

TABLE III—Mean Values of Serum Calcium, Phosphorus, Alkaline Phosphatase, and Urea for Patients on Peritoneal Dialysis and Haemodialysis Recorded during Periods with and without Bone Loss

Treatment	Bone State	No. of Periods	Calcium (mg/100 ml)	Phosphorus (mg/100 ml)	Ca $\times$ P	Alkaline Phosphatase (K.A. Units)	Urea (mg/100 ml)
Peritoneal dialysis	Steady or Gain	3	9.0	7.7	69	13	192
	Loss	2	9.8	7.1	69	20	159
Haemodialysis	Steady or Gain	6	9.9	4.2	41	13	93
	Loss	4	9.9	4.2	42	14	96
All Groups:							
Peritoneal dialysis		5	9.3	7.4	69	14.7	178
Haemodialysis ..		10	9.9	4.2	41	13.1	94

from renal rickets and maintained on peritoneal dialysis (case 1) was given vitamin D (10,000 IU daily), but no reduction in bone loss occurred until treatment with calcium carbonate had been started; only then was the fall reversed. Another patient with severe metabolic bone disease (case 14) was given vitamin D in large doses (40,000 IU daily) in addition to calcium carbonate (7.5 g/daily), and a highly significant increase in bone index occurred. Another patient (case 3) was given calcium carbonate (7.5 g/daily) but no significant change in bone index was seen.

An attempt was made to relate femoral bone loss with the biochemical findings, results being averaged for different periods during the two and a half year study. Periods in which bone was lost were distinguished from those where no loss occurred and these were subdivided for each type of dialysis (tables I and II). Results were excluded if vitamin D or other steroid therapy was used. No data were available for one patient (case 11); for others there was often more than one period, even when there was no change in dialysis, as in case 7. Results were obtained for 15 periods (12 patients) and are shown in table III. Different numbers of biochemical observations were made on each patient. However, since the patient variation for each observation was small, the mean value for the results was used in each case. The mean for each group of patients was then obtained from these figures. Only the results for calcium, phosphorus, alkaline phosphatase, and urea showed changes (table III). There were no significant differences $P > 0.1$ (Student's *t* test) in blood chemistry between patients who showed a bone loss and those who did not. Blood urea and serum phosphate were significantly higher on peritoneal dialysis than on haemodialysis. The Ca $\times$ P product was also higher on peritoneal dialysis because of the raised phosphate.

Discussion

Changes in femoral bone index have been measured over a period of two and a half years in 15 patients, aged between 18 and

55 years, undergoing treatment for chronic renal failure. There is evidence that the observed changes were representative of the whole skeleton, since the site used is susceptible to resorption in normal ageing subjects (Atkinson and Weatherell, 1967; Reed *et al.*, 1970) and in lactating mothers (Atkinson and West, 1970). It has also been shown to be representative of the skeleton in a study of dried human bones (West, 1973).

Loss of bone was a common finding but was influenced by changes in treatment. Two patients tended to lose bone mineral after renal transplantation, progressive loss being observed immediately in one (case 8) but not until one year after transplantation in the other (case 11). Though high doses of steroids were given after both transplantations (100 mg or more daily for six weeks (case 8) and two weeks (case 11)) it is unlikely that they alone predisposed to this increased loss since the dose was progressively reduced to 15 mg/day during three months (case 8) and six months (case 11) respectively. By reducing the urea and creatinine in the plasma, transplantation might have been expected to reverse any osteodystrophy that developed during the period of renal failure. The rate of bone loss, however, increased in both patients, one of whom had shown no loss before transplantation (case 11). Since the serum calcium tended to be high (10.0 mg/100 ml) and the phosphorus usually less than 2.5 mg/100 ml in both patients, it might reasonably be expected that a hyperparathyroid effect was responsible for this increased loss, but this expectation does not explain the apparent delayed effect in case 11.

The change from peritoneal dialysis to haemodialysis produced a significant reduction in plasma urea and creatinine in three patients (cases 2, 3, and 5), but surprisingly it led to a reduction of bone loss in only one (case 5) (table II). However, this reduction might have been associated with dihydrotachysterol therapy rather than the change in method of dialysis. No significant change in bone index was observed in the other two while on haemodialysis, though one (case 2) had gained while on peritoneal dialysis. Treatment with calcium carbonate (7.5 g/day) during haemodialysis might have been instrumental in preventing loss of bone in case 3. Failure to produce improvement in bone index might have been due to different calcium

concentrations in the respective dialysates. The dialysate used for peritoneal dialysis (calcium 7.2 mg/100 ml) would be more likely to lead to a positive calcium balance than that used for patients on haemodialysis (calcium 6.2 mg/100 ml). Curtis *et al.* (1969) emphasized the need to maintain a high calcium level in haemodialysis fluids, while more recently Bone *et al.* (1972) increased the dialysate calcium to 7.0 mg/100 ml and were able to reverse the mineral loss previously observed on lower calcium levels.

Despite attempts to prevent calcium loss in haemodialysis patients there was very little evidence to suggest that either changing the sodium/chloride ratio of the dialysate or adding calcium to the system reduced bone loss. In only two patients (cases 7 and 13) might the reduction in loss be accounted for in this way. In one instance (case 14) bone index increased significantly, but this could well have been the result of vitamin D therapy.

The reduction of the uraemia during dialysis might, under certain circumstances, lead to increased bone loss. Sarnethsiri *et al.* (1969) suggested that the toxic effects of uraemia might mask a hyperparathyroid response, but bone loss was no greater after the change to haemodialysis which consistently led to lower urea and creatinine values in the plasma. This finding is in agreement with Hampers and Schupack (1967) who showed that osteodystrophy progressed despite a reduction of plasma urea. Other workers who had observed osteodystrophy in nephrectomized rats were unable to produce similar changes by raising the blood urea alone (Krempien and Ritz, 1971). Maintaining a low blood phosphorus has also reduced hyperparathyroidism (Slatopolsky *et al.*, 1971), which presumably diminished overall bone resorption. However, the lower blood phosphorus maintained in haemodialysed patients in contrast with the higher phosphorus values of peritoneal dialysed patients apparently had no effect on those showing a bone loss. Thus, uninhibited hyperparathyroidism is unlikely to be the only cause of bone loss in dialysed patients.

In the present study bone loss was not irreversible but the only convincing improvement occurred during the administration of vitamin D when supplemented with calcium.

Low levels of bone index suggest that the demand for bone mineral occurs at an early stage of the disease. It may arise because of an inadequate absorption of calcium from the small intestine, which is emphasized by the failure to find the active metabolite 1-25 dihydrocholecalciferol in the blood of these patients (Mawer *et al.*, 1973). Bishop *et al.* (1972) expected a greater susceptibility to osteomalacia after total nephrectomy, though they were not able to confirm this by means of bone biopsies. However, parathyroid hormone can inhibit renal production of 1-25 dihydrocholecalciferol (Galante *et al.*, 1972), and this might occur when blood calcium levels fall in periods between dialysis. Thus, when patients do not lose bone it may not be the bone's resistance to the action of parathyroid hormone (Massry *et al.*, 1966) so much as the patient's ability still to produce 1-25 dihydrocholecalciferol. The inability to produce this metabolite might occur if renal tissue were damaged (Lawson *et al.*, 1971), but would be most evident after bilateral nephrectomy.

Considering the present results in the light of this hypothesis it is found that of six patients who had had total nephrectomy (cases 7, 8, 9, 12, 13, and 15) four (cases 7, 9, 13, and 15) showed a bone loss; of two patients (cases 5 and 14) who had only one kidney removed one (case 5) showed a bone loss while the other showed a gain as a result of supplementing with high doses of vitamin D; of seven patients who had two non-excreting kidneys (cases 1, 2, 3, 4, 6, 10, and 11) one (case 1) had received vitamin D supplements, but four others (cases 2, 4, 10, and 11) showed no bone loss. (Cases 8 and 11 showed a bone loss only after transplantation.)

Though patients who have had total nephrectomy may appear to be more susceptible to bone loss than the others, it is not possible to draw definite conclusions from such a small number of subjects. Nor is the loss of bone after transplantation explained. It is necessary to know the level of both circulating parathyroid hormone and 1-25 dihydrocholecalciferol before the value of this and other similar metabolites can be ascertained. This is presently being investigated.

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