BONE MINERAL LOSS DURING CENTRE AND HOME HAEMODIALYSIS. INFLUENCE OF VITAMIN D METABOLITES AND SERUM PARATHYROID HORMONE

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Summary

Twenty-seven patients on chronic haemodialysis were investigated for a mean of 4.8 years (3.0–6.5 years). Mean bone mineral content fell constantly and similarly at a rate of three to four per cent per year in both centre (n=14) and home (n=13) haemodialysis patients. Mean serum values of 25(OH)D₃ (normal), 24,25(OH)₂D₃ (decreased to half the normal level and 1,25(OH)₂D₃ (severely decreased and almost non-detectable) were similar in patients with a rapid bone mineral content loss (>10%/3 years) and a slow bone mineral loss (<10%/3 years). Mean serum parathyroid hormone was markedly elevated, but significantly higher (about twice the level) in the ‘rapid losers’ than in the ‘slow losers’; whereas the two groups did not differ with regard to mean serum concentrations of calcium, phosphate and alkaline phosphatase.

Introduction

Metabolic bone disease is a well-known complication of chronic renal failure and maintenance haemodialysis. The nature of this bone disease, known as uraemic osteodystrophy, is complex, but secondary hyperparathyroidism [1] and disturbances in vitamin D metabolism [2] seem to be of major importance in the pathogenesis. However, neither parathyroidectomy nor treatment with high potency vitamin D analogues, such as 1,25-dihydroxy vitamin D (1,25(OH)₂D₃), invariably cure bone lesions despite normalisation of biochemical abnormalities.

Longitudinal studies of the bone mineral content have shown marked differences in the natural history of bone mineral content loss during haemodialysis, indicating that some haemodialysis patients are rapid losers of bone calcium [3]. In the present longitudinal bone mineral content study of haemodialysis patients, the influence of the serum levels of parathyroid hormone (iPTH) and the vitamin D metabolites (25(OH)D₃, 24,25(OH)₂D₃ and 1,25(OH)₂D₃) on the rate of bone
mineral content loss during haemodialysis was assessed. Moreover, a comparison was made between patients on centre and home haemodialysis as regards bone mineral content loss.

**Patients and methods**

Twenty-seven consecutive patients (12 females, 15 males; mean age 42 years (20–68 years)) entering chronic haemodialysis in the period 1977–1979 were studied. Fourteen of them were on centre haemodialysis, 13 on home haemodialysis. Excluded were patients with a previous renal transplant, bilateral nephrectomy, treatment with anticonvulsants, vitamin D derivatives and corticosteroids. They were haemodialysed four to six hours thrice weekly on a C-DAK 1.8m² or 2.5m² kidney. The dialysate was aluminium-free deionised tap water with a calcium concentration of 3.0mEq/L and a magnesium concentration of 1.0mEq/L. Heparin was routinely given, and all patients took 3g aluminium aminoacetate daily as a phosphate binder. They had received no calcium supplements and were on an unrestricted diet.

Bone mineral content was measured by two dimensional scanning photon absorptiometry (¹²⁵I) on both forearms as the mean of 12 scans. Measurements were made at the start of haemodialysis and usually at six month intervals for a mean of 4.8 years (range 3.0–6.5 years). Serial measurements were corrected for the physiological bone mineral content loss with age [4]. Long-term reproducibility of bone mineral content measurements is 1.2 per cent in normals and about two per cent in osteopenic patients [5]. Bone mineral content values were calculated as: 1) per cent of published reference values [6], 2) per cent of individual start value (=100%) in serial measurements, and 3) individual bone mineral content slope (mean percentage bone mineral content change/year) by linear regression in each patient in order to compare patients with differing periods of observation.

Serum values of immunoreactive parathyroid hormone (iPTH) (measured by a C-terminal assay), calcium (albumin corrected), phosphate and alkaline phosphatase were measured at three month intervals and mean values for the period of haemodialysis were calculated for each patient.

Serum values of 25(OH)D₃, 24,25(OH)₂D₃ and 1,25(OH)₂D₃ were measured by previously described methods [7]. Interassay variation in our laboratory for the three metabolites was: 11.5 per cent, 10.5 per cent and 9.8 per cent, respectively. All blood samples were drawn in October to eliminate the seasonal variation in 25(OH)D₃ and 24,25(OH)₂D₃.

**Results**

At the start of haemodialysis the mean bone mineral content (89.0% ± 18.2%) was significantly lower than in matched controls (p<0.05). There was no significant difference between males (92.9% ± 16.2%, SD) and females (84.0% ± 19.8%) or between centre (85.9% ± 20.1%) and home (92.2% ± 16.2%) haemodialysis patients. Figure 1 shows individual percentage slopes during haemodialysis
Figure 1. Individual bone mineral content changes during haemodialysis in 27 patients (○=centre haemodialysis, ♦=home haemodialysis). The bone mineral content slope (=mean percentage bone mineral content change/year) was calculated from serial measurements by analysis of regression.

Figure 2. Mean annual bone mineral values (% of initial value) in patients on centre (○) and home (♦) haemodialysis.
**TABLE 1.** Serum values (mean ± SD) of 25(OH)D₃, 1,25(OH)₂D₃, 24,25(OH)₂D₃, iPTH, calcium, phosphate and alkaline phosphatase in 14 patients on centre and 13 patients on home haemodialysis, and in haemodialysis patients with rapid bone mineral content loss (>10%/3 years) and slow bone mineral content loss (<10%/3 years) estimated by individual slope of serial bone mineral content measurements for a mean of 4.8 years (range 3.0–6.5 years) of haemodialysis.

<table>
<thead>
<tr>
<th></th>
<th>25(OH)D₃ (ng/ml)</th>
<th>1,25(OH)₂D₃ (pg/ml)</th>
<th>24,25(OH)₂D₃ (ng/ml)</th>
<th>iPTH (μg/ml)</th>
<th>Calcium (mmol/L)</th>
<th>Phosphate (mmol/L)</th>
<th>Alkaline phosphatase (U/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Centre haemodialysis (n=14)</td>
<td>28.7±18.4</td>
<td>2.6±3.2**</td>
<td>1.4±0.5*</td>
<td>7.1±5.8**</td>
<td>2.60±0.24</td>
<td>1.69±0.39*</td>
<td>180±51</td>
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<tr>
<td>Home haemodialysis (n=13)</td>
<td>33.6±13.8</td>
<td>3.5±2.8**</td>
<td>1.6±0.4*</td>
<td>7.7±7.3**</td>
<td>2.54±0.13</td>
<td>1.92±0.50*</td>
<td>201±77</td>
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<tr>
<td>rapid bone mineral content loss (n=13)</td>
<td>31.8±15.8</td>
<td>3.1±2.7**</td>
<td>1.5±0.6*</td>
<td>10.5±8.1**</td>
<td>2.55±0.17</td>
<td>1.76±0.49*</td>
<td>196±73</td>
</tr>
<tr>
<td>slow bone mineral content loss (n=14)</td>
<td>30.4±17.2</td>
<td>3.0±3.3**</td>
<td>1.4±0.6*</td>
<td>4.6±2.7**</td>
<td>2.61±0.23</td>
<td>1.86±0.43*</td>
<td>184±58</td>
</tr>
<tr>
<td>Controls</td>
<td>26.1±11.3</td>
<td>28.6±10.8</td>
<td>3.1±2.7</td>
<td>0.20–0.55†</td>
<td>2.50±0.10</td>
<td>1.18±0.19</td>
<td>70–275†</td>
</tr>
</tbody>
</table>

Difference from control value: *=p<0.05; **=p<0.01; †=range
calculated from serial measurements and Figure 2 mean annual bone mineral content values (per cent of starting value) in centre and home haemodialysis patients; the mean bone mineral content loss was similar in the two groups, and amounted to three to four per cent per year of haemodialysis.

Table 1 lists the mean serum values in patients on centre and home haemodialysis, and in patients with rapid bone mineral content loss (>10%/3 years) and slow bone mineral content loss (<10%/3 years), respectively. In the total group mean serum 25(OH)D₃ was normal, 24,25(OH)₂D₃ reduced to half the normal level, and 1,25(OH)₂D₃ severely reduced to almost non-detectable levels. Mean serum iPTH was markedly elevated (about 15 times upper normal limit), and was significantly higher (p<0.05) in patients with rapid than in those with slow bone mineral content loss; whereas the vitamin D metabolites were similar in the two groups. Mean serum calcium was normal, whereas both serum phosphate and alkaline phosphatase were significantly elevated. Serum iPTH did not correlate significantly to individual bone mineral content loss (r=0.22) nor to any of the biochemical parameters. Patients on centre and home haemodialysis did not differ significantly with regard to any of the biochemical parameters.

**Discussion**

The bone mineral content results suggest the presence of osteopenia at the start of haemodialysis and progressive bone loss during haemodialysis in both centre and home haemodialysis patients. A less pronounced bone mineral content loss in home haemodialysis patients might have been expected since they are usually in better general health and less immobilised than centre patients. However, normal serum 25(OH)D₃ in the two groups suggest a similar nutritional status; moreover, they did not differ in either degree of hyperparathyroidism or in serum calcium or phosphate. Therefore, it must be concluded that home haemodialysis as such does not prevent development of uraemic osteodystrophy.

Besides measuring the intact C-84 molecule and the C-34 fragment, the C-terminal iPTH assay also detects biologically inactive polypeptides which are normally cleared by the kidney. This is probably the main reason for the lack of correlation between serum iPTH and serum calcium and phosphate, which are kept in a narrow range due to haemodialysis and treatment with phosphate binders; however, also a shift in 'set point' or autonomy of the parathyroid gland is likely. Despite difference in iPTH between the rapid and slow losers of bone calcium (the former group about twice as high), individual iPTH values correlated poorly to rate of bone mineral content loss mainly due to a considerable variation and overlapping of iPTH values between the two groups. Thus the iPTH was of no value in predicting bone mineral content loss in the individual patient.

The findings in serum of normal 25(OH)D₃ and severely reduced or non-detectable 1,25(OH)₂D₃ values are in accordance with most other reports and confirm that there is no impairment of liver C-25 hydroxylation of vitamin D in patients with chronic renal failure whereas the C-1α hydroxylation is severely reduced due to progressive destruction of the nephron mass. No extra-renal C-1α hydroxylation of 25(OH)D₃ seems to take place. In contrast, our findings
of only moderately reduced \(24,25(\text{OH})_2\text{D}_3\) values, although at variance with some reports of non-detectable serum \(24,25(\text{OH})_2\text{D}_3\) values in anephric patients [8], indicate an extra-renal C-24 hydroxylase activity, which may be of significance in the development of renal osteodystrophy. Some reports point to a specific effect of \(24,25(\text{OH})_2\text{D}_3\) on bone mineralisation [9].

However, the present results showing virtually identical serum concentrations of vitamin D metabolites in haemodialysis patients with rapid and slow bone mineral content loss point to the importance of factors other than impaired vitamin D metabolism in the pathogenesis of renal osteodystrophy. The possible role of \(24,25(\text{OH})_2\text{D}_3\) in the development of bone disease is particularly difficult to assess.

References

2 Stanbury SW. Clin Endocr 1977; suppl: 7: 25
3 Rickers H, Christensen M, Rødbro P. Clin Nephrol 1983; 20: 302
4 Smith DM, Khairi MRA, Johnston CC, J Clin Invest 1975; 50: 311