Whole Body Calcium Changes During Long Term Dialysis

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Study of the bone disorders which may complicate renal failure, whether or not treated by intermittent dialysis, is hampered by the lack of sensitivity and reproducibility of existing techniques for the investigation and assessment of metabolic bone disease. Conventional radiology will not detect metabolic bone disease until it is gross, for changes of bone calcium content of the order of 30 to 40% may be required before they can be observed with certainty. More specialised radiological techniques involving densitometry and absorptiometry of particular bones are more sensitive, but of uncertain reproducibility. Bone biopsy is essentially qualitative. Problems of calcium dynamics limit the value of isotope tracer studies. The limitations of conventional metabolic balance studies over long periods are increased by regular haemodialysis treatment (RDT). Attempts have been made to derive data for net calcium transfer during dialysis by measurement of the differences between dialyser inflow and outflow calcium concentrations in the blood (Kaye et al, 1966) or the dialysate (Curtis et al, 1968). Apart from the limitations imposed by analytical techniques, this approach cannot reflect accurately long term changes. There is a need for an accurate technique for measuring changes in skeletal calcium in patients receiving long term dialysis to assess the progress of the bone disease and the influence of treatment or of varying dialysate composition.

In an attempt to overcome these difficulties we have begun to measure whole body calcium in patients with chronic renal failure by the technique of whole body neutron activation analysis. This method has been in routine clinical use in Birmingham for two years (Chamberlain et al, 1970). It depends upon the fact that the small but constant proportion of naturally occurring ^{48}Ca can be converted by incident slow neutrons to the high energy gamma ray emitting isotope ^{49}Ca, half-life 8.9 minutes. The ^{49}Ca activity induced in any natural calcium is proportional to the mass of calcium present and the neutron dose delivered. Skeletal calcium represents more than 99% of the whole body calcium so the technique in effect measures skeletal calcium.

TECHNIQUE OF WHOLE BODY CALCIUM DETERMINATION

The patient is exposed to a uniform field of cyclotron-produced fast neutrons so designed as to give a uniform slow neutron flux throughout the body after moderation of the fast neutrons by the tissues.

A small proportion of calcium wherever it occurs in the body is activated to ^{49}Ca. The ^{49}Ca activity induced is measured by transferring the patient to a whole body radiation monitor of the steel room low background type. Speed is essential because of the 8.9 minute half-life of ^{49}Ca. The 512 Channel Analyser facility of the whole body monitor allows the ^{49}Ca activity to be detected and measured in the presence of other activity induced by neutron activation. The spectrum of induced activity is analysed by the KDF 9 computer of the University of Birmingham. For the patient the procedure is quick and painless. The neutron exposure takes $6\frac{1}{2}$ minutes and the whole body counting approximately 20 minutes. The radiation dose received is comparable with that of a conventional radiological skeletal survey.

Whole body calcium was estimated as ^{49}Ca activity induced per unit of neutron dose received measured by a modified boron trifluoride counter. The measured activity in a given patient will depend upon the mass of calcium within the body and upon the efficiency of counting the induced activity in the individual patient. Because of these variables it is not yet technically possible to express whole body calcium in absolute terms, nor would such an expression have value until we know to what aspect of body habitus this value should be related. There is little prospect with this technique of obtaining a comprehensive 'normal range'. We have therefore concentrated on sequential studies of whole body calcium in individual patients for whom such factors as counting efficiency and efficiency of activation are likely to remain constant.

PATIENTS AND METHODS

Sequential studies of whole body calcium were made in 8 patients in chronic renal failure. Clinical details are summarised in Table I. Studies were usually performed before or within a few weeks of starting intermittent haemodialysis and repeated at approximately six monthly intervals. Four patients have remained on regular dialysis treatment throughout the study. Three have been restudied after successful cadaveric renal transplantation. The eighth patient (PS) has on two occasions acutely rejected cadaveric renal transplants. Since neither graft has functioned he may be regarded as having continued on long term dialysis throughout the period of study.

Haemodialysis was performed, usually on three occasions in each week, for a minimum total of 28 hours per week. In the majority the modified Kiil dialyser was used, with PT 150 cuprophone, but in 4 patients some or all dialyses were performed using a cellophane coil ('Minicoil') artificial kidney. In all cases dialysate calcium concentration was 6 mg/100 ml.

Table I. Details of Patients Studied

Patient	Age	Sex	Diagnosis	Probable duration of Uraemia before study	Bone histology and Radiology at start	Bone histology and Radiology, 1970	Mean Serum Calcium, 1970 mg/100 ml	Alkaline Phosphatase KAu/100 ml
HS	47	M	Retroperitoneal Fibrosis	2 years	Normal	Normal	10.9	9
TM * **	21	M	Glomerulonephritis	3 months	Normal	Normal	9.2	11
WR * **	42	F	Glomerulonephritis	5 years	Osteomalacia and Osteitis fibrosa	Osteitis fibrosa	9.6	228
PS **	27	M	Malignant Nephrosclerosis	6 months	Normal	Normal	11.4	8
MW	22	F	Glomerulonephritis	3 years	Normal	Osteitis fibrosa	9.5	64
MS	35	F	Chronic Pyelonephritis	4 years	Normal	Minor changes of Osteitis fibrosa	9.8	17
FW	37	M	Malignant Nephrosclerosis	6 months	Normal	Normal	9.8	7
MG * **	18	M	Glomerulonephritis	5 years	Osteomalacia	Osteomalacia and Osteitis fibrosa	10.1	19

* Indicates successful renal transplantation
** Indicates periods of RDT with 'Minicoil'

Post transplant patients were maintained on conventional doses of azathioprine and prednisone. None of the patients received dietary calcium supplements or Vitamin D. Serum calcium was determined by an auto-analyser technique based on the murexide method. Alkaline phosphatase was determined by the method of Kind and King. Bone biopsies were obtained from the iliac crest and studied in undecalcified section.

RESULTS

Seven patients were studied on two or three occasions, while receiving RDT over periods of between six months and two years. The results are summarised in Table II. The results of whole body calcium determinations are expressed as ratios of ^{49}Ca activity induced to neutron dose received as measured by the boron trifluoride counter. In the second and later studies percentage change in total calcium from the initial study is also given. The results of representative serum calcium and alkaline phosphatase determinations during the period of study are included in Table I with results of bone biopsy and radiological survey of the skeleton.

Table II. Whole Body Calcium at Approximately Six Month Intervals in Patients on RDT

Patient	Whole Body Calcium as ^{49}Ca/Neutron Dose			Percentage Change
	1	2	3	
HS	0.290	0.266	0.269	-8.3 - 7.3
TM	0.310	0.255		-17.7
WR	0.173	0.147		-15.1
PS	0.311	0.294	0.275	-5.5 - 11.5
MW	0.168	0.168	0.195	0 + 16.1
MS	0.194	0.187	0.198	-3.6 + 2.1
FW	0.295	0.313		+6.1

No consistent pattern of change in whole body calcium during RDT has so far emerged from this study. Four patients have shown some fall in whole body calcium although in two this has been slight. One patient (HS) showed a fall during the early months of RDT followed by a rise towards pre-treatment values. Two patients (TM and PS) in whom the total period of renal insufficiency preceding the initiation of RDT was six months or less, and in whom no evidence of renal bone disease was anticipated nor found, showed marked loss of skeletal calcium during the first six months of treatment. One patient with osteomalacia, evident before the initiation of dialysis, showed progressive reduction in whole body calcium during six months of RDT, but in contrast MW, who had a normal bone biopsy before starting RDT, has shown a

significant increase in whole body calcium over 2 years in spite of the development of gross radiological changes of secondary hyperparathyroidism as shown by a typical 'rugger jersey' spine and subperiosteal erosions of the phalanges.

Table III. Whole Body Calcium Before and Approximately Six Months after Renal Transplantation

Patient	Whole Body Calcium as ^{49}Ca/Neutron Dose		Percentage Change
	Before Transplant	$^{6}/_{12}$ After Transplant	
TM	0.255	0.231	-9.4
WR	0.147	0.135	-8.2
MG	0.143	0.161	+12.5

Table III summarises the whole body calcium changes in three patients restudied after successful cadaveric renal transplantation. In WR, who had osteomalacia before starting RDT, a further decline in whole body calcium has occurred following renal transplantation, but the decline has been at a slower rate. A similar sequence has occurred in TM in whom demonstrable bone disease was not present at the start of RDT. One patient (MG) with evidence of bone disease before treatment, has shown a significant rise in whole body calcium following transplantation.

DISCUSSION

The method of whole body calcium determination by neutron activation analysis has been validated in cases of metabolic bone disease which are less complex than those occurring in chronic renal failure and in which the changes in whole body calcium might reasonably be predicted. Such a case is illustrated in Figure 1. This shows the changes in whole body calcium in a man with osteomalacia, due to a malabsorption syndrome, treated with large doses of calciferol. At six months the bone histology was indistinguishable from normal yet at 12 months the radiological appearances were unchanged. The changes in skeletal calcium are clearly revealed by neutron activation analysis. It is apparent that this technique can also be applied to the study of patients receiving RDT. For reasons stated direct comparisons of total body calcium content have not been attempted between patients or between patients and normal subjects. But patients may be compared in terms of pattern of behaviour and rate of change of whole body calcium in particular conditions. The time scale in dealing with metabolic bone disease is necessarily a long one and results for patients with chronic renal failure are thus at a very preliminary stage.

The results of this study do not so far give a clear indication as to the

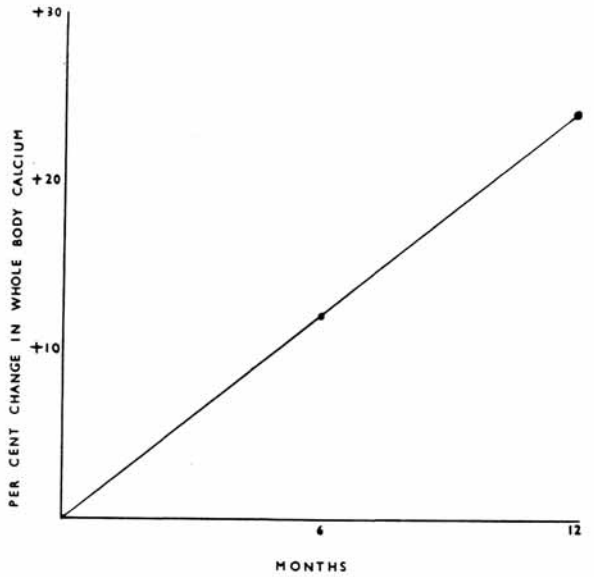

Figure 1. Percentage changes in whole body calcium in a patient with osteomalacia and normal renal function treated for one year with Vitamin D

determinants of calcium loss during dialysis. Calcium absorption is known to be impaired in renal failure (Kleeman et al, 1969). We have found impaired calcium retention in patients on this dialysis programme using orally administered ^{47}Ca, and this impairment is little affected by dialysis. The changes do not seem to be influenced by pre-existing bone disease but there is a suggestion that in some patients calcium loss may continue during the early months of RDT, possibly because of poor nutrition and deficient muscle power and activity, but that in some patients at least this loss may diminish or reverse with improved health.

We have attempted to identify differences between patients who continue to lose calcium significantly on RDT, and others. None were significantly acidotic before dialysis and all were adequately dialysed by accepted criteria. Six patients have been dialysed throughout using dialysate made from tap water containing 0.1 part per million of fluoride. This group comprises patients whose whole body calcium has fallen markedly, remained little changed or risen. The greatest falls in body calcium have been in patients dialysed for long periods with cellophane coils. None of these have shown a rise. However, the data is inadequate to draw firm conclusions.

The technique described requires sophisticated equipment and is unlikely to be generally available, but it does provide a sensitive tool for intensive and prolonged study of a small group of patients from whom one hopes to derive information applicable to a wider population.

SUMMARY

There is a need for a technique to monitor changes in skeletal calcium in patients receiving treatment by dialysis or renal transplantation. Whole body neutron activation analysis provides such a technique which can be repeated at intervals and administers to the patient a radiation dose comparable with standard radiological survey procedures. Eight patients have been repeatedly studied by this method during RDT and after renal transplantation. No consistent pattern of change has yet emerged in the patients in the particular dialysis programme studied, but further and more prolonged studies with this technique promise to throw additional light on the problems of bone disease in renal failure.

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REFERENCES

Chamberlain, M. J., Fremlin, J. H., Peters, D. K. and Philip, Helen (1970) Proceedings of the IX Bad Gastein International Conference on Radioisotopies in Clinical Medicine and Research. Urban and Schwarzenburg, Munich (in press)

Curtis, J. R., Wing, A. J., Eastwood, J. B., Smith, E . K. M. and De Wardener, H. E .(1968) Proceedings of the European Dialysis and Transplant Association. Volume V. Page 300. Excerpta Medica, Amsterdam

Kaye, M., Mangel, R. and Neubauer, E. (1966) Proceedings of the European Dialysis and Transplant Association. Volume III. Page 17. Excerpta Medica, Amsterdam

Kleeman, C. R., Massry, S. G., Coburn, J. W. and Poportzer, M. M. (1969) Archives of Internal Medicine, 124, 262