This article discusses common and rare causes of hypophosphataemia, appropriate investigations, and when to refer for specialist opinion.

A 55 year old man with a squamous cell carcinoma of the head and neck was investigated before referral for chemotherapy. He was asymptomatic and not taking any drugs. Blood test results showed phosphate 0.7 mmol/L (reference limit 0.8-1.5) and total calcium 2.34 mmol/L (2.15-2.60).

The concentration of circulating phosphate depends on intestinal absorption, renal handling, and skeletal storage, and consequently is regulated by parathyroid hormone, vitamin D, and fibroblast growth factor 23. Internal cellular redistribution of phosphate is also important and results in hypophosphataemia under specific circumstances. The box outlines the causes of hypophosphataemia, based on the physiological regulation of phosphate metabolism.

Chronic or mild hypophosphataemia (plasma phosphate 0.6-0.8 mmol/L; 1.86-2.5 mg/dL) may be asymptomatic and therefore can be easily overlooked. A history outlining recent bone pain, muscle weakness, use of prescription drugs (including aminoglycosides, cisplatin, tenofovir), or exposure to toxins, heavy metals, or antacids containing magnesium, aluminium, and zinc, should be obtained. Inquiring about a family history of skeletal disease is important. Short stature skeletal deformities consistent with rickets, such as bowed extremities, widened wrists, cranial and chest deformities, or a familial history of hypophosphataemia or rickets should alert clinicians to a heritable cause. X linked hypophosphataemic rickets is, however, rare, occurring in 1 in 20000 live births but accounting for more than 80% of familial disease.

**What are the next investigations?**

The next investigations are to consider preanalytical causes or analytical interference; to measure electrolytes, including potassium, bicarbonate, magnesium, and calcium; and to assess ionised calcium, parathyroid hormone, and vitamin D under certain circumstances. The figure outlines a suggested approach to the investigation of hypophosphataemia.

**RATIONAL TESTING**

**Investigating hypophosphataemia**

Paul Glendenning,12 Damon A Bell,12 Roderick J Clifton-Bligh3

Hypophosphataemia is relatively uncommon but can occur in up to 5% of patients admitted to hospital. In certain clinical settings such as alcoholism, sepsis, malnutrition, or intensive care, however, the incidence of acute hypophosphataemia may be as high as 30-50%, due to a combination of phosphate redistributed between extracellular and intracellular compartments, low phosphate intake, or reduced intestinal absorption of phosphate. Patients with severe hypophosphataemia (plasma phosphate <0.3 mmol/L; <0.93 mg/dL) more commonly have clinical symptoms or signs, including muscle weakness or bone pain. The diagnosis should also be considered in certain clinical circumstances: respiratory or cardiac failure, haemolysis, altered mentation, and myopathy or rhabdomyolysis, which could present with muscle pain.

**Consider preanalytical causes or analytical interference**

Preanalytical factors that may cause spurious hypophosphataemia include those related to biology (age), physiological (acid base or fasting status), and sampling (for example, plasma versus serum sample or delayed sample testing). Hypophosphataemia in an adult is defined as a plasma phosphate concentration of less than 0.8 mmol/L. Newborn infants and young children have a higher reference limit, and therefore age specific intervals are necessary. Spurious hypophosphataemia can occasionally occur in the presence of paraproteinemia and transiently with respiratory alkalosis or after meals. Paraproteinemia should be considered if the serum globulin level is increased, hypophosphataemia is severe, or there are other suspicious clinical symptoms or signs such as anaemia, renal dysfunction, bone pain, or hypercalcaemia. Light chain paraproteins are directly toxic to the renal tubule and may cause true hypophosphataemia as a result of acquired Fanconi syndrome (proximal tubulopathy resulting in failure to reabsorb phosphate as well as other nutrients). Phosphate levels are marginally lower in serum than in heparinised plasma and there is some diurnal variation, but neither accounts for major changes in phosphate concentration. Even if mild, persistent hypophosphataemia should be investigated because more serious diagnoses (such as inherited or malignant causes) could be missed. Delayed sample separation or haemolysis can falsely increase phosphate levels and mask the diagnosis of hypophosphataemia.

**Case review**

A plasma sample was collected from the patient after an overnight fast to retest his phosphate level. The test result was within reference limits.

The patient re-presented to an emergency department seven days after the fourth dose of chemotherapy with severe muscle pain and weakness. He was only taking paracetamol (acetaminophen). Serum creatine kinase was appreciably increased, at 4600 U/L (30-170). The patient

**LEARNING POINTS**

Chronic or mild hypophosphataemia is often asymptomatic or may present with non-specific symptoms; severe cases may present with myopathy, respiratory or cardiac failure, altered mentation, haemolysis, or rhabdomyolysis.

Beware of spurious preanalytical or analytical causes of hypophosphataemia such as a non-fasting sample or paraproteinemia.

Useful initial tests include serum electrolytes (potassium, bicarbonate, magnesium, and calcium) to assess for renal tubular disease or extrarenal causes.

Check ionised calcium, parathyroid hormone, and 25 hydroxyvitamin D if the cause is unknown or if muscular skeletal symptoms, hypomagnesaemia, or hypoalbuminaemia are present.

Referral for specialist management is advised if the cause of hypophosphataemia remains uncertain, severe (0.3 mmol/L), or symptomatic, or if there is a family history of short stature or skeletal deformities consistent with rickets.

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This series of occasional articles provides an update on the best use of key diagnostic tests in the initial investigation of common or important clinical presentations. The series advisers are Steve Atkin, professor, head of department of academic endocrinology, diabetes, and metabolism, Hull York Medical School; and Eric Kilpatrick, honorary professor, department of clinical biochemistry, Hull Royal Infirmary, Hull York Medical School. To suggest a topic for this series, please email us at practice@bmj.com.
Investigation algorithm for hypophosphataemia

Hypophosphataemia

- Plasma phosphate <0.8 mmol/L

Consider preanalytical cause or analytical interference cause
For example, postprandial sample, respiratory alkalosis, paraproteinaemia?

Clinical assessment
- Muscle weakness or bone pain, conditions associated with rickets or hypophosphataemia
  (for example, alcoholism, sepsis, malnutrition), drugs, short stature, skeletal deformities consistent with rickets (or a family history of this)?

Check electrolytes and calcium
- Potassium, magnesium, bicarbonate, total calcium, and renal function

Check ionised calcium, parathyroid hormone, vitamin D
If no cause yet identified, musculoskeletal symptoms, hypomagnesaemia, or hypoalbuminaemia

Check urine phosphate and calculate renal tubular reabsorption of phosphate (TmP/GFR)
If no apparent cause

Possible causes of hypophosphataemia

Extrarenal (common)
- Gastrointestinal—reduced intestinal absorption; insufficient oral, enteral, or parenteral phosphate intake
- Increased intracellular sequestration (common)—refeeding syndrome; leukaemia or lymphomas; bone matrix uptake (hungry bone syndrome); diabeti c ketoacidosis; respiratory alkalosis

Renal
- Parathyroid hormone dependent (common)—primary, secondary, or tertiary (chronic kidney disease) hyperparathyroidism
- Fibroblast growth factor 23 dependent causes (rare)—acquired (tumour induced disease) hyperparathyroidism
- Parathyroid hormone dependent (common)—primary, secondary, or tertiary (chronic kidney disease) hyperparathyroidism

Hypophosphataemia is almost universal (>95%) in patients with hyperparathyroidism, as both can present with hypophosphataemia. In primary hyperparathyroidism, the serum phosphate level is typically <0.5 mmol/L (1.25 mg/dL), whereas in secondary hyperparathyroidism, it is typically >1.5 mg/dL. In tertiary hyperparathyroidism, the serum phosphate level is typically between 1.5 and 2.0 mg/dL.

Check electrolytes, including magnesium and calcium plus renal function
- Serum electrolytes, magnesium, and calcium should be assessed, as renal tubular disease or extrarenal causes are common and may result in deficiencies of other electrolytes.
- Dietary intake of phosphate is typically more than sufficient to meet daily requirements unless severe malnutrition is present. However, chronic diarrhoea can cause hypophosphataemia by reducing intestinal absorption of phosphate, and steatorrhoea may be associated with hyperparathyroidism secondary to vitamin D deficiency resulting in parathyroid hormone induced renal phosphate wasting. Antacids that contain magnesium, zinc, or aluminium may reduce phosphate absorption by the formation of insoluble complexes.
- Rapid redistribution of intracellular phosphate can cause sudden onset hypophosphataemia in certain clinical sce

narios: treatment of diabetic ketoacidosis; hungry bone syndrome, which can occur after parathyroidectomy for severe hyperparathyroidism; sudden rapid cell formation, which occurs in certain haematological malignancies; and refeeding after malnutrition. A reduced serum calcium indicates possible hungry bone syndrome.

Case review
The results of subsequent investigations were: sodium 136 mmol/L (134-146), potassium 2.6 mmol/L (3.4-5.0), bicarbonate 26 mmol/L (22-32), urea 2.8 mmol/L (3.0-8.0), creatinine 89 μmol/L (60-110), estimated glomerular filtration rate 74 (90-120), albumin 24 g/L (35-50), magnesium 0.6 mmol/L (0.7-1.1), and adjusted total calcium 2.49 mmol/L (2.15-2.60).

In this patient the degree of hypophosphataemia was severe and the coexistent less severe hypokalaemia along with hypomagnesaemia in the context of known cancer and treatment are highly suspicious of refeeding syndrome. Refeeding syndrome results in multiple changes to electrolytes that may occur when nutrition is administered after a period of low or absent oral intake. The patient’s low serum urea and albumin levels reflect recent malnutrition. Electrolyte changes may occur after as little as 48 hours of impaired oral intake. Enteral or parenteral carbohydrate preparations are the most common precipitants because they induce glycolysis and as a consequence there are large, sudden, and non-sustainable increased requirements for phosphate worsened by the redistribution of phosphate between extracellular and intracellular compartments. Hypophosphataemia is almost universal (>95%) in patients with refeeding syndrome; half of cases also experience hypomagnesaemia or hypokalaemia, and hypocalcaemia occurs in approximately a quarter of cases. Refeeding syndrome is often clinically mild, but severe muscle weakness, paraesthesias, congestive heart failure, arrhythmias, and cardiac arrest have been described.

Check ionised calcium, parathyroid hormone, and vitamin D
- When hypophosphataemia occurs in the presence of musculoskeletal symptoms, hypomagnesaemia, or hypoalbuminaemia, or the cause is still unknown, then ionised calcium, parathyroid hormone, and vitamin D should be assessed. Calcium and phosphate homeostasis are important, as both are essential for cellular function, predominantly stored in bone, and regulated by the same factors: parathyroid hormone, vitamin D, and fibroblast growth factor 23.

Measurement of calcium and parathyroid hormone are important to exclude primary and secondary hyperparathyroidism, as both can present with hypophosphataemia. In case series, ionised calcium identified 25% more cases of primary hyperparathyroidism than did either total calcium or albumin adjusted total calcium, especially in the presence of major hypoalbuminaemia (as in this case), critical illness, or chronic kidney disease. According to a large observational case series, approximately 10-20% of patients with primary hyperparathyroidism will have hypophosphataemia,
although it is usually mild. In a recent case series, phosphate levels were appreciably lower in patients with 25-hydroxyvitamin D (25(OH)D) <60 nmol/L and therefore concomitant vitamin D deficiency and primary hyperparathyroidism may present more commonly with hypophosphataemia. Secondary hyperparathyroidism in association with severe vitamin D deficiency leads to hypophosphataemia, hypocalcaemia, and osteomalacia, with a characteristic finding of increased alkaline phosphatase levels and muscle weakness. The threshold 25(OH)D concentration that is associated with osteomalacia is debated but current consensus suggests that osteomalacia occurs with prolonged moderate or severe vitamin D deficiency (25(OH)D <30 nmol/L). Conversely, under-mineralised bone is rare when 25(OH)D concentration is >50 nmol/L.

In patients with chronic kidney disease, secondary hyperparathyroidism typically occurs before appreciable changes in serum calcium or phosphate levels. In view of the respective hormonal changes and the decline in nephron mass, hypophosphataemia does not occur in early chronic kidney disease. Hypophosphataemia is, however, reported often in patients after transplantation for end stage renal disease and is attributed to autonomous parathyroid function (tertiary hyperparathyroidism).

Case review
Subsequent investigations revealed: 25(OH)D 55 nmol/L (reference limit >50 nmol/L), parathyroid hormone 6.4 pmol/L (1.2-7.8), and ionised calcium 1.22 mmol/L (1.12-1.30).

An ionised calcium within reference limits helped to exclude primary parathyroid disease, especially in the presence of severe hypoalbuminaemia. Measurement of ionised calcium may not always be available in regional centres, although most tertiary hospital laboratories will offer this service. Timely analysis is required for optimal interpretation.

What subsequent specialist investigations are appropriate?
Patients need to be referred for specialist management if the cause is uncertain, hypophosphataemia is chronic, severe (phosphate <0.3 mmol/L), or symptomatic, and is accompanied by short stature or skeletal deformities consistent with rickets, or a family history of skeletal deformities or hypophosphataemia. If hypophosphataemia is mild and the diagnosis is clear, continued monitoring is appropriate in such cases. Measurement of urine phosphate with calculation of TmP/GFR (renal tubular phosphate reabsorption) is useful, and serum fibroblast growth factor 23 should be measured if TmP/GFR is reduced—that is, when renal phosphate wasting is present.

Urine phosphate and calculation of TmP/GFR
Assessment of urine phosphate excretion helps to determine if the cause is due to renal phosphate wasting. TmP/GFR requires the measurement of phosphate and creatinine in a fasting plasma sample and second voided urine sample in the morning. TmP/GFR approximates the fraction of filtered phosphate that appears in the urine, is determined by nomogram or algorithm, and normative reference limits are age and sex specific, although in adults the reference limits for TmP/GFR are approximately the same as for plasma phosphate. A low urine TmP/GFR indicates renal phosphate wasting, which may be due to hyperparathyroidism, increased fibroblast growth factor 23 levels, or a primary renal tubular process such as Fanconi syndrome.

Case review
This patient’s result for urine TmP/GFR was >0.8 mmol/L, excluding renal phosphate wasting and supporting the diagnosis of refeeding syndrome.

Measuring fibroblast growth factor 23 if urine TmP/GFR is reduced
Fibroblast growth factor 23 is the phosphaturic substance produced by mesenchymal tumours associated with osteomalacia and the gene responsible for autosomal dominant hypophosphataemic rickets. Fibroblast growth factor 23 is typically increased in tumour induced osteomalacia but low in more common causes of hypophosphataemia with renal phosphate wasting, such as drug induced tubulopathies or Fanconi syndrome (see box). The diagnosis of tumour induced osteomalacia is often delayed owing to small tumour size, scattered location, and clinical inattention to hypophosphataemia as the cause of bone pain and muscle weakness.

Outcome
The patient began eating a solid diet 10 days before attendance after resolution of dysphagia following chemotherapy treatment. Consequently, he represented one of the higher risk groups for refeeding syndrome. The presence of reduced albumin and urea were consistent with recent malnutrition, and the acute onset of symptomatic hypophosphataemia with rhabdomyolysis and coexistent hypokalaemia and hypomagnesaemia were consistent with refeeding syndrome. In view of the severity of hypophosphataemia and symptoms, intravenous replacement was started. Plasma phosphate and serum magnesium, potassium, and creatine kinase normalised uneventfully and muscle symptoms resolved within seven days.

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A PATIENT’S JOURNEY

Lymphoma

Michael Frank Harris,1 Christopher Knechtli2

Two years ago, standing in front of the bathroom mirror, I noticed that I had a right inguinal swelling. Palpation showed it to be a rubbery, mobile mass, 2.5 cm in diameter. Examining more generally, I found that I had bilateral inguinal adenopathy, the contralateral glands being only 1 cm in diameter. I was unable to palpate any cervical or axillary glands.

I was a fit 55 year old general practitioner. I was aware that the pattern was unusual, but any malignant glands that I have felt in my career have been hard and fixed. Also, like most competitive road cyclists, I shave my legs, so I hoped that the adenopathy was due to razor rash.

After a month my wife made an appointment for me to see my general practitioner, but I cancelled it as I was convinced that the swellings were getting smaller. Another month later, I realised that there had been no significant change, so I saw my general practitioner. She examined me carefully, and, even though I had felt something catch her fingers when she was palpat ing my left upper quadrant, it was still a surprise when she said “I think you’ve got a spleen.” It was just palpable, halfway through deep inspiration.

Spending an hour googling “splenomegaly” and “regional adenopathy” made me realise that I had diagnosis of lymphoma until proved otherwise. My general practitioner and consultant colleagues kindly let me organise an urgent inguinal node biopsy. Histology showed follicular lymphoma. I became anorexic and lost weight, so I assumed that I had the B type symptoms.

By the time I saw Dr Knechtli, the consultant haematologist, my appetite was returning, making me realise that my “B type symptoms.” I was inclined to accept that diagnosis and, in view of my lack of any relevant symptoms, wait until it caused problems. The haematologist, however, told me that lung infiltration was not typical of lymphoma and persuaded me to accept a respiratory referral.

The chest consultant explained that there were four possible causes of the computed tomography findings: lymphoma, infection, sarcoidosis, and “a surprise,” which I took to be a euphemism for carcinoma. Bronchoscopy was normal, so I was listed for a lung biopsy. As a medical student in the late 1970s, I had spent time on a chest surgery ward and had vivid memories of patients with uncontrolled postoperative pain. To my relief, modern video-assisted thoracic surgery with excellent general and local anaesthetics, as well as nurses who ensured that I had sufficient analgesia, meant that my postoperative progress was not nearly as unpleasant as I had feared.

I was on holiday in France when the chest physician phoned with the histology: sarcoidosis. This was a huge relief. My knowledge of sarcoidosis was minimal, as I had never encountered a patient with it, so I spent a lot of time reading it up. I found that many cases, like mine, are asymptomatic, coincidental findings that may resolve spontaneously.

An interesting finding was that sarcoidosis can cause splenomegaly and inguinal adenopathy, as well as lymphopenia. I felt so well that it was difficult to believe that I had widespread lymphoma, so the overlap between the clinical findings in the two conditions made me start to question my lymphoma staging. When I saw Dr Knechtli for a follow-up appointment, I asked him whether all my clinical findings, apart from the single larger, biopsied inguinal gland, could actually be due to sarcoidosis. Unlike the haematologist, I had had two weeks to think and read up about that as a possible alternative explanation for my clinical signs. As a general practitioner, I know just how difficult it is when patients come up with a completely different way of interpreting their symptoms, and I could see in the haematologist’s face his struggle to analyse the alternative diagnosis and lymphoma staging that I had sprung on him.

He agreed that my lymphoma staging was now uncertain but said that the only way to confirm it absolutely would be to have an excision biopsy of my spleen, a mediastinoscopic lymph node biopsy, and a computed tomography guided...
biopsy of my abdominal glands. Given the risks and morbidity attached, these were not attractive options.

After discussion, I requested a biopsy of my mildly enlarged contralateral inguinal nodes. To my delight, they were reported as being reactive rather than due to lymphoma or sarcoidosis. That led me to hypothesise that all my clinical findings could be due to sarcoidosis or be reactive, apart from a single gland on the right side that had undergone lymphomatous change. If true, it would mean that I had stage I follicular lymphoma with an 80% chance of cure by radiotherapy.

Discussions with Dr Knechtli and a clinical oncologist confirmed that radiotherapy was a reasonable option. They ensured that I was aware that I may indeed have stage IV lymphoma, making a course of radiotherapy futile. However, given the “sporting chance” that I had only stage I disease, the risks and morbidity associated with the relatively low dose of treatment seemed acceptable, so I had a course of radical radiotherapy to my right hemi-pelvis.

I have been in the unusual position of having moved from an early diagnosis of stage IV (and probably incurable) follicular lymphoma to the possibility that I may have a much earlier, potentially curable stage. Because of my dual diagnoses, each of which can mimic the other, there have been 19 rate limiting steps from my initial working diagnosis to starting definitive treatment. Whereas the mean waiting time for each of them was two weeks, I needed to arrange private treatment three times to avoid considerably longer waits, and the overall nine month delay felt never ending. My observation of other European health systems suggests that the process would have been much faster in them, and I suspect that is one of the many reasons for their better cancer survival rates.

Modern evidence based treatment and superb clinical skills meant that I experienced far fewer side effects from investigations and radiotherapy than I would have experienced when I qualified in 1980. One surprise has been that, of all the clinicians who have examined me, by far the most skilled and thorough clinical examinations have been done by my general practitioner and the haematologist. That may be because they are less reliant on imaging to tell them what is going on. I would urge all my colleagues to follow their example: although in many cases clinical examination does not tell us anything unexpected, sometimes it does. My own general practitioner’s knowledge that she needed to look for my spleen, and her competence in finding it, were key in accelerating my initial investigations.

A year has passed since my radiotherapy. My blood markers are back to normal; a recent scan showed a normal sized spleen and no adenopathy. Although this is encouraging, follicular lymphoma is a very slow growing malignancy. It will be some years before I know with any degree of confidence whether my “stage I” hypothesis is correct and whether the treatment was successful.

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