Assessment of Renal Osteodystrophy following Renal Transplantation

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Summary
Serial histological studies in patients after successful renal transplantation indicate that with restoration of adequate renal function osteomalacia invariably improves with symptomatic relief in bone pain.

Histological changes of osteitis fibrosa resolve more slowly and radiological changes may persist longer, occasionally in the absence of confirmatory histological evidence of secondary hyperparathyroidism.

For accurate and sensitive follow-up a combination of biochemistry, histology and radiology is desirable.

Introduction
Following successful renal transplantation, secondary hyperparathyroidism appears gradually to resolve and radiological improvement occurs (Alfrey et al 1968; Hampers et al, 1969). Carroll et al (1973) were able to demonstrate steady histological improvement in 47 of their patients studied with serial bone biopsies.

The purpose of this paper is to present the early results of serial, biochemical, radiological and histological studies carried out on renal transplant patients in Newcastle-upon-Tyne and also to attempt to correlate the individual findings. The Newcastle dialysis population still features considerable symptomatic bone disease with a strong osteomalacic component.

MATERIAL AND METHODS

24 patients transplanted from January 1972 onwards, had a transilial bone biopsy at the time of transplantation and one year later while 9 other patients had a bone biopsy 2 years after transplantation.

Transilial bone biopsies were obtained using the NOH trephine which has an
internal diameter of 0.7 cm. The specimen is a cylinder of bone comprising inner and outer tables of compact bone with intervening cancellous bone and measures from 1.0 to 1.5 cm in length.

The severity of any osteitis fibrosa present is assessed in decalcified sections on a scale of 0–5 depending upon the extent of active osteoclasia, marrow fibrosis and woven bone formation (Ellis and Peart, 1973). Undecalcified sections double embedded using low-viscosity nitrocellulose, are stained by the von Kossa technique with silver nitrate and counterstained with toluidine blue to define mineralised and non-mineralised bone. Undecalcified sections stained with toluidine blue are used to demonstrate the calcification front. The amounts of mineralised and non-mineralised bone, expressed as a percentage of a measured area, are determined using a point-counting technique. The maximum number of birefringent lamellae in osteoid seams is determined under the polarising microscope. It should be noted that in the presence of osteitis fibrosa an excess of osteoid may be the result of osteoblastic activity over an increased proportion of the bone surface and does not necessarily indicate osteomalacia. A diagnosis of osteomalacia is only made when there is an excess of osteoid with abnormally thick osteoid seams comprising five or more birefringent lamellae and showing a reduced or absent calcification front (Ellis, 1973).

Radiological skeletal surveys taken shortly before transplantation were available on all patients. These were repeated six and twelve months later and then at yearly intervals. These skeletal surveys were reviewed for evidence of renal osteodystrophy as described by Simpson et al (1973) and the progression of radiological changes assessed.

In addition to histological and radiological follow-up, patients were reviewed regularly in the transplant out-patient clinic and blood was withdrawn for general biochemistry including alkaline phosphatase and parathyroid hormone. Parathyroid hormone was measured by a radio-immunoassay method (Pierides et al, 1974) and alkaline phosphatase by a modification of the method of Bowers and McComb (1966).

RESULTS

Figure 1 summarizes the results of histological studies in the 24 patients biopsied both at the time of transplantation and one year later. 20 patients started with histological osteitis fibrosa and 16 had osteomalacia. At one year 81% of the patients with osteomalacia and 45% of the patients with osteitis fibrosa showed complete resolution. In the group of nine patients where a bone biopsy had been performed two years after transplantation, four showed changes of mild osteitis fibrosa and one showed minimal osteomalacia, all in the presence of excellent renal function (plasma creatinine < 2 mg%). In addition to the number of patients that showed complete resolution of individual lesions a general improvement
Mean % mineralization ± SD
92.6: 5.5 96.1: 3.6 97.8: 2.2
Grading of Osteitis fibrosa

No. of patients studied
Pre-transplant One year Two years
OSTEOMALACIA

No. of patients studied
Pre-transplant One year Two years
OSTEITIS FIBROSA

Figure 1. Results of serial transiliac bone biopsies.

Table I. Results of Radiological Findings and Correlation with Histology

<table>
<thead>
<tr>
<th>Sub-periosteal Erosions</th>
<th>Skeletal Fractures*</th>
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<tbody>
<tr>
<td>No. of patients with radiological osteitis fibrosa</td>
<td>Simultaneous histological grading</td>
</tr>
<tr>
<td>Pre-transplant skeletal survey (24)</td>
<td>7</td>
</tr>
<tr>
<td>One-year skeletal survey (24)</td>
<td>6</td>
</tr>
<tr>
<td>Two-year skeletal survey† (9)</td>
<td>2</td>
</tr>
</tbody>
</table>

* Characterised by chronicity and failure to heal
† Different population from above patients

Trend was observed and patients with persisting osteitis fibrosa showed a milder form, while the % mineralization in osteomalacic patients improved. At the time of transplantation the most severe osteitis fibrosa grade was 3.5, at one year 2.5 and at two years 1.5. Over the same period, the number of osteoid lamellae and amount of osteoid decreased and the percentage of mineralization improved from a mean of 92.6 at the time of transplantation to 96.1 a year later and 97.8 two years later.
Figure 2. Serum alkaline phosphatase in transplant patients.

Table I summarizes the results of radiological skeletal surveys and correlation with histology. Sub-periosteal erosions were the earliest and most consistent radiological signs of secondary hyperparathyroidism, while skull changes appeared in some patients only. At the time of transplantation only seven patients showed radiological changes of secondary hyperparathyroidism, while these and 13 other patients, a total of 20 patients, had histological osteitis fibrosa. Thus radiology correlated well with 33% of patients with histological hyperparathyroidism. At one year after transplantation six patients had radiological osteitis fibrosa but simultaneous histology confirmed secondary hyperparathyroidism in only three patients. These six patients did not all exhibit sub-periosteal erosions at the time of transplantation, and in two patients, sub-periosteal erosions at one year were new findings. The remaining four patients had sub-periosteal erosions accompanied by histological osteitis fibrosa at the time of transplantation but by the end of the first year there was no evidence histologically of osteitis fibrosa in three of them while radiological changes of osteitis fibrosa persisted.

Skeletal fractures characterized by chronicity, delayed healing and failure of callus formation were found in five patients at the time of transplantation and all five patients had histological osteomalacia. Four patients showed similar changes one year later but only two of these had histological osteomalacia.

Biochemical studies, recently described separately (Pierides et al, 1974) showed that immunoreactive parathyroid hormone levels remained elevated for several months in the presence of normal renal function. Figure 2 illustrates the changes in serum alkaline phosphatase in patients who had osteomalacia with or without osteitis fibrosa at the time of transplantation and also in patients who had no osteomalacia at that time. The former group invariably showed a progressive rise several weeks to months after transplantation, with an eventual
spontaneous return to normality several months later. The latter group of patients without osteomalacia showed no changes in serum alkaline phosphatase.

DISCUSSION

Symptomatic bone disease is certainly one of the most incapacitating complications of regular haemodialysis. The evidence presented here, together with previously published data (Carroll et al, 1973) suggest that successful renal transplantation with restoration of normal renal function leads to gradual and steady improvement in renal osteodystrophy. Histological osteomalacia which features prominently in the dialysis bone disease of our patients appears to heal quickly, most likely the result of the restored, normal vitamin-D metabolism and free synthesis of 1–25 dihydroxycholecalciferol. The serum alkaline phosphatase in patients with osteomalacia rose further soon after transplantation and, after a variable length of time, returned spontaneously to within normal limits. No relationship could be demonstrated to the time of the year the transplant was performed. This behaviour of serum alkaline phosphatase was taken as an extra sign of active metabolic changes and remodelling occurring in the bones of affected patients during the early transplant period, although its exact pathophysiologic importance is still not fully clear. All but three patients with initial osteomalacia recovered completely during the first 12 months after transplantation, but it is uncertain as to why these three patients failed to do so. Their initial degree of osteomalacia was not more severe than that of other patients and their renal function was excellent in one and moderate in the other two. One patient remained mildly hypophosphataemic as described by Moorhead et al (1974) in spite of a previous partial parathyroidectomy while on regular haemodialysis, and interestingly all three patients had received barbiturates during the same period. Following the demonstration of persisting osteomalacia at the end of the first post-transplant year all three patients were given vitamin-D supplements and a repeat biopsy 12 months later, two years after transplantation, showed complete recovery and healing of osteomalacia, in all three patients.

In contrast to osteomalacia, histological osteitis fibrosa was slower to resolve, possibly reflecting the slow involution of the enlarged hypertrophied parathyroid glands that are known to accompany end-stage renal failure and regular haemodialysis (Ellis and Peart, 1973).

Johnson et al (1972) demonstrated elevated parathyroid hormone levels for a variable length of time after successful transplantation and recent results from our centre (Pierides et al, 1974) confirm the same findings. It appears that the rate of resolution of secondary hyperparathyroidism would depend on the final level of renal function attained and also the extent of the hypertrophied parathyroid glands at the time of transplantation. Even at two years post-transplant four patients out of a group of nine had histological changes of mild osteitis fibrosa.

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The interesting finding in post-transplant patients was the time difference in resolution between radiological and histological changes. Before transplantation, radiological osteitis fibrosa tended to correlate with the most severe cases of histological osteitis fibrosa, whereas after transplantation instances were encountered where radiological changes persisted in the absence of histological confirmation. It seems likely that histology can reflect more acute and dynamic changes in bone structure, consequently, radiological changes that take longer to appear are slower to resolve.

The different levels of diagnostic sensitivity between histology and radiology and different rates of resolution of radiological and histological changes suggest that radiology alone is an insensitive way to assess rapidly changing metabolic bone disease, particularly after effective therapy such as renal transplantation. A combination of histology, radiology and biochemistry would appear desirable and necessary in order to follow the serial changes in renal osteodystrophy.

References

Bowers, N G and McComb, R B (1966) Clinical Chemistry, 12, 70
Ellis, H A and Peart, K M (1973) Journal of Clinical Pathology, 26, 83
Hampers, C L, Katz, A I, Wilson, R E and Merril, J P (1969) Archives of Internal Medicine, 124, 282

Open Discussion

Dr RITZ, Chairman (GFR) Thank you, Dr Pierides. Your findings are in good agreement with what Dr. Popovtzer reported in Les Trois Epis (Le Rein et Calcium, Sandoz Edition).

I would suggest that the persistence of osteodystrophy is due to the inability of osteocytes and endosteal cells to repair the resorptive damage, because under steroids the cohort of the cells shrinks and activity of individual cell is diminished. PIERIDES I think we would agree and we would also say that we find that patients with persisting osteitis fibrosa are the ones that have more severe osteofibrosa to begin with. We also find that people with less successful transplants
take much longer to heal their osteitis fibrosa.

O BETTER (Haifa) Thank you for a very cheerful depiction of the situation; I hate to be the devil’s advocate but I think that most of your patients, if not all of them, were live-donor transplants. Those of us who treat cadaver transplants unfortunately have to use greater amounts of steroids, which you didn’t mention at all. We substitute another crippling disease, sometimes, steroid osteoporosis. It is rare, but it is devastating.

PIERIDES First of all, for the record, we don’t do live-donor transplants. We use steroids, but we don’t have crippling steroid osteoporosis. I have not talked about osteoporosis because the time is limited.

Prof. NIK-AKHTAR (Iran) Am I correct that you intended to stress the fact that alkaline phosphate has equal value to parathyroid hormone in post-transplant cases in evaluating the healing process of the bone lesions?

PIERIDES No I want to show that alkaline phosphatase rises and eventually falls after transplantation.

S. MASSRY (Los Angeles) It’s true that a transplant will give good renal function but at most we can get a clearance of 80 ml/min for one kidney. Now, if with mild renal failure one has secondary hypoparathyroidism, I don’t see why transplanted patients should not get secondary hyperparathyroidism and osteitis fibrosa. I think those who have a GFR of 80 ml/min will have mild and those who have 40 or 50 ml/min will have severe osteitis fibrosa.

PIERIDES I think the point of renal function is important and it is surprising that we would get complete resolution. But 55% of patients after one year still had osteitis fibrosa. Patients with a serum creatinine level of less than 2.0 did quite well. But with a serum creatinine of between 2 and 3 almost 50% retain osteomalacia and 4 out of 6 have osteitis fibrosa. Resolution depends on the effective renal function.

RITZ Still there must be more to it than persistence of hyperparathyroidism, since according to the abstract you found fibro-osteoclastic changes even without abnormal serum-PTH levels.

J. MOORHEAD (London) Did you distinguish between liver and bone alkaline phosphatase?

PIERIDES Yes, we used starch gel electrophoresis as described by Hodson, A W, Latner, A L and Raine, L (1962) Clinica Chimica Acta, 7, 255.