Hypercalcaemia

Calcium has a vital role to play in the effective working of the majority of cells in the body and it is therefore important that the optimal level be maintained by the body. A reduction in serum calcium can stimulate parathyroid hormone (PTH) release which may then increase bone resorption, increase renal calcium reabsorption, and stimulate renal conversion of 25-hydroxyvitamin D3, to the active 1,25-dihydroxyvitamin D3, which then will increase intestinal calcium absorption. These mechanisms restore the serum calcium to normal and inhibit further production of PTH and 1,25-dihydroxyvitamin D3\(^1\).

The normal range for serum calcium is 2.25-2.5 mmol/L*. However, in hypercalcaemia, just over half the circulating calcium is protein bound and therefore the level of circulating protein, principally albumin, must also be taken into consideration in making this measurement. The level for serum calcium is frequently given by laboratories as both an uncorrected level and a corrected level which has allowed for changes in albumin levels. It is only the ionised (unbound) calcium which is physiologically important, taking part in cellular activities such as neuromuscular contraction, coagulation and other cellular activities\(^2\).

Elevated calcium concentrations are associated with significantly reduced quality of life and increased healthcare consumption\(^3\).

*The normal range is quoted for guidance only. Ranges may vary between laboratories or regions.

**Correcting calcium levels**

Add 0.1 mmol/L to calcium concentration for every 4 g/L that albumin is below 40 g/L and a similar subtraction for raised albumin.

The ‘correction’ is only approximate and does not replace measurement of ionised calcium concentration. Take special care where the measured albumin is less than about 20 g/L because of the known inaccuracy of albumin measurement at low levels\(^4\).

**Epidemiology**

- Hypercalcaemia is an uncommon problem. Primary hyperparathyroidism is the most common cause. It affects mainly postmenopausal women\(^5\). The incidence rate in the UK is 30 per 100,000\(^6\).
- Hypercalcaemia is the most frequently encountered endocrine/electrolyte disorder in malignancy-associated hospitalised patients. Its incidence is 15 per 100,000 person-years\(^7\).
- The incidence in children is unknown but is thought to be even less common than in adults\(^7\).
As effective calcium regulation is required for the healthy working of most cells in the body, a rise in the level can produce a diverse collection of symptoms.

<table>
<thead>
<tr>
<th>Presentation of Hypercalcaemia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At levels &lt;2.8 mmol/L</strong></td>
</tr>
<tr>
<td>Polyuria and polydipsia</td>
</tr>
<tr>
<td>Dyspepsia - due to calcium-regulated release of gastrin</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Mid cognitive impairment</td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

If the hypercalcaemia is long-standing, calcium may be deposited in soft tissues or may result in stone formation - eg, nephrocalcinosis, nephrolithiasis or chondrocalcinosis.

### Aetiology

Causes of hypercalcaemia may be grouped into those secondary to raised PTH levels and those mediated by other factors. Primary hyperparathyroidism and malignancy are responsible for greater than 90% of all cases[8].

**PTH-mediated hypercalcaemia**

Primary hyperparathyroidism is the most common cause of raised calcium levels, usually producing a mild hypercalcaemia.

**Non-PTH-mediated hypercalcaemia**

- Malignancy - the most common cause of non-PTH-mediated hypercalcaemia.
- Granulomatous conditions - eg, sarcoidosis and tuberculosis.
- Endocrine conditions - eg, thyrotoxicosis, phaeochromocytoma and primary adrenal insufficiency.
- Drugs - eg, thiazide diuretics, vitamin D and vitamin A supplements [9].
- Familial - eg, familial hypocalciuric hypercalcaemia[7].
- Other - eg, prolonged immobilisation, calcium-alkali syndrome, AIDS.

Hypercalcaemia of malignancy can occur as a result of four different mechanisms: ectopic production of parathyroid hormone-related peptide by tumour cells, osteolytic hypercalcemia, ectopic calcitriol (1,25-dihydroxyvitamin D), and ectopic PTH produced by tumour cells [10].

### Investigations

Corrected calcium level - this will by definition be raised. Compared with the hypercalcaemia of malignancy, hyperparathyroidism tends to be associated with lower serum calcium levels (<3 mmol/L) and a longer duration of hypercalcaemia (more than six months)[8].

In the presence of a raised corrected calcium [9, 11]:

- A raised albumin level in the presence of a raised urea indicates dehydration.
- A raised albumin level in the presence of a normal urea suggests a cuffed specimen.
- An abnormal alkaline phosphatase is indicative of myeloma (raised plasma protein), calcium-alkali syndrome (formerly milk-alkali syndrome)[12], thyrotoxicosis or sarcoidosis.
- A raised alkaline phosphatase suggests bony metastases, sarcoidosis or thyrotoxicosis.
- A raised calcitonin level is suggestive of B-cell lymphoma.
The following table may be helpful in interpreting laboratory results:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Serum Phosphate</th>
<th>Serum Alkaline Phosphatase</th>
<th>Urine Calcium</th>
<th>Urine Phosphate</th>
<th>PTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperparathyroidism</td>
<td>Low</td>
<td>Normal-high</td>
<td>High (in 67% of patients)</td>
<td>High</td>
<td>High</td>
</tr>
<tr>
<td>Vitamin D excess</td>
<td>Normal-high</td>
<td>Low</td>
<td>High</td>
<td>High</td>
<td>Low</td>
</tr>
<tr>
<td>Malignancy</td>
<td>Often low</td>
<td>High (except in haematological malignancy, when normal)</td>
<td>Variable</td>
<td>High</td>
<td>Variable</td>
</tr>
<tr>
<td>Granulomatous disease</td>
<td>Normal-high</td>
<td>Normal-high</td>
<td>High</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Calcium alkali syndrome</td>
<td>Normal-high</td>
<td>Normal</td>
<td>Normal</td>
<td>Normal</td>
<td>Low</td>
</tr>
<tr>
<td>Familial hypocalciuric hypercalcaemia</td>
<td>Normal or low</td>
<td>Normal</td>
<td>Low (&lt;200 mg/day)</td>
<td>Normal</td>
<td>High</td>
</tr>
</tbody>
</table>

Interpreting PTH levels[^11^]

- Raised PTH levels are suggestive of primary, secondary or tertiary hyperparathyroidism, or familial hypocalciuric hypercalcaemia.
- Low PTH levels are seen in granulomatous disease, iatrogenic causes (eg, renal dialysis), adrenal insufficiency, thyrotoxicosis, and vitamin D intoxication.
- The levels in malignancy may be low, normal or high.

Radio-imaging[^13^]

- Plain X-rays may show features indicative of bone abnormalities, such as demineralisation, bone cysts, pathological fractures or bony metastases.
- Ultrasound scan, computerised tomography (CT) scan or intravenous pyelogram (IVP) may be required to detect abnormalities of the urogenital tract, such as calcification or stones.
- Ultrasound or technetium scan of the parathyroid glands may be indicated if hypertrophy or adenoma is suspected.

Management

This can be considered under the headings of the immediate management of acute hypercalcaemia and the longer-term management of the underlying condition. National Institute for Health and Care Excellence Clinical Knowledge Summaries (NICE CKS) recommend that GPs should refer all patients with non-acute hypercalcaemia to the appropriate specialist, depending on the suspected cause (or to an endocrinologist if no cause can be found[^11^]).

Acute hypercalcaemia[^14^]

Treatment should be initiated in hospital on the advice of a specialist and should include:

- Increasing the circulating volume with 0.9% saline, helping to increase the urinary output of calcium.
- A loop diuretic such as furosemide. This is occasionally used where there is fluid overload but it does not reduce serum calcium.
- After rehydration, bisphosphonates (which act by reducing bone turnover) should be administered intravenously. Pamidronate and zolendronic acid are commonly used. Salmon calcitonin may also be given. It has fewer side-effects than bisphosphonates but is less effective in reducing hypercalcaemia[^15, 16^].
- Glucocorticoids are useful for hypercalcaemia due to vitamin D toxicity, sarcoidosis and lymphoma[^16^].
- Gallium was identified as a useful drug when it was found that patients with malignancy having gallium scans did not develop hypercalcaemia. It may be given intravenously to patients with malignant hypercalcaemia who do not respond to bisphosphonates[^17^].
Cinacalcet hydrochloride is a calcimimetic (= mimicking the action of calcium) agent that effectively reduces parathyroid levels in patients with secondary hyperparathyroidism[15].

Paricalcitol is also licensed for the prevention and treatment of secondary hyperparathyroidism associated with chronic kidney disease[16].

Denosumab, a human monoclonal antibody, is licensed for the prevention of osteoporotic fractures but is also useful for patients with persistent or relapsed hypercalcaemia of malignancy[18].

Patients with advanced underlying kidney disease and refractory severe hypercalcaemia should be considered for haemodialysis[19].

Non-PTH-mediated hypercalcaemia
Treatment depends on the underlying condition.

PTH-mediated hypercalcaemia[11]
- Asymptomatic patients may be treated conservatively with regular monitoring of bone density, renal function and serum and urinary calcium levels.
- For symptomatic patients, dietary calcium should be reduced - eg, minimise the intake of dairy products and leafy vegetables.
- Bed-bound patients should be mobilised if possible. Symptomatic patients will respond well to having the affected part of the parathyroid gland removed.
- There is no consensus on the operative treatment of asymptomatic patients. In general, it tends to be reserved for patients who have impaired renal function, hypercalciuria, low bone mineral density or severe hypercalcaemia[20].

Further reading & references
- Biochemical Calculations; Sydpath
- NHS Standard contract for specialised endocrinology services (Adult); NHS England, 2013/14
- British National Formulary; NICE Evidence Services (UK access only)
- Emergency management of acute hypercalcaemia in adult patients; Society for Endocrinology, September 2016

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