PART XII

NEPHROLOGY: Renal Osteodystrophy

Chairmen: D O Oliver
A Kasanen
COMPARISON OF WHOLE BODY AND REGIONAL ASSESSMENTS OF CALCIUM BALANCE IN RENAL OSTEODYSTROPHY IN THE RESPONSE TO 1α-HYDROXY VITAMIN D₃

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Summary

Ten patients with renal bone disease have been treated with 1α-hydroxycholecalciferol for periods of 10-18 months. Responses in bone histology, plasma alkaline phosphatase, whole body calcium, spinal calcium content and bone mineral content of the forearm were compared. Improvements in histology of bone were seen in 5 patients. These patients showed greater increases in total body calcium, and the increments in total body calcium correlated significantly with decrements in alkaline phosphatase. Changes in forearm bone mineral content or spinal calcium were less predictable and did not invariably reflect measured changes in whole body calcium. We conclude that total body calcium may provide a useful and early index of response to treatment with 1α-hydroxycholecalciferol. In contrast, skeletal changes noted by regional methods of assessment should not be judged as reflecting changes occurring in the whole skeleton, and may even be misleading.

Introduction

Renal osteodystrophy is the result of a variety of skeletal abnormalities which include osteomalacia, osteitis fibrosa, osteosclerosis and osteopaenia. These disorders may occur singly but are more frequently found in combination. Accurate diagnosis of the skeletal lesion can be made most reliably by bone histology, but a variety of techniques have been developed which can estimate the amount of mineral in the skeleton with a surprising degree of accuracy. These include photon absorption to measure bone mineral content, in vivo neutron activation analysis to measure calcium content, and a variety of radiographic techniques to measure density or cortical width of bone. Unlike bone histology, these techniques are unsuitable for diagnostic purposes,
except perhaps in the case of osteopaenia. Their value lies more in the serial assessment of skeletal status since the reproducibility of these measurements is generally within 5 per cent. They may yield information about bone loss and provide an indirect assessment of the value of therapeutic manipulations such as varying the dialysate calcium content, and treatment with vitamin D$^5$.

A source for concern when regional assessments of bone loss are made is that changes in one part of the skeleton may not reflect changes occurring elsewhere. In order to examine whether this possibility is a serious limitation of regional techniques in the study of renal bone disease, we have measured the regional changes in mineral by two techniques, spinal calcium content and forearm bone mineral content, and compared these with changes occurring in whole body calcium following the administration of 1α-hydroxy-vitamin D$_3$ (1α(OH)D$_3$).

Patients and Methods

Ten adults (Table I) with chronic renal failure and renal bone disease were treated with 1α(OH)D$_3$ 1 - 3 μg daily by mouth for periods of 10 - 18 months. The daily dose was adjusted from time to time to maintain the plasma level of calcium below 3.0 mmol/l in the seven patients treated by regular haemodialysis and below 2.70 mmol/l in three patients not treated by dialysis. All patients took a dietary supplement of calcium (1 gram as the gluconate). Dialysate calcium was 1.6 mmol/l except for one patient. (Table I).

The following measurements were made before and at the completion of treatment: whole body calcium was estimated by whole body neutron activation analysis$^6$. The coefficient of variation in control patients using this method is 3 per cent. Bone mineral content was measured at the junction of the medial and distal third of the radius using$^{125}$I photon absorption (Norland Cameron Bone Mineral Analyser). Two consecutive determinations were made and the mean value presented, the coefficient of variation being 5 per cent. Measurements of spinal calcium were made using partial body neutron activation analysis$^7$. The coefficient of variation in controls using this method is between 3 and 5 per cent. Transiliac bone biopsies were taken under local anaesthetic. Changes were scored on an arbitrary 4 point scale; worse, no change, improved, or healed$^8$. Serial determinations of plasma calcium, immunoreactive parathyroid hormone, activity of alkaline phosphatase and bone derived alkaline phosphatase were measured as previously described$^5,9$.

Results (Table I)

Overall calcium balance, as measured by the change in total body calcium, became more positive during treatment in 7 of the 10 patients (mean increase = 1.55 ± SEM 0.60% per patient per treatment month). The change in total body calcium reflected changes in bone morphology in the sense that a significant correlation was noted between the increase in total body
<table>
<thead>
<tr>
<th>Number</th>
<th>Duration of Treatment (months)</th>
<th>Bone Histology Before Treatment</th>
<th>Response</th>
<th>Percentage change over period of Study</th>
<th>Forearm bone mineral content</th>
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<td>Plasma bone derived alkaline phosphatase</td>
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<td>7</td>
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<td>OF + OM</td>
<td>Healed</td>
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<td>Improved</td>
<td>- 94</td>
<td>+ 29</td>
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<tr>
<td>10*</td>
<td>12</td>
<td>OF</td>
<td>No change</td>
<td>- 96</td>
<td>+ 45</td>
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* = Patients treated by intermittent haemodialysis (Cordis Dow or Kiil dialysers, 20–30 hours/week.
Dialysate calcium = 1.60 mmol/L except Patient No.3, = 2.0 mmol/L. OM = osteomalacia; OF = osteitis fibrosa
calcium and the decrement in plasma activity of bone-derived alkaline phosphatase (r = 0.77; p < 0.01), and that greater increments were noted in patients with improvement in bone histology (mean change in total body calcium = 2.5 ± 0.6% per patient per treatment month) than in those with less favourable histological responses (mean = + 0.6 ± 0.9). All the patients with improved bone histology showed increases in total body calcium. Correlations between changes of spinal calcium and of forearm bone mineral content and the decrements in bone-derived alkaline phosphatase (r = 0.55 and 0.46 respectively) did not reach levels of statistical significance.

A significant correlation was noted between the changes in total body calcium and spinal calcium content (r = 0.68, p = 0.05). The measurement of spinal calcium content was of less value than total body calcium as an index of histological response as shown by the observation that changes in spinal calcium in patients with good or with poor histological responses did not differ significantly (mean change = + 0.7 ± SEM 0.6; + 0.4 ± 0.9% per patient per treatment month, respectively - p = 0.76).

Before treatment there was a significant correlation between total body calcium and forearm mineral content (r = 0.9; p = < 0.001) but there was no significant relationship between the treatment-induced changes of the one with the other (r = + 0.44; p = 0.5, Figure 1).

The serial measurement of spinal calcium or bone mineral content frequently yielded information which might have been misleading were the changes interpreted as reflecting changes in bone morphology or changes in total body calcium. (Figure 2).

Discussion

The present study suggests that patients who showed the most favourable histological and biochemical responses to treatment with 1α(OH)D₃ also showed the greatest changes in total body calcium i.e. external calcium balance. The serial measurements of spinal calcium or bone mineral content at the forearm were less useful in this respect. Perhaps of greater importance was the finding that changes measured by regional methods did not invariably reflect changes in total body calcium. (Figure 2, Table I).

The present study confirms that the response of renal bone disease to 1α(OH)D₃ is not uniform,5,8 and that, at least over the period of observation in this series, histological response may be confined to 50 per cent of patients treated. The serial determination of total body calcium may provide a useful early index of morphological response to treatment. The detection of loss of skeletal calcium might identify a group of patients in whom deficient production of 1α-hydroxylated metabolites of vitamin D were not of major aetiological importance, and in whom 1α-hydroxylated metabolites may indeed be harmful5.

Whole body neutron activation analysis is expensive and not available to the majority of clinicians who treat renal bone disease. Of the two regional
Figure 1. Treatment of renal bone disease with 1α-hydroxycholecalciferol. The relationship between treatment-induced changes in bone mineral content of the forearm (BMC) and in total body calcium (both expressed as percentage change from initial values). Symbols denote the histological diagnosis of patients before treatment (○=osteomalacia; ●=osteitis fibrosa; ●●=osteitis fibrosa and osteomalacia; □=improvement in bone histology noted after treatment. (From Naik et al.16 with permission)
Figure 2. Responses of 3 patients to long-term treatment with 1α-hydroxycholecalciferol.

A) Patient no. 10, Table I, showed a favourable biochemical, radiographic and histological response to treatment. This was associated with increases in total body calcium and bone mineral content.

B) Patient no. 6, Table I, showed a poor histological, radiographic and biochemical response to treatment. Total body calcium did not increase. In contrast increases were observed in bone mineral content of the forearm.

C) Patient no. 5, Table I. A favourable histological, biochemical and radiographic response was associated with increases in total body calcium but bone mineral content of the forearm was unchanged during the period of observation.
methods of measuring skeletal response that we have assessed, the facilities to measure bone mineral content are the more widely available. Because of the site chosen, our measurements of bone mineral content assessed predominantly cortical bone. Our results suggest that such measurements do not accurately reflect changes occurring elsewhere in the skeleton and may be frankly misleading. Whether these conclusions would pertain if a different site for scanning had been chosen is uncertain. Certainly the measurements of spinal calcium gave a better but still imprecise index of global changes.

It should be noted that before treatment there was a good correlation between total body calcium and bone mineral content. The disappearance of this relationship in the response to treatment, and the greater changes noted in total body calcium compared to those seen in bone mineral content, suggest that the increased mineral content of the skeleton in patients receiving 1α(OH)D₃ was not equally distributed throughout the skeleton. Alternatively a component of the increase in total body calcium might have been due to an increase in soft tissue and vascular calcification. This appears unlikely since there were large increases in total body calcium in some patients but no radiographic evidence of ectopic calcification; and those patients who showed the greater increase in total body calcium also showed the more favourable clinical and histological response to 1α(OH)D₃. Changes in spinal calcium measured by regional body neutron activation analysis correlated better with changes in total body calcium than did forearm bone mineral content and this would suggest that increase in skeletal calcium was more marked in trabecular bone. With longer term use of 1α(OH)D₃ these disparities in response might decrease but at present we would conclude that it is necessary to exercise caution when extrapolating the changes in calcium content obtained by regional measurement, to other parts of the skeleton.

Acknowledgments

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Open Discussion

GURA (Israel) You stated that you administered almost no aluminium hydroxide. Now vitamin D and the related compounds are known to enhance the absorption of phosphorus. Therefore you might be increasing the amount of phosphorus as well as that of calcium and perhaps then getting a high calcium phosphorus product. I then wonder whether your phosphorus levels increased and this would tend to cause soft tissue calcification, which I am a little bit surprised you did not see.

NAIK In our patients the overall serum phosphorus levels did actually fall. There is every possibility that there might have been some soft tissue calcification but we were not able to demonstrate this. Examination of the eyes showed no calcification either but one cannot exclude soft tissue calcification completely—there certainly was no evidence of this in the investigations that we did.

KOKOT (Katowice), Poland In one of your slides I saw an increase of plasma parathyroid hormone concentration at the beginning of treatment with 1α(OH)D₃. Similar observations were made in our centre. Have you some original explanation for this fact?

NAIK This is the second patient. She showed no response to 1α(OH)D₃. Initially there was a fall in parathyroid hormone but this subsequently went up, her bone lesions did not heal and alkaline phosphatase came down but not completely to normal. I have no explanation for the parathyroid hormone changes you have mentioned.

KERR (Newcastle) As you say Dr Naik, whole body calcium measurements are not available to most of us and never will be. So we are most anxious to know whether we can make do with the available measurements. You did not have a very good correlation between the quantitative changes, but was the direction of the change always the same: if whole body calcium increased, did you always get some increase at least in bone mineral content?

NAIK In general, there were parallel changes but in individual patients I think one needs to be rather cautious. In some of the patients there was an increase in whole body calcium, and whole body calcium was the only parameter that correlated well with other changes, e.g. total alkaline phosphatase, bone alkaline phosphatase and histology. Bone mineral content on the other hand did not. In some cases there was an increase in whole body calcium but no change in bone mineral.