The Effects of Renal Transplantation on Renal Osteodystrophy

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INTRODUCTION

The realisation that the diagnosis of renal osteodystrophy can only be established reliably by histology has been emphasised by several authors (Katz et al, 1969; Bishop et al, 1971). For more than five years we have been carrying out sequential iliac crest bone biopsies on patients requiring renal substitution therapy, and subjecting the bones to histoquantitative analysis. Four years ago we reported on the early histological changes following successful renal transplantation (Carroll et al, 1969). At that time, in a group of twelve patients followed for up to one year, we recognised a noticeable reduction in osteoid and resorption in about half the patients. The purpose of this paper is to describe the histological changes which we have observed in a group of 47 patients, some of whom have been followed for up to four years and more after successful transplantation.

MATERIALS AND METHODS

The 47 patients studied have been divided into three groups on the basis of their renal function after transplantation. The serum creatinine was monitored regularly in all patients, and was shown to be the best and most consistently available index of renal function. The mean serum creatinine level was calculated for each patient from the numerous estimations for each year. Patients were allocated to the good renal function group if the serum creatinine was less than 1.5mg/100ml, to the moderate renal function group if the serum creatinine was between 1.5mg/100ml and 2.5mg/100ml, and to the poor renal function group if the serum creatinine was more than 2.5mg/100ml. A small number of patients showed deterioration in renal function, and did not remain in their original group throughout the study. Each patient has been followed up for a minimum of one year.

The patients in the good and moderate renal function groups were allowed unrestricted protein diets, whereas those in the poor group were restricted
to 40g protein intake daily. Except for those patients who had undergone parathyroidectomy, none of the patients were receiving vitamin D therapy. The daily maintenance anti-rejection therapy consisted of prednisone 15mg and azothioprine 100-200mg.

Forty-seven patients (21 females and 26 males) aged 18 to 54 received 48 transplants. Twenty-seven patients had pre- and post-transplant biopsies carried out and 20 patients post-transplant biopsies only. The only modification in the bone biopsy technique and processing from our original description (Carroll et al, 1969) is that the sections in this study were stained with the Von Kossa stain. The bone biopsies for the control group were obtained from 24 patients aged 18 to 50 who died unexpectedly, mostly as a result of trauma.

Quantitation of the changes in the trabecular bone was carried out using a magnification of 240 times and a Weibel grid. Each intercept of a grid line through the surface of a trabeculum was counted, and the type of bone surface assessed as 'inactive', 'resorption' or 'osteoid covered'. Smooth, unbroken, calcified surfaces were recognised as inactive, whereas an irregular, calcified, scalloped-out surface represented resorption. The unmineralised fibrous matrix, whether overlying smooth or scalloped bone was recognised as osteoid. The figures for each component are expressed as a percentage of the total bone surface measured. In this presentation, the main emphasis in the presentation of the results is in the change in inactive surface, which, of course, is a reflection of the healing processes which take place after successful transplantation.

RESULTS

Controls

Twenty-four males and females aged 18 to 50 had a mean inactive surface of 78.8% and a standard deviation of ±8.2% (Aung, 1970).

Pre-transplant

Bone histology is available on 27 patients. The mean inactive surface is 27.6% (range 0-65%).

Post-transplant

Good renal function (Figure 1). In this group, the pre-transplant inactive surface mean is 27.1% (range 5-58%). At one, two, three and four years after transplantation, the mean inactive surfaces are 47.6% (range 16-73%), 66.2% (range 45-84%), 61.8% (range 47-80%) and 76.3% (range 67-95%) respectively. The mean serum creatinine was 1.2mg/100ml, with a range of 0.9-1.4mg/100ml.

Moderate renal function (Figure 2). In this group, the pre-transplant inactive
Figure 1. The changes in inactive surface with time after renal transplantation when renal function is good. The mean ± SEM for pre- and post-transplant data is shown. In calculating the mean the parathyroidectomy data has been excluded. The mean ± SD is shown for normal controls (hatched area).

The mean inactive surface is 25.4% (range 0-65%). At one, two, three and four years after transplantation, the mean inactive surfaces are 32.1% (range 5-69%), 55.1% (range 35-74%), 56.0% (range 33-70%) and 65.3% (range 48-79%) respectively. The mean serum creatinine was 2.0mg/100ml, with a range of 1.8-2.5mg/100ml.

**Poor renal function (Figure 3).** In this group, the pre-transplant inactive surface mean is 28.9% (range 0-65%). At one and two years after transplantation, the mean inactive surfaces are 32.1% (range 10-57%), and 30.6% (range 5-57%). The mean serum creatinine was 3.8mg/100ml for the first year, and 4.8mg/100ml for the second year, with a range of 3.0-6.0mg/100ml.
Figure 2. The changes in inactive surface with time after renal transplantation when renal function is moderate. The mean ± SEM for pre- and post-transplant data is shown. In calculating the mean the parathyroidectomy data has been excluded. The mean ± SD is shown for normal controls (hatched area).

In calculating the means and standard errors of the means, the data on parathyroidectomy patients has been excluded. The means would be slightly higher in the relevant groups if this data is included. Three kidneys were classified in the good group for the first year, but during the second year as their function deteriorated they were then re-classified in the moderate group. Similarly, there were three kidneys which started in the moderate group and were relegated to the poor group during the second year.

DISCUSSION
Most of the histological interest in renal osteodystrophy has been concentrated on the study of both non-dialysed (Stanbury & Lumb, 1966) and dialysed chronic renal failure patients (Stanbury, 1969; Ellis & Peart, 1971; Siddiqui & Kerr,
Inactive Surface
Poor Renal Function
S.Creatinine Mean 3.8-48 mgs% Range (30-60 mgs %)
Pre Transplant Post Transplant

Figure 3. The changes in inactive surface with time after renal transplantation when renal function is poor. The mean ± SEM for pre- and post-transplant data is shown. In calculating the mean the parathyroidectomy data has been excluded. The mean ± SD is shown for normal controls (hatched area).

1971; Bishop et al, 1972). In contrast, very little has been reported on the changes following successful renal transplantation. In our original report (Carroll et al, 1969) on the early histological changes following successful renal transplantation, we took no account of renal function in describing our results. Although renal function had been maintained for one year in each patient, the group was too small to warrant subdivision into groups based on renal function. At that time we reported regression in renal osteodystrophy in about half the patients at the end of one year.

Our facile arbitrary division of the transplanted patients into those with good, moderate and poor renal function could be criticised on the grounds that it is too broad and was made in retrospect. But most practising transplant
surgeons will recognise that their own patients could be so classified and moreover that some patients with good or moderate renal function in the first year can subsequently deteriorate.

When we now assess our longer term results there is a clear and not unexpected relationship to renal function. Before transplantation there is no significant difference in the bone disease between the various groups. After transplantation the poor renal function group shows no real improvement, while the moderate group shows a slow but definite improvement, well seen in the second year's figures, when the inactive bone surface is more than double that seen before transplantation. In the patients with good renal function after transplantation there was a marked improvement in bone histology by the end of the first year, but the majority of biopsies did not fall into the normal range until four or more years after transplantation. These results are not significantly affected by the small number of patients who were transferred from one group to another. The major factor in the return towards normality of inactive bone surfaces is a reduction in the amount of osteoid covered surface; the findings for osteoid and resorption will be presented in detail in a later communication. Our findings that the return of renal bone disease towards normality after transplantation is dependent upon renal function, and even in the best group may take four years, must be interpreted in the light of the recent observations on the role of the kidney in vitamin D metabolism.

Fraser and Kodicek and their colleagues (Fraser & Kodicek, 1970; Kodicek et al, 1970; Lawson et al, 1971) working with the rat and chick have shown that the active metabolite of vitamin D₃, namely 1,25-dihydroxycholecalciferol (1,25 DHCC), is produced in the kidney and that this increases calcium absorption in the small intestine. More recently, Mawer and her colleagues (Mawer et al, 1973) have demonstrated the inability of patients suffering from chronic renal failure and who are also vitamin D deficient, to produce 1,25 DHCC following the injection of radioactive cholecalciferol. They suggest that this inability to produce 1,25 DHCC contributes to the deficient osteomalacia seen in chronic renal failure. It would seem, therefore, that with progressive renal destruction the ability of the kidney to produce the active metabolite 1,25 DHCC falls off and thereafter histological osteomalacia becomes evident.

Our findings are consistent with the suggestion that the hydroxylation of cholecalciferol in the kidney is important in renal osteodystrophy. We find that some degree of osteomalacia is extremely common in patients with renal failure, and that the reversion of this towards normality after transplantation is dependent upon the level of function of the transplant, which reflects the amount of normally functioning renal tissue available. However, the rate of return to normality is surprisingly slow, even in the group with the best renal
function, and this suggests to us that an additional mechanism must be operating. It has already been suggested (Carroll, 1972) that the immunosuppression regime in these patients may play a role in this. The data we have presented here support this possibility.

REFERENCES

Stanbury, S. W. and Lumb, G. A. (1966) Quarterly Journal of Medicine, 137, 1

OPEN DISCUSSION

F P BRUNNER (Basle): When you call your bones normal, does this refer to the active and non-active surfaces or does it also mean the density as well? I think it is true to say that it is the experience with most transplants that after a few years we are faced with the problem of osteoporosis - possibly as a result of steroid therapy. What can one do about this problem?

CARROLL: In the time allocated to me I could not discuss the problem of bone density. In the last few years we have been noticing extraordinary changes in the bone volume and bone area in the transplant group, but I have confined my remarks to what we term 'conventional renal osteodystrophy', ie the surfaces. But I do agree with you that there are changes: they are not easily understood, but we are not at all sure that osteoid in transplant patients is the same as osteoid in patients on dialysis, and it may even be different in people who are otherwise normal. This requires a histological study which is very difficult to do, but I would agree with you that we have a number of patients whose bone density is a cause of great concern.
V POSBORG PETERSEN (Aarhus): I wonder if you could tell us whether you have had any cases of aseptic bone necrosis, or spontaneous fracture in your patients? I ask this question because I think it is one of the major problems in recipients, including those with good function, and it seems quite independent of steroid dosage and graft function.

CARROLL: We have at least two patients with avascular necrosis of the femoral head. In one of these patients the bone histology is normal at 4 years; in the other patient it is abnormal, and has been throughout. In both of these patients the bone density is very greatly reduced. We do not know whether aseptic necrosis is a steroid induced problem, a dose related response, or an individual susceptibility. We are not even very sure at the present time whether we can detect it very early. We have been doing density studies on our patients and there are a number of them whose bone densities have fallen dramatically, but they have normal bones as far as radiology is concerned: certainly the femoral heads are quite normal. The problem may just be individual susceptibility, but I have been unable to isolate this factor. We are also looking at the number of rejection episodes, and seeing if this is related to a massive dose over a short period of time when the body weight is low. The suggestion has been made that if the transplanted kidney has a number of rejection episodes which are treated promptly, then the massive dose of steroids acts as an enormous 'insult' initially and this may, in some way, be responsible.

C van YPERSELE de STRIHOU (Louvain): Last year we reported a 15% incidence of bone necrosis in transplanted patients, and in our analysis we tried to evaluate the role of rejection episodes, and the total amount of cortisone that had been given, and were unable to show any relationship between steroids and the occurrence of osteonecrosis.

B A van der WERF (Florida): Could you comment upon the indication for parathyroidectomy in dialysis and transplant patients?

CARROLL: The short answer is that we would be unhappy to recommend a parathyroidectomy on the basis of our histological studies. The patients who had a parathyroidectomy are a mixed group: some had a parathyroidectomy before transplantation and some afterwards. Sub-total or total parathyroidectomy was performed for secondary hyperplasia and autonomy; because of this mixed group and the small numbers we are not prepared to recommend parathyroidectomy.

L R DUFRESNE (Montreal): Do you have any PTH levels to correlate with
your histological data?

CARROLL: No, we do not have PTH levels throughout the five year period. The PTH levels that we do have are in the four year group, and these appear to be normal.