Resolution of Secondary Hyperparathyroidism after Cadaveric Renal Allograft

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Introduction

Recent progress in the understanding of the intermediary metabolism of vitamin D has led to the concept that renal osteodystrophy is a hormone-deficiency syndrome — a disease initiated either by a lack of or diminished effectiveness of 1,25-(OH)₂-D₃ as a result of the failure of the source organ. A series of compensatory adjustments take place in this situation and the end result is a pleomorphic syndrome which is progressive and persistent. The progressive nature of the disease state is more apparent in patients maintained on haemodialysis (Tatler et al, 1973a). The present study was undertaken to assess the effectiveness of renal transplantation in reversing the derangement of calcium homeostasis and in resolving secondary hyperparathyroidism in a group of patients maintained on haemodialysis before transplantation.

PATIENTS AND METHOD

Twenty-four patients on maintenance haemodialysis treatment for varying periods of time (9 to 106 months) who underwent successful renal transplantation were investigated. The group consisted of 13 males and 11 females with an age range of 20 to 57 years. Details regarding pre- and post-transplant care and management of the patients have been described previously (Moorhead et al, 1969; Ku et al, 1973; Moorhead et al, 1974a). The post-transplant follow-up studies were carried out at times ranging from 4 to 61 months after operation.

Various biochemical parameters including plasma calcium, magnesium, phosphate, alkaline phosphatase and hydroxyproline were measured before transplantation while the patients were on maintenance haemodialysis, and these measurements were repeated periodically after the establishment of stable renal
function as indicated by plasma creatinine and creatinine clearance. Serum immunoreactive parathyroid hormone levels (i-PTH) were carried out on 16 patients before and after transplantation. Standard biochemical methodology was used for the estimation of these parameters as described by Varghese et al (1973) and Wills et al (1974). Radiological surveys were carried out before and after transplantation as described by Tatler et al (1973b)

RESULTS

Sixteen of the 24 patients achieved a creatinine clearance of above 40 ml/min following transplantation. The time required before the creatinine clearance (Cr) reached a value of 20 ml/min varied from one to 82 days in the individual patients. The mean results obtained before and after renal transplantation for the biochemical variables studied are shown in Table 1. Comparison of pre-transplant biochemical values in patients with and without radiologically recognisable bone lesions showed plasma hydroxyproline, i-PTH and alkaline phosphatase to be significantly higher in patients with renal osteodystrophy.

<table>
<thead>
<tr>
<th>TABLE I. Plasma Concentrations of Biochemical Parameters Measured Before and After Renal Transplantation</th>
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<tbody>
<tr>
<td>Plasma concentration</td>
</tr>
<tr>
<td>Calcium (mg/100ml)</td>
</tr>
<tr>
<td>Magnesium (mg/100ml)</td>
</tr>
<tr>
<td>Total proteins (g/100ml)</td>
</tr>
<tr>
<td>Albumin (g/100ml)</td>
</tr>
<tr>
<td>Phosphate (mg/100ml)</td>
</tr>
<tr>
<td>Alk. phosphatase (KAU/100ml)</td>
</tr>
<tr>
<td>Hydroxyproline (mg/l)</td>
</tr>
<tr>
<td>i-PTH (pg/ml)</td>
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</tbody>
</table>

*Significance based on the difference between the means of paired observations.
**Student t-test based on the means of pre- and post-transplant observations (the post-transplant values exclude two patients with autonomous hyperparathyroidism).

Pre-and post-transplant biochemical values were compared by means of a 'paired t-test', showing significantly lower values for all biochemical parameters except for alkaline phosphatase. None of the patients developed hypercalcaemia at any time during the course of the study.

Hypophosphataemia was a common feature during the first few months after transplantation in 15 patients, but in four patients hypophosphataemia persisted for 12 to 46 months and three other patients developed hypophosphataemia three to 30 months after transplantation. The seven patients with persistent hypophosphataemia had normal levels of circulating i-PTH (Moorhead et al, 1974a).
Figure 1. Showing the relationship between the radiological features before transplantation and the time required for the plasma hydroxyproline to return to the normal range after establishing a stable renal function.

In 14 patients the plasma hydroxyproline fell into the normal range (0.4 to 2.8 mg/l) within the first three months after transplantation (Figure 1). Of the remaining 10 patients only one patient had no radiological evidence of bone disease. In this patient with a raised hydroxyproline and normal radiology, it took seven months for the plasma hydroxyproline to return to the normal range. The patient had a creatinine clearance of over 60 ml/min for more than six months after transplantation. Four of the remaining nine patients had osteitis fibrosa (Table II) before transplantation and two of these patients showed evidence of healing of their erosions and their plasma hydroxyproline returned to the normal range after 12 and 21 months; both patients had an average creatinine clearance of over 60 ml/min throughout this period. The third patient with osteitis fibrosa had a creatinine clearance of more than 90 ml/min for 31 months and the plasma hydroxyproline remained elevated throughout this period. Radiologically, this patient still had subperiosteal erosions. The fourth patient with osteitis fibrosa had a creatinine clearance above 50 ml/min for the first seven months and the plasma hydroxyproline fell from 44.1 to 5 mg/l during this period, but this patient later developed chronic rejection with very poor renal function. In this patient there was no improvement in renal osteodystrophy. Urinary hydroxyproline excretion was within the normal range in all patients except two. Two patients who developed chronic rejection after a period of good renal function were found to have marked subperiosteal erosions, and calcium infusion tests suggested that these patients have autonomous
TABLE II. Results of Regular Radiological Surveys Carried Out Before and After Transplantation

<table>
<thead>
<tr>
<th>Radiological findings</th>
<th>Before transplantation</th>
<th>After transplantation</th>
<th>New lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erosions</td>
<td>4</td>
<td>2</td>
<td>–</td>
</tr>
<tr>
<td>Fractures/Looser’s zones</td>
<td>6</td>
<td>11</td>
<td>5</td>
</tr>
<tr>
<td>Vascular calcification</td>
<td>5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Normal</td>
<td>9</td>
<td>5</td>
<td>–</td>
</tr>
</tbody>
</table>

hyperparathyroidism. Parathyroidectomy is currently being considered in these two individuals before they return to the haemodialysis programme.

Serum i-PTH concentration correlated well with plasma hydroxyproline values before \( r = 0.44, p < 0.05 \) and after renal transplantation \( r = 0.88, p < 0.001 \). The two patients with autonomous hyperparathyroidism had very high values of i-PTH (4,000 and 3,500 pg/ml) and in all other patients i-PTH values returned to normal range.

The results of regular radiological surveys carried out before and after transplantation are shown in Table II. Vascular calcification appeared for the first time in five patients and Looser’s zones appeared in five patients with hypophosphataemia after transplantation.

DISCUSSION

It has been generally accepted that renal osteodystrophy is the outcome of the interaction of a number of biochemical abnormalities such as hypocalcaemia, phosphate retention (Slatopolsky and Bricker, 1973) skeletal resistance to PTH (Massry et al, 1973) and a deficiency of active metabolites of vitamin D (Mawer et al, 1973). After the establishment of good renal function in transplant patients, these abnormalities would be expected to disappear with improvement in bone pathology. Although isolated or random measurements of biochemical parameters or radiological surveys are unlikely to offer a discriminatory diagnostic index in MHT patients, serial studies based on multifactorial analysis (Varghese et al, 1973; Wills et al, 1974; Moorhead et al, 1974b) are of use in studying the course of the disease process in chronic renal failure patients.

A number of workers have reported the development of hypercalcaemia after transplantation (Wilson et al, 1965; McIntosh et al, 1966; Allfrey et al, 1968), but in the present study plasma calcium and magnesium concentrations were significantly lower \( p < 0.001 \) after transplantation. This could have been due to corresponding changes seen in the concentrations of total protein and albumin. Twelve of the 24 patients developed significant proteinuria related or unrelated to rejection episodes. Steroids may also play a role in reducing the intestinal absorption of calcium and magnesium, but the maintenance dose of steroids was less than 15 mg/day. Stanbury (1971) suggested that post-transplant
hypercalcaemia may be partly due to the administration of pharmacological
doses of vitamin D prior to transplantation. The absence of hypercalcaemia in
these patients may also be due to the degree of parathyroid hormone suppression
obtained during MHT by the use of a dialysate calcium concentration of 7.5
mg/100 ml.

Although hypophosphataemia is generally considered to be a common transient
feature during the post-transplantation phase of the regression of parathyroid
hyperplasia, persistent hypophosphataemia in the absence of hypercalcaemia and
parathyroid over-activity has not been reported widely (Moorhead et al, 1974a).
The development of hypophosphataemia 3 to 30 months after transplantation
in three patients, at a time when steroid dosage was at a minimum and regression
of parathyroid glands was expected, indicates that the hypophosphataemia was
probably not related to either of these factors. These patients also developed a
mild hyperchloremic metabolic acidosis with a proximal tubular leak of bicar-
bonate (Moorhead et al, 1974c). Five of the seven patients with persistent hypo-
phosphataemia developed Looser's zones.

The time course of the reversibility of the secondary hyperparathyroidism in
this study was similar to that reported by other workers (Ogg et al, 1970;
Johnson et al, 1972). Plasma hydroxyproline values returned to the normal
range within eight months after transplantation in all patients except those with
osteitis fibrosa. The specificity of plasma hydroxyproline as an index of para-
thyroid activity has been demonstrated previously, and a significant correlation
has been obtained between plasma hydroxyproline and i-PTH values (Wills et al,
1974). The present study indicates that the resolution of secondary hyperpara-
thyroidism takes a much longer time course in patients with osteitis fibrosa.
Studies by Carroll et al (1973) based on serial histology indicated that the
resolution of renal osteodystrophy in transplant patients is dependent on renal
function and they demonstrated that in patients with good renal function it
may take up to four years for complete reversal of bone pathology.

In summary our results indicate that secondary hyperparathyroidism resolves
in the first year after transplantation in most of the patients with moderately
good renal function, but phosphate depletion may contribute to the development
of osteomalacia in some. The present study further demonstrates the usefulness
of plasma hydroxyproline estimation in assessing parathyroid status in these
patients.

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Open Discussion

Dr. D OREOPOULOS (Toronto) Hydroxyproline is normally excreted in the urine, so should be elevated in a renal-failure patient. A decrease after transplantation may have been due to failure of urinary excretion. Hydroxyproline is present in the skin, so some of the serum hydroxyproline may be coming from the skin as a result of the steroids. Would you comment on this?

VARGHESE Serial studies after parathyroidectomy in renal-failure patients have revealed striking falls in plasma hydroxyproline, usually into the normal range. The time course and predictability of this make a non-specific elevation very unlikely. Calcium infusion in our uraemic patients also causes hydroxyproline increase.
to fall sharply and significantly. Therefore, you cannot really say that a rise in plasma hydroxyproline is due to uraemia as such. Skin collagen produces a more stable form of hydroxyproline than bone collagen. Also, transplant patients without hyperparathyroidism, who are on steroids, have normal urinary hydroxyproline.

Dr. A M PIERIDES (Newcastle) The most striking aspect of this work is the absence of histology in monitoring renal osteodystrophy. I find it difficult to see how in a dynamic and rapidly changing system you feel justified to pool data over a period after transplantation and then obtain reliable results by comparing them with data before transplantation.

VARGHESE First we used a paired t-test to find the statistical significance, so the data were not pooled. About radiology, we have used this as a reliable trend finder. Histology is only one parameter; biochemical and radiological changes are others.

OREOPoulos Were you measuring C terminal or N terminal parathyroid hormone, and what were your normal values?

VARGHESE C terminal range 275 pg/ml to 1210 pg/ml. In this series 16 patients had a creatinine clearance of about 40 ml/min. Plasma hydroxyproline in chronic renal failure shows a rise when the creatinine clearance is about 15 ml/min.