Plasma Parathyroid Hormone Levels and Bone Histology in Patients Treated by Maintenance Haemodialysis and Renal Transplantation

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Although histological evidence of bone disease is extremely common in patients dying of chronic renal failure (Follis & Jackson, 1943), symptoms attributable to it are relatively rare and usually overshadowed by those due to the coincident uraemia. None the less, occasional patients are crippled by their osteodystrophy and this complex metabolic problem has fascinated many investigators. The success of maintenance haemodialysis and renal transplantation has transformed what was once a medical curiosity to a clinical problem of major importance.

It is now well recognised that most patients with osteodystrophy show evidence of osteomalacia, hyperparathyroidism and osteosclerosis in varying combinations (Stanbury, 1967). Biochemical and radiological assessment of these are extremely crude and there is an increasing tendency towards the use of bone biopsy. However, this produces only a small sample of tissue and is a relatively unpleasant procedure for the patient.

Recently techniques have been introduced for the radioimmunoassay of parathyroid hormone (PTH) in blood and it was soon realised that patients with chronic renal failure frequently showed very high levels which were usually greater than those found in patients with primary hyperparathyroidism (Berson & Yalow, 1966). The present study covers a period of 18 months, during which serial measurements of plasma PTH levels were made in a number of patients undergoing treatment by maintenance haemodialysis and renal transplantation. During this time skeletal changes were assessed by conventional biochemical, radiological and histological techniques.

PATIENTS

Forty-seven patients with ages ranging from 11 to 54 years were studied. All had terminal renal failure and had started treatment by maintenance haemodialysis. Only one had symptomatic bone disease at the start of treatment but another developed this after treatment lasting one year. Dialysis
was undertaken using modified Kiil dialysers with PT 300 cellulose membranes for 28 to 30 hours each week against dialysate containing 5.4 mg/100 ml of calcium and 1.2 mg/100 ml of magnesium. Successful renal transplantation was carried out in nine cases studied.

METHODS

Plasma parathormone levels were measured by radio-immunoassay using an antibody raised in the guinea pig against bovine PTH with phase separation using charcoal (Berson et al., 1963; Buckle, 1969). The upper limit of plasma PTH concentrations in normal subjects obtained by this method is 0.2 ng/ml. Blood samples were taken into heparinised tubes and the plasma separated immediately and stored at -10°C until the PTH levels were measured.

Bone biopsies were obtained from the iliac crest using a bone trephine under either general or local anaesthesia. After fixation in formol saline calcified and decalcified (EDTA) sections were prepared and examined using conventional illumination and polarised light. Staining was with haematoxylin and eosin and von Kossa's stain. Attention was paid to the number and structure of the bony trabeculae, to fibrous replacement of marrow and foci of osteoclastis, and to the width and regularity of osteoid seams and the prominence of osteoblasts. The presence or absence of osteosclerosis, osteitis fibrosa and osteomalacia was recorded on an arbitrary scale (0, +, ++, +++).

X-rays of the skeleton were obtained at the start of regular dialysis and periodically thereafter. The usual investigation was an x-ray of the hands taken on fine grain paper but eight patients had in addition, a partial skeletal survey. Routine measurements were made monthly of the plasma calcium, phosphate and alkaline phosphatase levels and aluminium hydroxide was given if predialysis phosphate levels were persistently greater than 6.0 mg/100 ml.

RESULTS

Parathyroid hormone levels were obtained within three months of the start of dialysis in 25 patients and the results are shown in Figure 1. It can be seen that in only three instances was a normal result obtained and that in the remainder the levels were raised often to very high levels indeed.

The effect of a single passage of blood through the dialyser was studied on 15 occasions. No difference in plasma PTH levels was found, the mean predialyser level was 2.84 ± 1.35 ng/ml and the mean postdialyser level 2.87 ± 1.36 ng/ml.

The effect of a single 14-hour dialysis was examined in ten cases. During this there was a small but insignificant increase in the plasma calcium level (mean predialysis level = 8.4 mg/100 ml, mean post-dialysis level 8.6 mg/100 ml). There was a small decrease in PTH level from a
Figure 1. Plasma parathyroid hormone levels within three months of the start of dialysis in 25 patients

predialysis level of 3.30 ± 1.43 ng/ml to a post-dialysis level of 3.02 ± 1.35 ng/ml. This change is in the direction that would be expected from the small change in calcium level and is not statistically significant.

Serial measurements of PTH levels were obtained in ten subjects during the course of dialysis lasting 12 to 18 months (Figure 2). Six of these were studied from the start of dialysis and the remainder were first studied after they had already been on dialysis for three to 18 months. Five subjects showed a progressive increase in plasma PTH level and five showed either a slight fall or no change in level.

Nine patients had successful renal transplants and serial PTH levels were obtained for up to six months after the onset of renal function (timed from the last dialysis). The results are shown in Figure 3.

It can be seen that the PTH level falls slowly with time but that high levels may be present even at six months after transplantation.

Satisfactory bone biopsies were obtained from 24 subjects. On 21 occasions biopsy was performed within three months of the start of dialysis while the remaining three specimens were obtained nine, ten and 12 months later. Sixteen samples showed definite histological abnormalities (Table I).
Figure 2. Plasma parathyroid hormone levels in 10 patients during regular dialysis treatment, lasting 12 to 18 months.

Figure 3. Plasma parathyroid hormone levels in nine patients treated by renal transplantation.

Table I. The findings in 24 bone biopsies from patients receiving regular dialysis treatment

<table>
<thead>
<tr>
<th>Normal</th>
<th>Total</th>
<th>Osteosclerosis</th>
<th>Hyperparathyroidism</th>
<th>Osteomalacia</th>
</tr>
</thead>
<tbody>
<tr>
<td>8</td>
<td>16</td>
<td>0 + ++ +++</td>
<td>0 + ++ +++</td>
<td>0 + ++ +</td>
</tr>
</tbody>
</table>

154
All the abnormal biopsies showed some degree of osteosclerosis; hyperparathyroidism was less common and osteomalacia occurred infrequently and was relatively mild. Serial hand x-rays obtained during the course of dialysis lasting six to 42 months were available for examination in 17 subjects (Table II). There was no change in 14 patients, deterioration with an increase in subperiosteal erosions in three and improvement in none. Arterial and/or periarticular calcification was present initially in two, both of whom showed an increase during dialysis treatment. Three other patients developed metastatic calcification later.

DISCUSSION

It is apparent that the great majority of our patients with terminal renal failure have raised plasma parathyroid hormone levels. This confirms earlier results obtained by Berson and Yalow (1966) and by Potts et al (1969).

Comparison between the results of PTH estimations and x-rays of the hands shows that the presence of radiological evidence of hyperparathyroidism is invariably associated with raised PTH levels. However, the severity of the radiological changes do not always correlate with the magnitude of the PTH level and 16 out of 19 patients with normal x-rays had raised PTH levels. This lack of detailed correlation may partly be explained by the different times required for the development of parathyroid hyperplasia and its skeletal manifestations and partly by the limited extent of the radiological investigation. Furthermore the PTH level in the plasma of an individual with secondary hyperparathyroidism may be affected acutely by changes in the plasma calcium level. Unfortunately it is impossible to correct any given PTH level for the plasma calcium level as the results of studies on the secondary hyperparathyroidism found in parturient cows (Buckle et al, 1968) predict that each individual with parathyroid hyperplasia will show a quantitatively different relationship between the plasma PTH and calcium levels.

Similar problems must be considered when the results of PTH estimations are compared with the results of bone biopsy. Again an abnormal biopsy was invariably associated with a raised PTH level while the absence of histological abnormality was not necessarily associated with a normal PTH level. An attempt was made to correlate the individual components of renal osteodystrophy with the plasma PTH levels. The results are shown in Figure 4. Obviously, there are many objections to this method of presentation. These include the small size of the skeletal sample, the subjective quantitation of the histological abnormality and, most important of all, the fact that the individual components of osteodystrophy are correlated to some extent with each other. None the less, it does seem as if osteosclerosis is the lesion which correlates best with PTH levels. Furthermore the three
patients who showed osteosclerosis as the only histological abnormality all had high PTH levels. This suggests that osteosclerosis is either the result of secondary hyperparathyroidism or the anatomical basis of resistance to the actions of PTH in uraemia (Evanson, 1966). In view of the occasional occurrence of osteosclerosis in children with primary hyperparathyroidism (Lloyd et al, 1965) the former explanation would seem to be the more likely, although neither excludes the other.

With increasing duration of dialysis circulating PTH levels tend to increase and this fits in with other indices of the progress of bone disease among our patients. Thus although only one out of 46 developed symptoms of renal osteodystrophy, 15 out of 20 showed a rise in alkaline phosphatase levels and three out of 17 who had serial hand x-rays showed evidence of increased subperiosteal erosions (Table II).

**Table II. Changes in hand x-rays and plasma alkaline phosphatase in patients dialysed for 6 to 42 months**

<table>
<thead>
<tr>
<th>Number of patients</th>
<th>Subperiosteal erosions</th>
<th>Alkaline Phosphatase</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Increased</td>
<td>Decreased</td>
</tr>
<tr>
<td>3</td>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>

The actual dialysis procedure did not affect PTH levels. The hormone (M. Wt. 9,000-11,000, Deftos & Potts, 1969) does not appear from our data to be dialysable, nor does it become fixed by the dialysis membrane.

Immediately after successful renal transplantation PTH levels remain high. At this time patients may show the conventional biochemical findings of hyperparathyroidism and several have been subjected to parathyroidectomy.
(McPhaul et al 1964; McIntosh et al, 1966). Alfrey et al (1968) have shown that these changes may regress spontaneously over six to 12 months and this fits with our own observations and the preliminary observations of Potts et al (1969), concerning the slow fall in PTH levels. We observed considerable individual variation in the rate of fall of PTH levels. The factors underlying this are obscure but clearly the quality of transplant function might be relevant. Changes with time of PTH level and creatinine clearance are shown in three of our patients and in these subjects at least this appears to be important (Figure 5). None the less, it can be seen that very high levels of PTH may persist even in the presence of excellent transplant function and the relative rarity of hypercalcaemia after transplantation requires an explanation. Only one out of 11 patients in the present series showed this and then only for a short period. One possibility is that the resistance to the hypercalcaemic action of PTH that exists in uraemia (Evanson, 1966) persists for

Figure 5. Plasma parathyroid hormone levels and creatinine clearance in three patients following renal transplantation.
a time after transplantation. Since the biochemical abnormalities of uraemia have been abolished the continuing resistance is likely to be due to anatomical changes at the surface of bone trabeculae which might take time to regress.

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