Bone disease following renal transplantation

B. J. R. Junor, B. F. Boyce *, J. D. Briggs, M. A. Forwell, M. Z. Mocan and D. Tsakiris

Renal Unit, Western Infirmary and * Pathology Department. Royal Infirmary. Glasgow (Scotland).

RESUMEN

Patología ósea postrasplante renal.
La complicación ósea más frecuente del trasplante renal ha sido la necrosis vascular en relación con el tratamiento esteroideo. Sin embargo, algunos datos parecen indicar que tanto la osteomalacia inducida por aluminio como el hiperparatiroidismo secundario severo serían factores predisponentes para el desarrollo de la misma. El uso de dosis bajas de esteroides postrasplante ha reducido la incidencia de enfermedad ósea en el trasplante renal.

SUMMARY

Bone disease following renal transplantation.
The most common complication affecting the bones following renal transplantation has been avascular necrosis mainly related to steroid treatment. However, it seems that aluminium-related osteomalacia and secondary hyperparathyroidism may be predisposing factors. Low-steroid regimes have reduced the incidence of bone disease in transplant patients.

Correspondencia:
Dr. B. J. R. Junor.
Renal Unit, Western Infirmary.
Glasgow, G11 6NT.
Scotland.

B. J. R. JUNOR, B. F. BOYCE, J. D. BRIGGS,
M. A. FORWELL, M. Z. MOCAN AND D. TSAKIRIS

Although some patients require surgery for hyperparathyroidism presenting as hypercalcaemia after successful renal transplantation [1] the most common complication affecting the bones of recipients of renal allografts has been avascular necrosis. Since it was first described by Starzl in 1964 [2] this condition has been the subject of many studies which have had contrasting conclusions [3-8].

Although steroids have been implicated as a contributory factor, some authors [3-5] but not all [1, 6-8] have found a positive correlation between steroid dose and bone necrosis despite the fact that avascular bone necrosis has been described in many other conditions where steroids have been used [7]. In our retrospective comparison of patients treated using two widely differing steroid regimes, bone necrosis was significantly more common in patients receiving the higher steroid doses [5]. However the patients in the low steroid group who developed bone necrosis received significantly less steroid than those patients who did not develop the problem in the high steroid group suggesting that there was an underlying individual predisposition. If all patients in a study receive similar doses of steroids and an individual predisposition exists the effect of steroids will not be evident. This might help to explain the differing views on the contribution of steroids to the aetiology of avascular bone necrosis.

What could this underlying predisposition be? In our survey, using multivariate analysis, there was a suggestion that bone necrosis might be more common in patients with particular HLA antigens, namely B8 and B12. Steroid pharmacokinetics differ between patients [9] and it has been reported that patients with reduced prednisolone clearances develop more steroid induced complications including bone necrosis [10-12]. In a prospective study prednisolone clearances in patients with HLA B8 and B12 who had developed bone necrosis were compared with those from renal transplant recipients without these antigens and who did not have bone necrosis. The difference in prednisolone levels between the two groups following a test dose of 30 mg orally was not significantly different at any time up to 12 hours later (unpublished data). Intersubject variations in prednisolone pharmacokinetics can therefore not be attributed to the presence of these antigens although it is possible that prednisolone metabolism may have been different at the time of transplantation.

As > 90 % of cases of avascular bone necrosis occur within the first 3 years after transplantation some change must occur to reduce the risk of bone necrosis developing later. Although this may be a reduction in the dose of steroids our data suggest that another factor or factors may be involved. A further change which takes place post transplantation is that hyperparathyroidism usually resolves spontaneously and vitamin D metabolism returns to normal. Renal osteodystrophy is therefore at its worst at the time of exposure to the highest dose of steroids and subsequently improves.

The state of underlying renal osteodystrophy has been alleged by some authors to predispose to the subsequent development of bone necrosis [4, 8, 13] but this has not been confirmed by others [1, 7, 14]. As most studies have been retrospective, these counter claims have usually depended on simple indices such as calcium, phosphate, alkaline phosphatase and radiological skeletal surveys. PTH levels did not correlate with the development of bone necrosis [12, 14] nor did serum 25-OH-vitamin D concentrations [14] but the assays were not carried out at the time of transplantation. One of us (BJRJ) was involved in a study of avascular bone necrosis in renal transplant recipients in Melbourne, Australia where a significantly higher alkaline phosphatase at the time of transplantation, presumed to reflect the state of bone turnover, was founf in patients who later developed bone necrosis [15]. This correlation was not found when patients in Glasgow were studied. Can these two findings be reconciled?

Patients in the areas surrounding Glasgow were previously exposed to high dialysate aluminium levels resulting in a number of cases of dialysis dementia [16]. Since 1978 effective water treatment has prevented further cases of dialysis dementia but aluminium related osteomalacia has been a common finding on iliac crest bone biopsy of dialysis patients in Glasgow and has been thought to be due to the use of aluminium containing phosphate binding agents. Patients with aluminium related osteomalacia tend to be hypercalcaemic and have normal or only mildly elevated PTH and alkaline phosphatase levels [17]. If patients with aluminium related osteomalacia at the time of transplantation are susceptible to the development of bone necrosis under the influence of steroids the alkaline phosphatase at the time of transplantation will not be significantly elevated. If bone necrosis affected a population consisting of patients with both aluminium related osteomalacia and hyperparathyroidism the mean alkaline phosphatase might well not be different from a control group. The effect of both types of underlying bone disease would then be masked which could explain the different findings between Glasgow and Melbourne with respect to alkaline phosphatase at the time of transplantation.

This hypothesis is supported by the fact that one of the only two patients since our study was completed to develop bone necrosis on low dose steroids was a young girl who had severe aluminium related osteomalacia. A bone biopsy at the time of transplantation showed significant deposition of aluminium within the calcification front (MH. Table I). Although her serum aluminium was not particularly high at the time of transplantation it was 4 months later

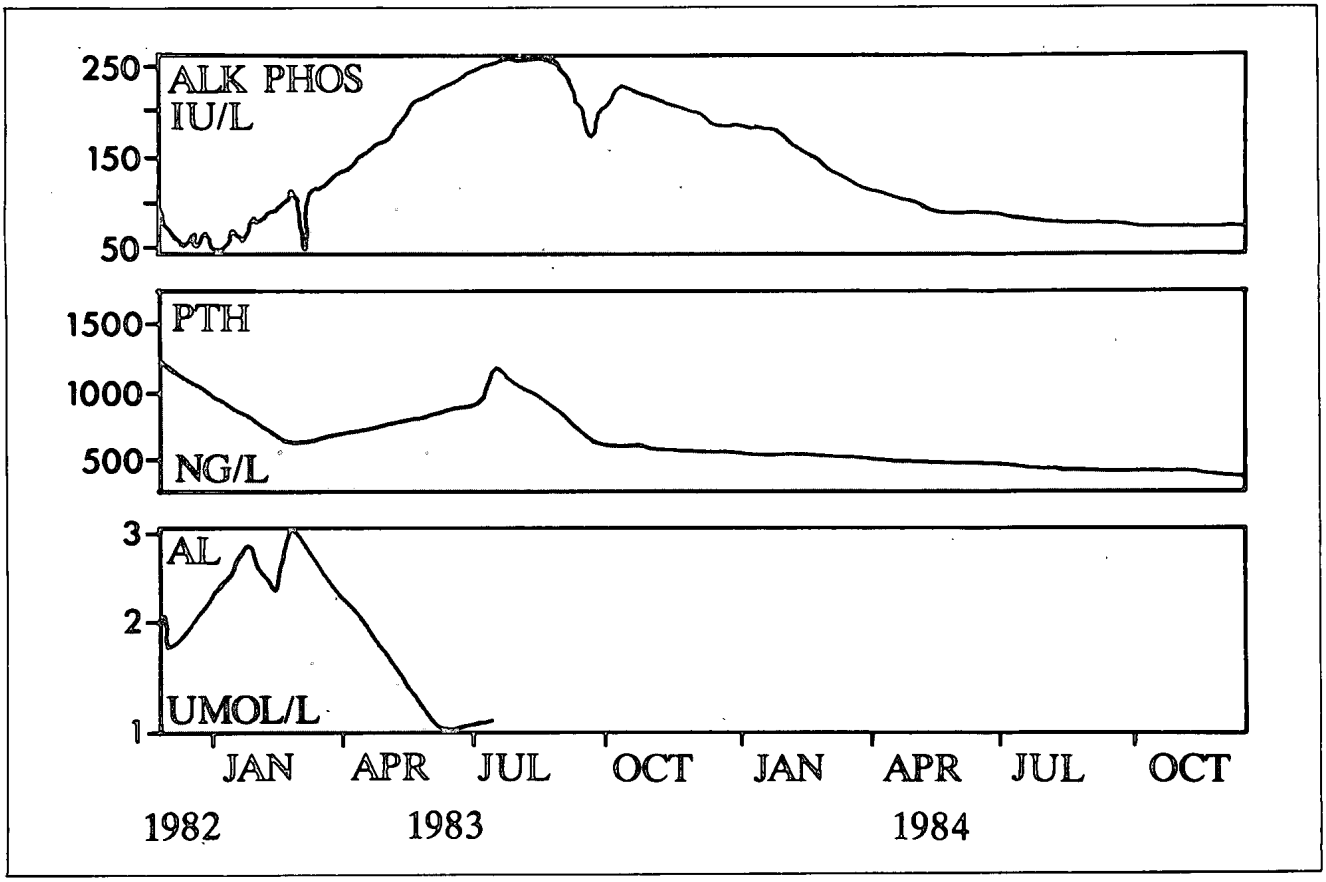
Table I

		Osteoid surface (OS)	Active osteoid surface	Al % OS	Calcification front	Resorption surface
MH	Pre	75.9	0.9	59.8	9.1	6.2
	8 mth	56.7	9.4	15.8	32.6	6.6
EK	Pre	52.2	6.3	54.9	8.0	17.7
	6 mth	70.0	11.2	15.9	33.5	7.9

before it began to fall towards 1 μmol/l (Fig. 1). At this time her PTH level also began to rise again after an initial fall post transplantation. The serum alkaline phosphatase also rose simultaneously to a peak 10 months after the operation before slowly falling to reach the normal range 7 months later. The PTH level also returned to normal around this time.

A second bone biopsy 8 months after transplant showed a marked improvement in the extent of aluminium present in the calcification front (table I). Despite this improvement a significant amount of aluminium remained although the serum aluminum levels were low. During the time of maximum exposure to steroids she therefore continued to have histological changes of aluminium related osteomalacia. As the aluminium slowly disappeared from the bones biochemical evidence of hyperparathyroidism became evident suggesting that this may have been present at the time of exposure to aluminium. The hyperparathyroidism later slowly resolved with both

Fig. 1.—MH. Serum alkaline phosphatase, PTH and aluminium levels from date of transplantation. Normal values: alkaline phosphatase, 114 IU; PTH, 600 ng/l.



the alkaline phosphatase and PTH levels returning to the normal range.

A second patient with known aluminium related osteomalacia at the time of transplantation (EK. Table I) showed similar changes in PTH and alkaline phosphatase levels, the latter being confirmed to be from bone by iso-enzyme studies. On bone biopsy 6 months later the histological changes were almost identical to the first patient but bone necrosis did not subsequently occur.

As avascular bone necrosis tends to affect predominantly weight bearing surfaces [3, 18] the pressure on that surface could be expected to influence the development of bone necrosis. This was shown by the correlation between weight gain post transplantation and bone necrosis in our study [5]. The state of the bone undergoing these stresses could also be expected to help determine whether bone necrosis occurred or not. The effect of steroids on bone is likely to be influenced by the presence or absence of significant histological changes during the period of treatment. Patients with aluminium related osteomalacia would therefore be at risk of developing avascular bone necrosis as well as those with secondary hyperparathyroidism. However the general change to low steroid regimens and the improved management of renal osteodystrophy have both probably contributed to the falling incidence of avascular bone necrosis following transplantation.

References

1. Gottlieb MN, Stephens MK and Lowrie EG: A longitudinal study of bone disease after successful renal transplantation. *Nephron* 22:239-248, 1978.
2. Starzl TE, Machioro TL, Porter KA, Moore CA, Rifkind D and Waddell WR: Renal transplantation. Late function and complications. *Ann Int Med* 61:470-497, 1964.
3. Harrington KD, Murray WR, Kountz SL and Belzer FO: Avascular necrosis of bone after renal transplantation. *J Bone Joint Surg* 53A:203-215, 1971.
4. Briggs WA, Hampers CL and Merrill JP: Aseptic necrosis in the femur after renal transplantation. *Ann Surg* 175:282-289, 1972.
5. Tsakiris D, Aitchison TC, Briggs JD, Davidson JK and Junor BJR: Risk factors associated with aseptic bone necrosis following renal transplantation. *Proc EDTA* 22:660-664, 1985.
6. Hawking KM: Avascular necrosis of bone after renal transplantation. *N Engl J Med* 294:397, 1976.
7. Ibels LS, Alfrey AC, Huffer WE and Weil R: Aseptic necrosis of bone following renal transplantation. *Medicine (Baltimore)* 57:25-45, 1978.
8. Nielsen HE: Bone mineral content in renal transplant patients. *Clin Nephrol* 10:196-200, 1978.
9. Pickup ME: Clinical pharmacokinetics of prednisone and prednisolone. *Clin Pharmacokinetics* 4:111-128, 1979.
10. Kozower M, Veatch L and Kaplan MM: Decreased clearance of prednisolone, a factor in the development of corticosteroid side effects. *J Clin Endocrinol Metab* 38:407-412, 1974.
11. Bergem H, Jervell J and Platmark A: Prednisolone pharmacokinetics in cushingoid and non-cushingoid kidney transplant patients. *Kidney Int* 27:459-464, 1985.
12. Ost L, Bjorkem I and Von Bahr C: Clinical value of assessing prednisolone pharmacokinetics before and after transplantation. *Eur J Clin Pharmacol* 26:363-369, 1984.
13. Chatterjee SN, Friedler RM, Berne TV, Oldham SB, Singer FR and Massry SG: Persistent hypercalcaemia after successful renal transplantation. *Nephron* 17:1-7, 1976.
14. Page CM, Hulme B, Papapoulos SE and O'Riordan JLH: Avascular necrosis of bone after renal transplantation: a role of parathyroid hormone and vitamin D. *Br Med J* 2:664-665, 1978.
15. Woo KT, Junor BJR, Vikraman P, d'Apice AJF and Kincaid-Smith P: Serum alkaline phosphatase as predictor of avascular necrosis of bone in renal transplant patients. *Lancet* i:620-621, 1979.
16. Elliot HL, Dryburgh F, Fell GS and Mac Dougall AI: Aluminium toxicity during regular Haemodialysis. *Br Med J* 1:1101-1103, 1978.
17. Boyce BF, Fell GS, Elder HY, Junor BJR, Elliot HL, Beastall G, Fogelman I and Boyle IT: Hypercalcaemic osteomalacia due to aluminium toxicity. *Lancet* 2:1009-1012, 1982.
18. Davidson JK, Tsakiris D, Briggs JD and Junor BJR: Osteonecrosis and fractures following renal transplantation. *Clin Radiol* 36:27-35, 1985.