

## **DETERMINANTS OF SERUM CALCIUM AFTER RENAL TRANSPLANTATION: THE ROLE OF 1,25(OH)<sub>2</sub>D<sub>3</sub>**

**P A Lucas, \*R C Brown, L Bloodworth, \*J S Woodhead, G A Coles**  
*Royal Infirmary, \*University Hospital of Wales, Cardiff, United Kingdom*

### **Summary**

Serum calcium, iPTH, 1,25(OH)<sub>2</sub>D<sub>3</sub>, alkaline phosphatase, phosphate and creatinine clearance were measured in 30 subjects chosen randomly at least three months after transplantation. Intestinal calcium absorption was measured in 17. Correlations were found between serum calcium and 1,25(OH)<sub>2</sub>D<sub>3</sub> (r=0.45, p<0.01) and between fractional calcium absorption and 1,25(OH)<sub>2</sub>D<sub>3</sub> (r=0.77, p<0.001). Comparison with chronic renal failure subjects with similar renal function revealed similar plasma iPTH and higher serum calcium (p<0.002), alkaline phosphatase (p<0.002) and 1,25(OH)<sub>2</sub>D<sub>3</sub> (p<0.05) after transplantation. 1,25(OH)<sub>2</sub>D<sub>3</sub> thus appears to be a major determinant of serum calcium after transplantation acting on the intestine and possibly on the skeleton.

### **Introduction**

Hypercalcaemia occurring after renal transplantation is generally thought to be caused by overactivity of parathyroid glands which have become hyperplastic over years of continual stimulation prior to transplantation [1]. The precise pathogenetic mechanisms of hypercalcaemia have not, however, been well defined and in particular, little information is available as to the role of 1,25(OH)<sub>2</sub>D<sub>3</sub> in this context. We therefore investigated the determinants of serum calcium after renal transplantation.

### **Subjects and methods**

Glomerular filtration rate was measured by creatinine clearance in 30 subjects who had undergone renal transplantation at least three months previously. No subject had proteinuria greater than 1g daily or had received vitamin D or its metabolites since transplantation. Metabolites of vitamin D<sub>3</sub> were measured by radioimmunoassay following lipid extraction (acetonitrile) and

HPLC (partisil 5 $\mu$  developed in hexane: 2-propanol: methanol, 90:5.5 v/v) ([2] with modifications). Antiserum (02282) was kindly provided by Professor A D Care, University of Leeds, United Kingdom. Normal 1,25(OH)<sub>2</sub>D<sub>3</sub>: 22–54pg/ml (mean  $\pm$  2SD, n=23), 25(OH)D<sub>3</sub>: 6–36ng/ml (n=23).

Oral <sup>47</sup>Ca was given with 20mg elemental calcium to 17 fasting transplant patients, 15 of whom were taking corticosteroids (5–20mg/day) with azathioprine or Cyclosporin A. Two subjects were taking Cyclosporin A alone. The fraction of administered radioactivity measured in plasma obtained 60 minutes later was taken as a measure of intestinal calcium absorption [3] (normal: 0.6–2.4%). Serum iPTH was measured by immunoradiometric assay [4] which recognizes the intact molecule. Normal range for serum iPTH: <0.7ng/ml.

Two tailed statistical tests were used throughout. Between group comparisons were made by means of the Mann-Whitney U test. Results are expressed as mean  $\pm$  SEM.

## Results

There was a correlation between total corrected serum calcium and circulating 1,25(OH)<sub>2</sub>D<sub>3</sub> (r=0.45, p<0.01) and between fractional calcium absorption and circulating 1,25(OH)<sub>2</sub>D<sub>3</sub> (r=0.77, p<0.001). No relationship was found between calcium absorption and corticosteroid intake.

Transplant patients were divided into two groups and compared with two groups of chronic renal failure patients with similar renal function (Table I).

TABLE I. Comparison of renal transplantation (RTX) with chronic renal failure (CRF) subjects at two levels of renal impairment

	GFR ml/min	1,25(OH) <sub>2</sub> D <sub>3</sub> pg/ml	PTH ng/ml	25(OH)D <sub>3</sub> ng/ml	P mmol/L	Calcium mmol/L	AP IU/L
45–75ml/min							
CRF (n=15)	58 $\pm$ 3	28 $\pm$ 3	1.6 $\pm$ 0.3	17.2 $\pm$ 1.5	1.3 $\pm$ 0.1	2.2 $\pm$ 0.3	76 $\pm$ 17
RTX (n=14)	55 $\pm$ 2 NS	44 $\pm$ 6 *	1.8 $\pm$ 0.6 NS	15.4 $\pm$ 3.1 NS	1.0 $\pm$ 0.1 NS	2.5 $\pm$ 0.1 **	179 $\pm$ 20 **
15–45ml/min							
CRF (n=14)	29 $\pm$ 2	18 $\pm$ 3	1.1 $\pm$ 0.2 (n=10)	15.9 $\pm$ 7.8	1.6 $\pm$ 0.2	2.2 $\pm$ 0.1	78 $\pm$ 10
RTX (n=16)	31 $\pm$ 19 NS	25 $\pm$ 2 *	1.7 $\pm$ 0.4 NS	12.1 $\pm$ 4.0 NS	1.2 $\pm$ 0.1 NS	2.4 $\pm$ 0.1 **	180 $\pm$ 23 **

\* p<0.05; \*\* p<0.002. NS=no significant difference  
P=Phosphate; AP=alkaline phosphatase

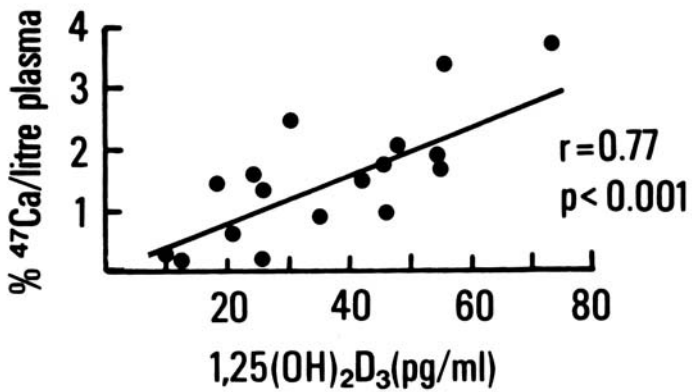


Figure 1. Relationship between fractional calcium absorption and circulating 1,25(OH)<sub>2</sub>D<sub>3</sub>

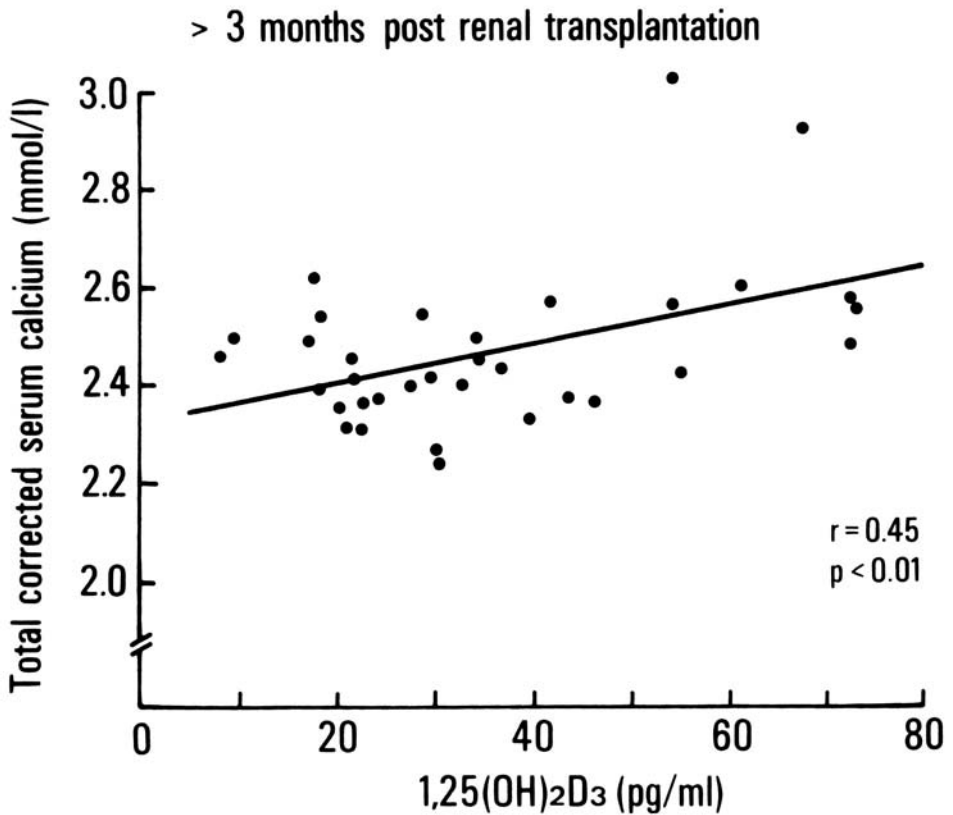


Figure 2. Relationship between total corrected serum calcium and circulating 1,25(OH)<sub>2</sub>D<sub>3</sub>

## Discussion

This study provides evidence that  $1,25(\text{OH})_2\text{D}_3$  is an important determinant of serum calcium after renal transplantation. It also suggests that following transplantation the normal relationship between circulating  $1,25(\text{OH})_2\text{D}_3$  and intestinal calcium absorption is preserved. This latter finding was not predictable, particularly in view of the reported inhibitory effect of corticosteroids on calcium absorption [5,6]. The fact that the subjects studied were receiving relatively low doses of corticosteroids may be relevant in this context. The comparison of transplanted with uraemic subjects suggests that the differences in serum calcium between groups with similar degrees of renal impairment may be at least partly explicable in terms of differences in plasma  $1,25(\text{OH})_2\text{D}_3$  (Figures 1 and 2). Single serum PTH values have been shown

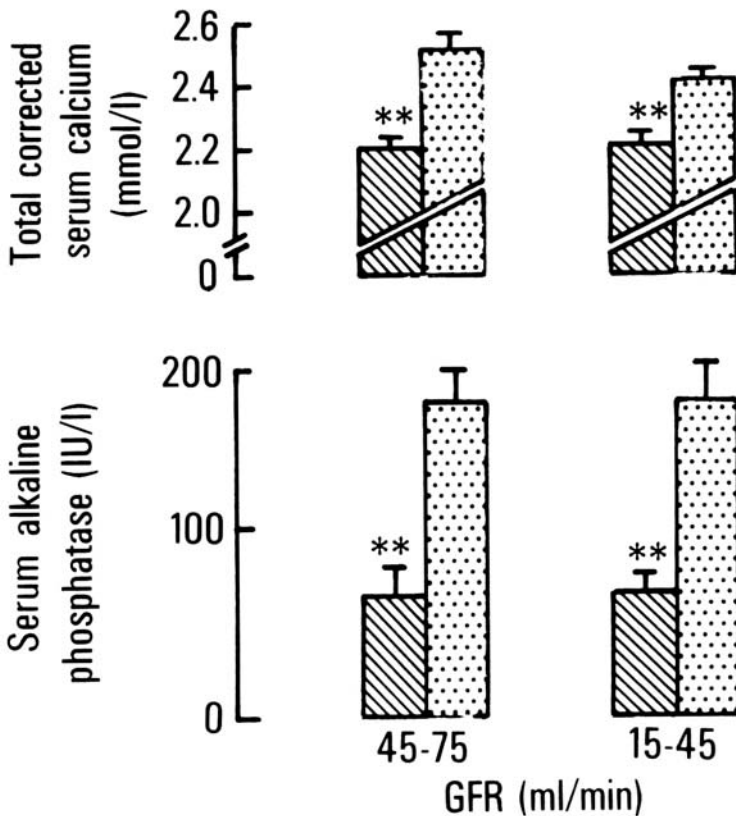


Figure 3. Serum calcium and alkaline phosphatase at glomerular filtration rate 45–75 ml/min and 14–45 ml/min in chronic renal failure and after renal transplantation. Hatched column=chronic renal failure; stippled column=renal transplantation. \*\*  $p < 0.002$

to correlate poorly with parathyroid gland size [7] but there is no such information to suggest a lack of correlation with overall parathyroid function. Although it is likely that gland size was greater in the transplant group, their PTH was not significantly higher than those found in the chronic renal failure group at either level of renal function. This may be because after transplantation, single PTH values represent potential glandular function suppressed by higher serum calcium whilst those found in the chronic renal failure group represent parathyroid function stimulated by lower serum calcium. Assuming the degree of hyperparathyroidism to be similar in the transplant and the uraemic subjects, the differences between plasma alkaline phosphatase (presumably reflecting increased bone turnover) could represent action of  $1,25(\text{OH})_2\text{D}_3$  on the skeleton. Obviously, other explanations are possible, including changes in bone metabolism consequent upon increased aluminium excretion after transplantation (Figures 3 and 4).

The reason for the difference in plasma  $1,25(\text{OH})_2\text{D}_3$  between transplant and uraemic subjects with similar degrees of renal impairment and hyperparathyroidism remains uncertain. Distinct pathological processes are likely to

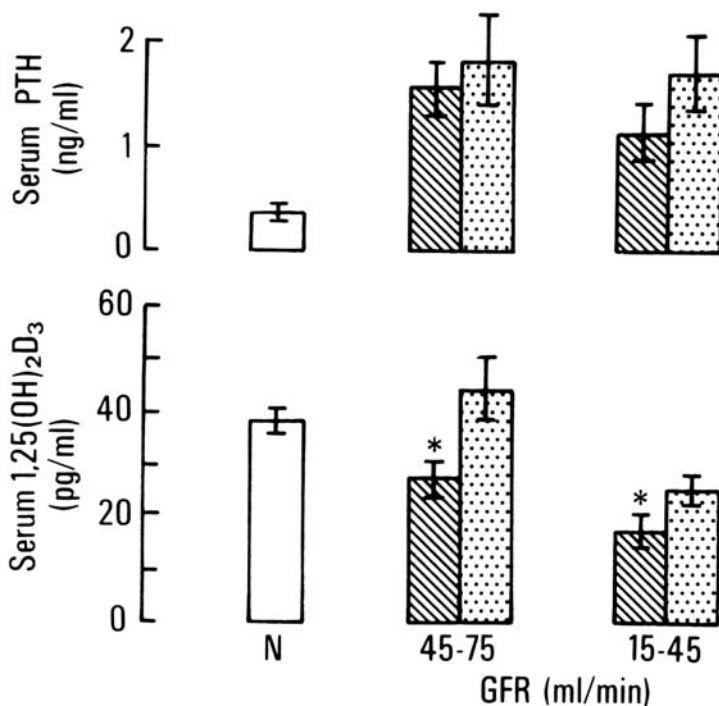


Figure 4. Serum PTH and  $1,25(\text{OH})_2\text{D}_3$  in normal subjects and at glomerular filtration rates 45-75ml/min and 15-45ml/min in chronic renal failure and after renal transplantation. Hatched column=chronic renal failure; stippled column=renal transplantation. \* $p < 0.05$

be the cause of renal impairment in transplant as opposed to uraemic subjects, processes which may affect glomerular and tubulo-interstitial tissue to differing degrees. Although a difference in serum phosphate between transplant and uraemic subjects might be anticipated [8] as an explanation of the difference in plasma  $1,25(\text{OH})_2\text{D}_3$  [9], we found serum phosphate to be similar in both groups.

In summary, plasma  $1,25(\text{OH})_2\text{D}_3$  appears to play an important role in the determination of serum calcium after renal transplantation, probably acting mainly by the stimulation of intestinal absorption of calcium.

## References

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