IS RENAL OSTEODYSTROPHY REVERSIBLE?

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Summary

In order to investigate the possible reversibility of renal osteodystrophy, eleven necrograft recipients were investigated six years after transplantation, when treatment with prednisone had been withdrawn for 1.5 years. Serum ionised calcium, phosphorus, alkaline phosphatases, PTH, skeletal radiography, Technetium polyphosphate (Tc-PP) bone scintigraphy and radial bone mineral content (BMC) were studied. Normal blood biochemistry, radiography and Tc-PP scintigraphy were found in nine (82%) of the patients, in contrast to the considerably higher frequency of abnormalities ordinarily found in haemodialysis patients. However, the radial BMC was significantly reduced (mean 13.5%) and identical with the BMC values in haemodialysis patients. We conclude that some regression of renal osteodystrophy may take place after a successful kidney transplantation, but that decreased mineralisation of the appendicular skeleton persists. Whether this latter finding is due to long-term steroid treatment or is an indicator of an irreversible component in renal osteodystrophy cannot be stated.

Introduction

Metabolic bone disease is a serious complication of long-term renal failure\(^1\) and progressive histological abnormalities in the bones are frequently detected in these patients\(^2\). We have recently reported that \(^{99}\text{mTc}\)Technetium-polyphosphate (Tc-PP) bone scintigraphy becomes increasingly abnormal with deterioration in renal function\(^3\) and that abnormal scintigrams are found in 90% of haemodialysis patients\(^4\). Further, we have found that the bone mineral content (BMC) of the radius in uraemic patients is inversely correlated with the duration of uraemia, indicating a progressive loss of bone from the appendicular skeleton\(^5\).

Two major pathogenic mechanisms have definitely been recognised in the development of renal osteodystrophy: disturbed vitamin D metabolism\(^6\) and
secondary hyperparathyroidism. Encouraging results have recently been reported from treatment of renal osteodystrophy with 1,25-dihydroxy vitamin D₃ and 1α-hydroxy vitamin D₃, which seems to normalise the decreased intestinal absorption of calcium and the decreased concentration of ionised calcium in serum and to suppress the hyperplastic parathyroid glands. In our centre uraemic patients have been treated with 1α-hydroxy vitamin D₃ for more than one year (0.5 – 2.2). Despite a sustained return to normal of calcium absorption and ionised calcium in the serum we did not observe significant improvement of Tc-PP scintigraphy and BMC. Three possibilities exist:

1. The bone disease is reversible by treatment with active vitamin D, but the improvement is extremely slow;
2. An inhibitory factor is present in uraemic patients, preventing healing of the bone lesions, and
3. Once established, the bone disease is not totally reversible.

Theoretically kidney transplantation would be the treatment of choice as regards improvement of renal osteodystrophy: uraemia disappears, the defect in 1-hydroxylation of vitamin D is restored and remission of hyperparathyroidism gradually takes place. In practice studies of bone parameters are, however, impeded by the fact that necrograft recipients receive prednisone, which may cause bone changes by itself. From our group it has recently been reported that complete withdrawal of prednisone is possible in a selected group of long-term survivors after necro-kidney transplantation, apparently without harmful effect on renal function. Eleven of these patients have had their well-functioning kidney graft for more than five years and prednisone treatment has been withdrawn for more than one year. This group of patients has been studied in order to investigate the possible reversibility of renal osteodystrophy.

Material and Methods

Eleven kidney transplanted patients (8 females and 3 males) with a mean age of 45.9 years (range 32–63) were investigated. The duration of uraemia (creatinine clearance < 20 ml/min) had been on average 5.8 years (range 2–12) and the patients had been treated with regular haemodialysis for ten months (range 0–36). After transplantation the patients received on average 20.5 grams of prednisone (range 13.1–29.3) for 56.3 months (range 46–70). At the time of investigation the treatment with prednisone had been withdrawn for 18.9 months (range 12–25) without rejection episodes. The graft function was excellent with a mean creatinine clearance of 77 ml/min (range 39–119), minimal proteinuria (mean 0.2 g/24 hr) and mean BP 127/80mmHg.

The following measurements were performed: Serum ionised calcium (Ca++)<sup>11</sup>, phosphorus, alkaline phosphatases, parathyroid hormone<sup>12</sup>, Tc-PP bone scintigraphy<sup>4</sup>, radiographic survey of the skeleton and <sup>241</sup>Am-photon-absorptiometry of the radial shaft.
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<th>Patient No.</th>
<th>Time on dialysis Months</th>
<th>Time after transplantation Months</th>
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Figure 1. Te-PP osteoscintigrams in kidney transplanted patients illustrating normal (left) and most severe generalised scintigraphic bone changes (right). Uptake of the tracer in the kidney grafts is seen in both patients.
Results

Biochemistry

Nine of the eleven patients had normal biochemical parameters. Two patients had increased levels of Ca\textsuperscript{++} (1.22 and 1.19 mmol/L; normal range 0.99–1.15) and the first of these patients had a slightly increased concentration of PTH (2.8 ng/L; normal range 1.1–2.5) and was moderately hypophosphataemic (serum phosphorus 0.62 mmol/L; normal range 0.80–1.48).

Tc-PP Bone Scintigraphy

Nine of the eleven patients were without generalised scintigraphic bone changes (group O, Table I). Two patients (18%) had generalised scintigraphic bone changes, one of them being the patient with persisting hyperparathyroidism and hypercalcaemia (Figure 1).

Thus, when compared to haemodialysis patients and long-term surviving kidney transplanted patients receiving conventional treatment with prednisone, significantly fewer scintigraphic bone changes were present in the eleven kidney transplanted patients in whom prednisone treatment had been withdrawn (Table I).

Radiography

By roentgenographic examination of the skeleton (using conventional X-ray film without any magnification or standardisation technique) generalised loss of bone mineral was found in two of the eleven patients and one of these was the patient with the most severe scintigraphic bone changes.

![Figure 2. Bone mineral content/width (g/cm\textsuperscript{2}) of normal adults (mean ± SD) and eleven kidney transplanted patients (●) not treated with prednisone for 1.5 years. Top: females; bottom: males](image)
<table>
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Bone Mineral Content

The bone mineral content/width (BMC/W) expressed in g/cm² in the eleven patients is shown in Figure 2. The BMC/W-values were on average 13.5% below the values found in normal adults, which is a significant reduction (p < 0.01) and identical to that found in haemodialysis patients (Table II).

Discussion

Compared with uraemic patients a marked improvement of biochemical parameters was found in eleven long-term survivors after kidney transplantation in whom prednisone treatment had been withdrawn for more than one year. Furthermore, generalised scintigraphic bone changes, previously found to be present in almost all haemodialysis patients⁴, were only present in two of the eleven kidney transplanted patients. However, the bone mineral content of the radial shaft remained significantly reduced and was indistinguishable from the degree of demineralisation found in patients on regular haemodialysis.

As compared to the progression of scintigraphic changes with advancing renal failure, the apparent improvement of scintigrams in the present material indicates that some facet of renal osteodystrophy may be reversible. The nature of this component, however, remains unclear, since the mechanism of accumulation of Tc-PP in the diseased bones of uraemic patients is poorly understood⁴.

In contrast to the improvement of the scintigrams the osteopenia, as determined by photon absorptiometry, remained at the same low level as in patients on long-term haemodialysis. Since irreversible osteopenia is a well known sequel of successfully treated Cushing’s disease¹³ and since the patients in the present material have been treated with large doses of steroids for several years, it is not possible to state from the present data whether the osteopenic component of renal osteodystrophy is reversible or not.

References

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Open Discussion

KAYE (Montreal) Dr Madsen, we believe that the abnormal uptake of technetium is due to binding to collagen in the bone and hence reversal of this would take a considerable period of time. The decrease in your technetium uptakes would have to be compared with a control group that were left on steroids, because during that ten month period there might be an improvement in collagen maturation which could have taken place in any case. My question therefore is, have you looked at a control group that were left on steroids for a similar period of time?

MADSEN We have made bone scintigraphs in 105 kidney transplanted patients receiving conventional treatment with prednisone and 54% had abnormal scintigrams, so we think there is a significant reduction compared to this large group of control patients.

MASSRY (Los Angeles) Some years ago Dr Popovitzer showed many years after transplant that recipients still exhibited active bone disease. Have you any data to tell us what these changes in uptake mean in terms of bone histology?

MADSEN The mechanism of accumulation of the tracer in the diseased bones is not definitely known. It may reflect the regional blood flow. We cannot state which facet of renal osteodystrophy we really see reversed in these patients and we have not examined bone histology.

PETERS (London) What you are talking about basically is the effect of steroids on bone, and I am not really sure that you are right in your title or in your content in talking about the effect of withdrawal on renal osteodystrophy as such. I would like to be reassured that the treatment group, the group of patients who were in such a state as to allow withdrawal of steroids, were in fact comparable with the control group that you showed us. I would imagine that renal function for example might be different.

MADSEN I quite agree it is nearly impossible to get an ideal control group for these patients. They are very selected.

PETERS You talked of the reversibility of renal osteodystrophy and what I suggest is that you are talking about reversibility of steroid-induced changes which is an altogether separate matter.

THAYSEN (Copenhagen) We are quite aware of this problem in a patient group which has received intensive steroid treatment. That was emphasised by Dr Madsen. Our question was: can we see a complete reversal in patients who are no longer on steroids? This would certainly indicate that renal osteodystrophy is reversible. Now we have found that scintigrams improve but BMC does not improve, indicating only partial improvement. The fact that scintigraphic changes are most pronounced in dialysis patients, less frequent in steroid-treated transplanted patients and least pronounced in the zero prednisone group, indicates that improvement in scintigrams is not simply a consequence of withdrawal of prednisone as suggested by you.
WALLS (Leicester) Your scintigram changes in group III show areas of uptake which can often be associated with aseptic necrosis in long-term transplant patients. I wonder if you have any information to tell us whether this technique will help us detect aseptic necrosis before radiological changes are present.

MADSEN We have used technetium scintigraphy in the detection of aseptic necrosis in kidney-transplanted patients too, and in fact we have found that this method is very sensitive in the early detection of these changes in the hip. Several times the patient has complained of pain in the hips when the radiography was quite normal. The scintigraphy, however, was abnormal at that time and 3–4 months later we have seen the radiography become positive. I think that bone scintigraphy is very useful in the early detection of aseptic necrosis in kidney-transplanted patients.