Hypohyperparathyroidism: a model for renal osteodystrophy?

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Summary

A child who presented with features of renal osteodystrophy but with normal renal function is described. Improvement occurred both on large doses of vitamin D and small doses of 1,α-hydroxy-vitamin D₃ (1,α-OHD₃). Investigations suggested that the primary defect was an impaired renal response to parathyroid hormone. The relationship between renal osteodystrophy, abnormalities of vitamin D metabolism and hypohyperparathyroidism is discussed and an alternative hypothesis for the development of renal bone disease suggested.

Introduction

The mechanism of development of renal osteodystrophy has been the subject of controversy for many years. Owing to this condition’s resemblance to nutritional rickets, vitamin D was initially considered to be the major factor involved. Albright and Reifenstein (1948) discounted this theory claiming that parathyroid hypofunction was the dominant feature. In 1968, Stanbury suggested that a defect in the metabolism of vitamin D was present in chronic renal failure. This was later shown to be a deficiency in 1,α-hydroxylase activity in the kidney resulting in low serum levels of 1,25 dihydroxy-vitamin D₃ (1,25(OH)₂D₃) in chronic renal failure (Mawer et al., 1973). There is also a high circulating level of immunoreactive parathyroid hormone (PTH) in renal failure, the origin of which is multifactorial (Papapoulos et al., 1977).

The investigation of the pathogenesis of renal bone disease is complicated by several of the features of uraemia including acidosis, inadequate nutrition and the effects of dialysis. A clinical model for renal osteodystrophy without the additional features of uraemia has not yet been described. The resemblance between a patient with hypohyperparathyroidism and patients with renal osteodystrophy suggests a unifying hypothesis for the pathogenesis of the major components of renal bone disease.

Case report

The patient was the first child of a non-consan-...
After 6 months of therapy 200 units of bovine PTH of known efficacy were given i.v. to measure the urinary and serum cyclic adenosine monophosphate (AMP) response. Plasma cyclic AMP values did not rise after injection (Fig. 5). Values for urinary phosphate, calcium and cyclic AMP excretion expressed as a percentage of creatinine clearance did not significantly alter (Table 2).

**Discussion**

The initial radiological appearances of renal rickets did not improve on doses of calciferol which heal vitamin D-deficient rickets. The phenobarbitone used to treat the convulsions (presumed to be hypocalcaemic) may have increased the requirement for vitamin D (Pierides et al., 1976) but both the amount required and subsequent events confirmed the presence of vitamin D resistance.

Vitamin D resistance was described by Albright, Drake and Sulkowitch in 1937 but the term was used to include conditions such as steatorrhoea, chronic renal failure and renal tubular abnormalities. In 1961 Prader, Illig and Heierli reported the syndrome of pseudo-vitamin D deficiency and further descriptions emphasized the need for high doses of vitamin D (Soriano et al., 1966; Stoop, Schraagen and Tiddens, 1967; Dent, Friedman and Watson, 1968; Fanconi and Prader, 1969; Birtwell et al., 1970; Salenius, Lindholm and Tiera, 1973). Arnaud et al. (1970) considered the abnormality to be due to defective synthesis of 25 OHD\(_3\) but Balsan and Garabedian (1972) and Cohamin, de Luca and Yendt (1973) demonstrated resistance also to 25 OHD\(_3\). Fraser et al. (1973) showed that minute doses of 1,25(OH)\(_2\)D\(_3\) were able to improve the bone lesions and postulated that a genetic defect in 25 OHD\(_3\)-1\(\alpha\) Hydroxylase activity was present.

Elevated PTH levels in pseudo-vitamin D deficiency rickets fell in response to calcium infusion (Falls et al., 1968) or treatment with vitamin D (Arnaud et al., 1970). Fanconi and Prader (1969) were able to find a response to exogenous PTH only when the rickets were radiologically healed. However, Rosen and Finberg (1973) found a prompt response in urinary cyclic AMP to PTH in 3 patients with pseudo-vitamin D deficiency.

Although there are some features in common between renal osteodystrophy and pseudo-vitamin D deficiency, the low serum phosphate in the latter condition makes direct comparison impossible.

Sub-periosteal bone resorption and elevated PTH concentrations confirmed the presence of hyperparathyroidism in the present patient. The radiological appearances of primary hyperparathyroidism can simulate rickets (Fretheim and Gardborg, 1965). Lack of response to exogenous PTH indicates ‘end-organ resistance’ described by Albright et al.
(1942) as pseudo-hypoparathyroidism. Chase, Melson and Aurbach (1969) demonstrated a marked impairment of urinary cyclic AMP excretion in response to PTH in pseudohypoparathyroidism. Although anatomical abnormalities of bone are present, most cases of pseudo-hypoparathyroidism show neither radiological defects in bone structure nor a raised serum alkaline phosphatase suggesting that the bones are also resistant to the action of PTH.

Singleton and Teng (1962) described a patient with biochemical features of pseudo-hypoparathyroidism but without the associated somatotype abnormalities. Radiographic evidence of bone resorption was present. The following year Costello and Dent (1963), describing a similar case in which radiological healing was achieved with large doses of vitamin D, named the condition hypohyperparathyroidism.

In a further 5 cases (Bell, Gerard and Bartter, 1963; Allen, Millard and Nassim, 1968; Cohen and Vince, 1969; Frame et al., 1972), histological examination of bone was performed before treatment. In 3 the appearances were compatible with osteitis fibrosa cystica but in the other 2 the predominant feature was an increase in osteoid. Only case 1 of Frame et al. (1972) failed to show radiological improvement in bone resorption on treatment with high doses of vitamin D, but in only 2 patients was the improvement confirmed by histology (Allen et al., 1968; Bell et al., 1963). The osteoid present in the present case was excessive both in volume and the extent of trabecular bone surface covered, while the radiological features were those of hyperparathyroidism.

**TABLE 1.** $^{45}$Ca absorption test: serum concentrations as % of oral dose

<table>
<thead>
<tr>
<th>Date</th>
<th>1 hr</th>
<th>2 hr</th>
<th>4 hr</th>
</tr>
</thead>
<tbody>
<tr>
<td>20/07/76 ... Before treatment</td>
<td>0</td>
<td>0.8</td>
<td>1.4</td>
</tr>
<tr>
<td>06/01/77 ... After 4 months' treatment</td>
<td>0.35</td>
<td>1.59</td>
<td>1.76</td>
</tr>
</tbody>
</table>
Case reports

Fig. 3. Iliac crest bone biopsy before (a) and after (b) 4 months' treatment with 1,α-OHD3.

Fig. 4. Serum calcium, phosphate and PTH concentrations before and during treatment with 1,α-OHD3.
The lack of renal response to PTH in the presence of response by bone does not explain the hypocalcaemia in hypohyperparathyroidism. Ca absorption improved on therapy in 3 of the previously described patients with hypohyperparathyroidism similar to the response, in the present patient, to 1αOHD$_3$. PTH is recognized not to act directly on the intestine but it increases Ca absorption by stimulating the production of 1,25(OH)$_2$D$_3$ (Garabedian et al., 1974; Ribovich and de Luca, 1976). The low serum 1,25(OH)$_2$D$_3$ level in this patient could be due to either a failure of response to PTH or a depression of synthesis secondary to raised phosphate concentrations (Tanaka and de Luca, 1973). In all 7 patients with hypohyperparathyroidism serum phosphate levels returned to normal on treatment with vitamin D or dihydrotachysterol. With 1αOHD$_3$ alone, serum phosphate and PTH concentrations progressively returned to the normal range preceded by a rise in serum Ca to the lower limit of normal.

1,25(OH)$_2$D$_3$ is required by PTH for mobilization of Ca from bone (Garabedian et al., 1974; Gerblich, Genuth and Haddad, 1977). Bone resorption in the present patient was less than might be expected with the concentrations of PTH similar to the resistance of bone to PTH in uraemia, attributed by Massry et al. (1976) to defective production of 1,25(OH)$_2$D$_3$.

Chase et al. (1969) concluded that the primary action of PTH on both skeletal and renal tissue was activation of adenylate cyclase AMP. Although lack of response to PTH could be explained by an abnormality in cyclic AMP synthesis, Sinha et al. (1976) demonstrated a normal adenylate cyclase response in the fat cells of patients with pseudo-hypoparathyroidism.

Features in common between hypohyperparathyroidism and renal osteodystrophy are elevated

### Table 2. Parathyroid hormone stimulation test: urinary PO$_4$, Ca and cAMP response

<table>
<thead>
<tr>
<th>Time (hr)</th>
<th>PO$_4$ clearance/ Ccr</th>
<th>Ca clearance/ Ccr</th>
<th>cAMP excretion/ Ccr</th>
</tr>
</thead>
<tbody>
<tr>
<td>0–1</td>
<td>3·25</td>
<td>0·25</td>
<td>1·21</td>
</tr>
<tr>
<td>1–2</td>
<td>3·57</td>
<td>0·28</td>
<td>0·59</td>
</tr>
<tr>
<td>2–3</td>
<td>4·76</td>
<td>0·16</td>
<td>0·70</td>
</tr>
<tr>
<td>i.v. 200 i.u. bovine PTH</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3–3·5</td>
<td>7·17</td>
<td>0·56</td>
<td>1·19</td>
</tr>
<tr>
<td>3·5–4</td>
<td>5·8</td>
<td>0·17</td>
<td>0·54</td>
</tr>
<tr>
<td>4–5</td>
<td>9·22</td>
<td>0·27</td>
<td>0·93</td>
</tr>
<tr>
<td>5–6</td>
<td>8·05</td>
<td>0·22</td>
<td>0·79</td>
</tr>
</tbody>
</table>

FIG. 5. Parathyroid hormone stimulation test: plasma cyclic AMP response in patient compared with normal.
serum phosphate, alkaline phosphatase and PTH concentrations, low serum calcium and 1,25(OH)₂D₃ concentrations, radiographic bone resorption with increased osteoid volume, absent renal and possibly impaired skeletal response to PTH and improvement with small doses of 1αOHD₃.

The pathogenesis of hypohyperparathyroidism is best explained by a defect in the renal receptor site for PTH. A common receptor site for both the effect on phosphate excretion and 1α-hydroxylase activity would result in hyperphosphataemia and low serum levels of 1,25(OH)₂D₃ leading to hypocalcaemia. The resultant elevated PTH levels would have no effect on the kidney and, owing to the low 1,25(OH)₂D₃ concentrations, there would also be a relative resistance of the skeleton to PTH.

Damage to the receptor site for PTH from ischaemia, reflux nephropathy or other tubular lesions would also lead to the above features. Thus a single pathological lesion could explain the previous controversy over the development of the major features of renal osteodystrophy.

Acknowledgments
We acknowledge the invaluable help of Dr J. L. H. O’Riordan and staff (Middlesex Hospital) for measurement of PTH, 25 OH D₃ and cyclic AMP concentrations and Dr E. B. Mawer and staff (University of Manchester) for measurement of serum 1,25(OH)₂D₃.

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doi: 10.1136/pgmj.57.668.371

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