CASE REPORT
TERTIARY HYPERPARATHYROIDISM AFTER LONG-TERM PHOSPHATE SUPPLEMENTATION IN ADULT-ONSET HYPOPHOSPHATAEMIC OSTEOMALACIA

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SUMMARY
We report the development of tertiary hyperparathyroidism in a patient with a sporadic form of adult-onset hypophosphataemic osteomalacia who had been treated with vitamin D or calcitriol and large doses of phosphate. This observation suggests that even with concomitant vitamin D or calcitriol therapy, long-term oral phosphate supplementation may lead to the development of hypercalcaemic hyperparathyroidism. Caution is recommended when relatively large doses of phosphate are used to treat hypophosphataemic osteomalacia of diverse causes.

KEY WORDS: Hypophosphataemic osteomalacia, Long-term phosphate therapy, Tertiary hyperparathyroidism.

Parathyroid function is generally described as normal in patients with hypophosphataemic osteomalacia before initiation of therapy with phosphate salts; however, hyperparathyroidism is an occasional complication of treatment.

The sporadic adult-onset form of hypophosphataemic osteomalacia responds to treatment with phosphate, calcium and vitamin D or calcitriol, and it is generally believed that this combination (especially when calcitriol is used) may prevent the development of harmful side-effects (hyperparathyroidism and nephrocalcinosis) [1-4].

We describe a male patient in whom long-term phosphate supplementation resulted in hypercalcaemic hyperparathyroidism associated with surgically proven adenomatous hyperplasia.

This complication occurred despite concomitant treatment with vitamin D or calcitriol. His course emphasizes the importance of carefully monitoring parathyroid function during therapy.

CASE REPORT
A 45-yr-old man was seen initially in June 1980 with a 12 yr history of generalized bone pain and severe muscle weakness, with difficulty in walking.

Physical examination revealed limitation of spinal movements, diffuse bony tenderness, pronounced dorsal kyphosis and moderate proximal muscle weakness. Laboratory study results (Table I) were as follows (normal ranges in parentheses): alkaline phosphatase 114 U/l (35-90), serum calcium 2.08 mmol/l (2.3-2.6), serum phosphorus 0.37 mmol/l (0.8-1.4), magnesium 0.7 mmol/l (0.82-1.23), total proteins 67 g/l (64-84); renal and hepatic function test, erythrocyte sedimentation rate and blood count were normal.

Parathyroid hormone (PTH) was 2.9 pmol/l (1.1-4.6); plasma 25-hydroxyvitamin D was normal.

Urinary calcium excretion was 1.03 mmol/day (2.5-7.4) and the urinary phosphorus level was 19.95 mmol/day (16.1-48.4); the tubular reabsorption of phosphate was reduced to 74% (85-95%). Aminoaciduria and glucosuria were absent. Radiography showed generalized osteopenia, dorsal hyperkyphosis, biconcavity of the lumbar vertebral bodies, pseudofractures (Looser's zones) in both pubic rami and upper femora, and fractures of the metatarsal.

Drugs, malnutrition and malabsorption were ruled out. He had no family history of rickets or bone disease, his growth and development had been normal, and there was no evidence of phosphaturic tumour.

These results led to a diagnosis of adult-onset hypophosphataemic osteomalacia. Therapy was commenced in June 1980 with oral phosphate 2 g daily, calcium supplements (1-3 g/day) and vitamin D 200 000 units daily; this latter dose was increased to 400 000 units daily 18 months later.

The patient's symptoms improved and the serum levels of calcium, phosphorus and alkaline phosphatase returned to normal.

An episode of vitamin D toxicity in May 1982

<table>
<thead>
<tr>
<th>Variable</th>
<th>Value</th>
<th>Normal range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blood</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alkaline phosphatase (U/l)</td>
<td>114.</td>
<td>35-90</td>
</tr>
<tr>
<td>Calcium (mmol/l)</td>
<td>2.08</td>
<td>2.3-2.6</td>
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<tr>
<td>Phosphorus (mmol/l)</td>
<td>0.37</td>
<td>0.8-1.4</td>
</tr>
<tr>
<td>Magnesium (mmol/l)</td>
<td>0.70</td>
<td>0.82-1.23</td>
</tr>
<tr>
<td>Proteins (g/l)</td>
<td>67.</td>
<td>64-84</td>
</tr>
<tr>
<td>PTH (pmol/l)</td>
<td>2.90</td>
<td>1.1-4.6</td>
</tr>
<tr>
<td>Urine</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Calcium (mmol/day)</td>
<td>1.03</td>
<td>2.5-7.4</td>
</tr>
<tr>
<td>Phosphorus (mmol/day)</td>
<td>19.95</td>
<td>16.1-48.4</td>
</tr>
<tr>
<td>Tubular reabsorption of phosphates (%)</td>
<td>74.</td>
<td>85-95</td>
</tr>
</tbody>
</table>

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Parathyroid stimulation may eventually lead to tertiary hyperparathyroidism in hypophosphataemic osteomalacia.

In January 1984, vitamin D was substituted for calcitriol 0.25 μg/day; therapy with inorganic phosphorus (2–2.5 g daily) was continued throughout. Between 1984 and 1990, laboratory data were unremarkable.

From October 1991, the serum level of calcium rose progressively to peak levels of 3.14 mmol/l, despite a stepwise reduction in the dose of calcitriol. The hypercalcaemia was accompanied by elevations in serum creatinine (210 μmol/l; normal 75–117), alkaline phosphatase (2.9 μkat/l; normal 0.6–1.6) and PTH (64.8 pmol/l). The treatment was discontinued in September 1994, and the serum level of phosphate decreased from 1.1 to 0.63 mmol/l. He did not have evidence of nephrocalcinosis on ultrasonography.

Parathyroidectomy was performed in November 1994, and the right upper, right lower and left lower glands were excised (the removed glands weighed 5.4, 2.7 and 1.2 g, respectively); one-half of the left superior gland was also removed (estimated weight 0.7 g). Histological examination showed chief cell hyperplasia in all specimens.

Postoperatively (1 month later), the serum level of calcium decreased to 1.79 mmol/l, the serum phosphorus decreased to 0.4 mmol/l and the PTH level decreased to 7.1 pmol/l; the impairment of renal function remains unchanged.

Phosphate and calcium supplements were continued.

**DISCUSSION**

Osteomalacia is characterized by the accumulation of increased amounts of unmineralized bone matrix (osteoid) and a decrease in the rate of bone formation. Basically, it may result from two major causes: vitamin D deficiency (secondary to dietary deficiency, deficient endogenous synthesis, intestinal malabsorption or acquired and inherited disorders of vitamin D metabolism) or chronic hypophosphataemia (with normal vitamin D).

Likewise, some different forms of hypophosphataemic osteomalacia have been identified: those resulting from renal tubular phosphate loss (familial X-linked hypophosphataemic rickets, adult-onset hypophosphataemic osteomalacia, tumour-associated osteomalacia, renal tubular acidosis and Fanconi’s syndrome) and those resulting from chronic phosphate depletion in patients with chronic parenteral nutrition or antacid abuse (nonabsorbable magnesium or aluminium hydroxide antacids, which interfere with intestinal phosphate absorption). Secondary hyperparathyroidism is characteristic of calciopenic forms of the disease (vitamin D deficiency), whereas parathyroid function is generally described as normal in untreated patients with hypophosphataemic osteomalacia. Orally administered phosphate supplementation is the mainstay of therapy for hypophosphataemic osteomalacia of diverse causes; however, it is well recognized that long-term phosphate therapy may induce a decrease in serum calcium levels and trigger the release of PTH, resulting in secondary hyperparathyroidism [4–9]. Occasionally, parathyroid adenomas are observed [4, 6].

In an attempt to prevent this complication, concomitant treatment with large amounts of vitamin D (which increases calcium availability and reduces phosphate-induced secretion of PTH, but not to normal values) [4, 5, 7–11] was initially recommended without result (several cases of autonomous hyperparathyroidism were reported that could only be treated surgically) [4, 6, 9]; subsequently, it was postulated that substitution of vitamin D for calcitriol allows a more precise control of PTH secretion throughout the treatment period.

It thus appears that 1,25 dihydroxyvitamin D, through its direct effect on PTH release, is able to maintain eucalciometric and eucalcemic hyperparathyroidism with adequate bone modelling and remodelling [2–4, 11, 12].

In our patient, calcitriol was ineffective and did not prevent the development of parathyroid hyperplasia; experience from several other cases is necessary to corroborate this finding.

In the meantime, we think that even with concomitant therapy with calcitriol, it is advisable to avoid large doses of phosphate and to closely monitor these patients, including routine PTH levels, to detect parathyroid hyperactivity. It is also important to carefully monitor renal function and urinary calcium excretion to avoid the development of nephrocalcinosis, a well-described complication of treatment (the development of hyperparathyroidism tends to correlate with the onset of nephrocalcinosis) [13, 14].

Detection of hyperparathyroidism at the early stages may lead to its successful treatment (with calcitriol and reduction of the phosphate dose) before the hyperparathyroid state leads to significant skeletal mineralization and becomes irreversible.

In symptomatic patients with established tertiary hyperparathyroidism, surgical treatment is recommended (subtotal parathyroidectomy and more recently total parathyroidectomy with autotransplantation have been effectively used to decrease functional parathyroid mass in these patients) [15]. It is hoped that familiarity with this complication may enable a physician to make an early diagnosis, when treatment may effect a more positive outcome.

**REFERENCES**


4. Firth RG, Grant CS, Riggs BL. Development of hypercalcemic hyperparathyroidism after long-term


