A patient with unexplained hyperphosphataemia

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Introduction

Hyperphosphataemia is not a common biochemical alteration outside the context of renal failure. In fact, phosphate homeostasis is mainly regulated by kidney function and parathyroid hormone (PTH) activity [1–4]. In the presence of normal renal function and normal PTH activity, serum phosphate values are tightly regulated within a reference range of 0.8–1.5 mmol/l (2.5–4.5 mg/dl). As phosphates are filtered by the glomerular barrier and excreted into the urine with a renal clearance of 15–20 ml/min, serum phosphate levels do increase early from the beginning of renal failure, reaching levels as high as 4–5 mmol/l in the case of end-stage renal failure in patients with poor compliance to therapeutic schedules [1,2]. Furthermore, true hyperphosphataemia can also result from impaired PTH activity, as PTH is the main factor responsible for phosphate secretion by renal tubular cells, eventually leading to the typical picture of hyperphosphataemia and hypocalcaemia in the presence of hypoparathyroidism [3,4]. Lastly, true hyperphosphataemia could be caused by phosphate poisoning, mainly attributed to phosphate enemas in children, even in the absence of renal failure [5,6].

From a clinical point of view, severe hyperphosphataemia stimulates PTH secretion, induces and worsens extra-osseous tissue calcification and can cause acute paralysis, convulsions and cardiac arrest mainly due to complexes with free serum calcium, resulting in hypocalcaemia [7,8].

We report a case of a patient with normal renal function, IgG myeloma and persistent hyperphosphataemia, in whom further laboratory analyses allowed a diagnosis of ‘pseudo-hyperphosphataemia’ caused by interferences of his paraproteinaemia with analytical procedure for phosphate measurement.

Case report

A 56-year-old female patient was admitted to our unit because of proteinuria. Her past history included poliomyelitis (1952) and kidney stones (right kidney colic in 1988). In 2000 she was diagnosed with IgG-k multiple myeloma (Salomon Durie stage IA), and she was on a regular haematological follow-up. Due to the absence of end-organ damage, no specific therapy for myeloma was started. Arterial hypertension was also diagnosed and she was put on a carvedilol and doxazosine association.

In 2004, proteinuria was first detected (around 1 g/day) and urinary immunoelectrophoresis showed that monoclonal ‘kappa’ light-chain accounted for most of it (Bence Jones proteinuria), whereas albumin was only minimally represented. Urinary sediment was unremarkable. Renal function was normal [serum creatinine 64 μmol/l (=0.8 mg/dl) and creatinine clearance 1.77 ml/s (=106 ml/min)].

As it was impossible to find reasonable causes for a true hyperphosphataemia, an interdisciplinary briefing with the head of the biochemical laboratory stimulated further in-depth analyses including two simultaneous assays for phosphate concentration in the patient’s
plasma, one in a whole sample and the other one in a deproteinized sample. The inorganic phosphate assay used in our laboratory is based on the Daly and Ertinghausen procedure [9], which relies on the formation of a UV-absorbing complex between phosphate and molybdate. In fact, inorganic phosphate reacts with ammonium molybdate in the presence of sulphuric acid to form an unreduced phosphomolybdate complex, which is measured as an end point at 340 nm using a Bayer Advia 1650 Clinical Chemistry Instrument. Reaction curves for phosphate measurement of the two samples from our patient were completely different (Figure 1A), leading to the result of high levels in the whole sample but absolutely normal value in the deproteinized sample. On the contrary, the two patterns of whole and deproteinized samples from a patient with severe renal failure and true hyperphosphataemia were superimposable (Figure 1B). To further confirm the essential role of an abnormal protein component in causing pseudo-hyperphosphataemia, the whole plasma from the patient was filtered through a microcentrifuge filter with a 100,000 Da cut-off. The filtrate was subsequently assayed and showed a phosphate concentration superimposable to that obtained in the deproteinized sample, with a typical reaction curve.

As no indication for renal biopsy was done, the patient was discharged with a diagnosis of IgG myeloma, normal renal function, overflow Bence Jones proteinuria and pseudo-hyperphosphataemia caused by paraproteinaemia.

**Discussion**

Our report focuses on a somewhat overlooked laboratory or clinical problem, the recognition of hyperphosphataemia which is not biologically 'true hyperphosphataemia' but 'spurious hyperphosphataemia' due to analytical interference by abnormal serum components.

This result depends on an increase in optic density due to interference between monoclonal immunoglobulin and the molybdic reagent used in some

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**Table 1. Main biochemical data of the patient with normal renal failure, IgG-myeloma and unexplained hyperphosphataemia**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Normal rangea</th>
<th>Valuea</th>
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<tbody>
<tr>
<td>Serum urea</td>
<td>2.9–8.9 mmol/l (8–25 mg/dl)</td>
<td>2.9 mmol/l (8 mg/dl)</td>
</tr>
<tr>
<td>Serum creatinine</td>
<td>53–97 μmol/l (0.6–1.1 mg/dl)</td>
<td>64 μmol/l (0.8 mg/dl)</td>
</tr>
<tr>
<td>Creatinine clearance</td>
<td>1.3–2 ml/s (80–120 ml/min)</td>
<td>1.77 ml/s (106 ml/min)</td>
</tr>
<tr>
<td>Serum phosphorus</td>
<td>0.8–1.5 mmol/l (2.5–4.5 mg/dl)</td>
<td>2.22–2.59 mmol/l (6.9–7.8 mg/dl)</td>
</tr>
<tr>
<td>Serum uric acid</td>
<td>154–356 μmol/l (2.6–6 mg/dl)</td>
<td>356 μmol/l (6 mg/dl)</td>
</tr>
<tr>
<td>Serum calcium</td>
<td>2.1–2.6 mmol/l (8.5–10.5 mg/dl)</td>
<td>2.4 mmol/l (9.6 mg/dl)</td>
</tr>
<tr>
<td>Serum total protein</td>
<td>60–78 g/l (6–7.8 g/dl)</td>
<td>86 g/l (8.6 g/dl)</td>
</tr>
<tr>
<td>IgG</td>
<td>7–16 g/l (700–1600 mg/dl)</td>
<td>27.4 g/l (2740 mg/dl)</td>
</tr>
<tr>
<td>IgA</td>
<td>0.7–4 g/l (70–400 mg/dl)</td>
<td>2.46 g/l (246 mg/dl)</td>
</tr>
<tr>
<td>IgM</td>
<td>0.4–2.3 g/l (40–230 mg/dl)</td>
<td>1.8 g/l (180 mg/dl)</td>
</tr>
<tr>
<td>i-PTH</td>
<td>5–39 ng/l</td>
<td>11.5 ng/l</td>
</tr>
<tr>
<td>1-25Vitamin D</td>
<td>23–99 pmol/l</td>
<td>23 pmol/l</td>
</tr>
<tr>
<td>Urine phosphate excretion/24 h</td>
<td>129–429 nmol (400–1300 mg)</td>
<td>379 nmol (1175 mg)</td>
</tr>
<tr>
<td>Calcium excretion/24 h</td>
<td>0–7.5 mmol (0–300 mg)</td>
<td>5.45 mmol (218 mg)</td>
</tr>
<tr>
<td>Urate excretion/24 h</td>
<td>1–5 mmol (250–750 mg)</td>
<td>4.2 mmol (713 mg)</td>
</tr>
<tr>
<td>Phosphate clearance</td>
<td>0.25–0.38 ml/s (15–20 ml/min)</td>
<td>0.30 ml/s (15 ml/min)</td>
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</tbody>
</table>

*Values are expressed in SI units with conventional units in brackets.
automated systems, eventually leading to a proteinaceous suspension in the reaction mixture. On the contrary, deproteinization of the same samples yielded normal phosphate concentrations. In fact, the insolubility of these paraproteins eventually leading to interference in photometric/turbidimetric assay is responsible for artefacts that can cause both falsely increased or decreased results in multiple parameters—bilirubin, creatinine, iron, urea, uric acid, glucose, cholesterol, HDL-cholesterol [9]. Furthermore, even falsely low serum phosphate concentrations have been occasionally described in serum samples of patients with myeloma [10].

**Teaching points**

1. The literature reports an incidence of up to 8% of pseudo-hyperphosphataemia in patients with paraproteinaemias [11–20], mainly associated with IgG paraproteinaemia, rarely with IgA [21] even up to extreme levels (8 µmol/l) [15] without clinical manifestation attributable to such laboratory abnormalities. In any case, globulin-depleted sera were found to have normal inorganic phosphate levels.

2. Knowledge of this phenomenon may obviate confusion, unnecessary testing and expenditure.

3. Another important point is that unexplained hyperphosphataemia may also provide clinicians with a clue as to the presence of a dysproteinemia.

4. Both laboratory staff and clinicians should be aware of interference in the clinical laboratory since clinical consequences could be serious.

**Conflict of interest statement.** None declared.

**References**

1. Indridason OS, Quarles LD. Hyperphosphataemia in end-stage renal disease. *Adv Ren Replace Ther* 2002; 9: 184–192


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