Hyperparathyroidism

What is hyperparathyroidism?

Hyperparathyroidism (HPT) results when there is excessive secretion of parathyroid hormone (PTH).[1] PTH is secreted by the four parathyroid glands, located in the neck behind the thyroid gland. Parathyroid hormone regulates serum calcium and phosphate levels and also plays a part in bone metabolism. High levels of PTH cause serum calcium levels to increase and serum phosphate levels to fall.

Hyperparathyroidism may be:

- Primary - one parathyroid gland (or more) produces excess PTH. This may be asymptomatic.
- Secondary - there is increased secretion of PTH in response to low calcium because of kidney, liver, or bowel disease.
- Tertiary - there is autonomous secretion of PTH, usually because of chronic kidney disease (CKD).

A reminder of calcium and phosphate homeostasis

- Maintenance of normal serum calcium levels involves the regulation of the flux of calcium between the intestinal tract, kidneys and bone.
- Calcium itself, PTH and 1,25-dihydroxyvitamin D3 (calcitriol) all play a role in calcium regulation.
- Calcitonin (produced by C cells of the thyroid) can also affect calcium homeostasis. It inhibits osteoclast activity and reduces the release of calcium and phosphate from bone.[1]

- Parathyroid hormone:
    - Increases the release of calcium from bone matrix.
    - Increases calcium reabsorption by the kidney.
    - Increases phosphate excretion.
    - Increases renal production of 1,25-dihydroxyvitamin D3, which increases intestinal absorption of calcium.
- High concentrations of serum calcium inhibit PTH secretion, while low concentrations stimulate it.

Primary hyperparathyroidism

Epidemiology [2]

- Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder.
- About 1 to 4 people per 1,000 are known to have the condition. Women are twice as likely as men to develop primary hyperparathyroidism. It can develop at any age, but in women in the UK, it is most often diagnosed between the ages of 50 and 60.
- There is considerable geographical and racial variation. In the USA, the incidence has been estimated at a mean of 66 per 100,000 person-years in women, and from 13 to 36 per 100,000 person-years in men. [3]

Primary hyperparathyroidism causes [4]

- Excess PTH is produced by one or more of the parathyroid glands, due to:
    - A single parathyroid gland adenoma (85% of cases).
    - Parathyroid hyperplasia (10-12%).
    - Double adenomas (4-5%).
    - Parathyroid carcinoma (less than 1%).

- The aetiology of adenomas or hyperplasia is largely unknown.
- There may be an association with ionising radiation.[1]
- Familial cases can occur as part of the multiple endocrine neoplasia syndromes (MEN 1 or MEN 2a), hyperparathyroid-jaw tumour (HPT-JT) syndrome, or familial isolated hyperparathyroidism (FIHPT).

Presentation[1]

70-80% of people are asymptomatic and diagnosis is made after incidental hypercalcaemia is found. In those who are symptomatic, remember: 'bones, stones, abdominal groans, and psychic moans'.

Clinical features are due to:

- Excessive calcium resorption from bone:
    - Osteopenia and osteoporosis, presenting as bone pain and pathological fractures.
    - Osteitis fibrosa cystica can occur in severe cases. It presents with subperiosteal resorption of the distal phalanges, tapering of the distal clavicles, salt and pepper appearance of the skull, and brown tumours of the long bones.
- Excessive renal calcium excretion:
    - Renal calculi (the most common presentation).

- Hypercalcaemia:
    - Muscle weakness, proximal myopathy, fatigue.
    - Anorexia; nausea and vomiting; constipation; abdominal pain; peptic ulcer disease (hypercalcaemia can increase gastric acid secretion); acute pancreatitis.
    - Polyuria, polydipsia, dehydration.
    - Renal colic, haematuria, hypertension.
    - Long-standing hypercalcaemia causes corneal calcification, which is usually asymptomatic.
    - Neuropsychiatric manifestations are particularly common and may include depression, dementia, confusion, inability to concentrate and memory problems.
    - Hypertension, shortened QT interval on ECG and cardiac arrhythmias (rare).
    - Severe cases may lead to coma and death.

Differential diagnosis

- Familial benign (hypocalciuric) hypercalcaemia (FBHH) - presents with hypercalcaemia and modestly raised or normal PTH. Autosomal dominant inheritance. A gene defect leads to inappropriate secretion of PTH at high serum calcium levels. Parathyroidectomy will be ineffective.[1]
- Lithium-induced hypercalcaemia.
- Tertiary HPT.
- Other causes of hypercalcaemia, especially malignancy; other causes include thyrotoxicosis, sarcoidosis, Paget's disease of bone and Addison's disease.

Investigations[2]

PHPT is the most common cause of hypercalcaemia in many studies.[1]

There is also evidence that raised PTH levels can reduce when low 25(OH)D levels are corrected. See also 'Secondary hyperparathyroidism', below.

Investigations in primary care

Albumin-adjusted serum calcium

- Measure albumin-adjusted serum calcium for people with any of the following features, which might suggest primary hyperparathyroidism:
    - Symptoms of hypercalcaemia - eg, thirst, frequent or excessive urination, or constipation.
    - Osteoporosis or a previous fragility fracture.
    - A renal stone.
    - An incidental finding of elevated albumin-adjusted serum calcium (2.6 mmol/L or above).
- Consider measuring albumin-adjusted serum calcium for people with chronic non-differentiated symptoms.
- Do not measure ionised calcium when testing for primary hyperparathyroidism.
- Repeat the albumin-adjusted serum calcium measurement at least once if the first measurement is either:
    - 2.6 mmol/L or above; **or**
    - 2.5 mmol/L or above and features of primary hyperparathyroidism are present.

Any decision to carry out further repeat measurements should be based on the level of albumin-adjusted serum calcium and the person's symptoms.

Parathyroid hormone

- Measure parathyroid hormone (PTH) for people whose albumin-adjusted serum calcium level is either:
    - 2.6 mmol/L or above on at least two separate occasions; **or**
    - 2.5 mmol/L or above on at least two separate occasions and primary hyperparathyroidism is suspected.
- When measuring PTH, use a random sample and do a concurrent measurement of the albumin-adjusted serum calcium level.

- Do not routinely repeat PTH measurement in primary care.
- Seek advice from a specialist with expertise in primary hyperparathyroidism if the person's PTH measurement is either:
    - Above the midpoint of the reference range and primary hyperparathyroidism is suspected; **or**
    - Below the midpoint of the reference range with a concurrent albumin-adjusted serum calcium level of 2.6 mmol/L or above.
- Do not offer further investigations for primary hyperparathyroidism if:
    - The person's PTH is within the reference range but below the midpoint of the reference range; **and**
    - Their concurrent albumin-adjusted serum calcium level is below 2.6 mmol/L.
- Look for alternative diagnoses, including malignancy, if the person's PTH is below the lower limit of the reference range.

Investigations in secondary care

Measure vitamin D

- Measure vitamin D for people with a probable diagnosis of primary hyperparathyroidism. Offer vitamin D supplements if needed.
- Exclude familial hypocalciuric hypercalcaemia.
- To differentiate primary hyperparathyroidism from familial hypocalciuric hypercalcaemia, measure urine calcium excretion using any one of the following tests:
    - 24-hour urinary calcium excretion.
    - Random renal calcium:creatinine excretion ratio.
    - Random calcium:creatinine clearance ratio.

Assessment after diagnosis

- Assess symptoms and comorbidities
- Measure estimated glomerular filtration rate (eGFR) or serum creatinine.

- Do a dual-energy X-ray absorptiometry (DXA) scan of the lumbar spine, distal radius and hip.
- Do an ultrasound scan of the renal tract.

Treatment

> See also the separate **Hypercalcaemia** article.

Mild, asymptomatic disease [5]

- Surveillance can be used in patients with mildly elevated calcium levels and close to normal renal and bone status. [6]
- All patients should be replete in vitamin D, aiming for a minimum serum level of 25(OH)D >20 ng/dL. 800 to 1000 IU are a useful starting dose.
- Such patients may continue for long periods without deterioration in bone mineral density.
- However, progression can occur: at 15 years one third of patients will have overt features of HPT, such as kidney stones, worsening hypercalcaemia and reduced bone density.
- Monitor for overt signs and symptoms of PHPT. However there is controversy over what constitutes 'asymptomatic', as the symptoms of PHPT can be nonspecific and subtle, such as fatigue, weakness and muscle pains. [7]
- Check serum creatinine level and calcium levels every six months.
- 3-site DXA study should also be obtained every 1-2 years.
- Avoid dehydration (advise a high fluid intake).
- Avoid thiazide diuretics.
- There is no recommendation to limit calcium intake.

Surgical treatment [5]

- Parathyroid surgery offers the only potential for cure.

- Parathyroid surgery to remove abnormal parathyroid gland(s) is suggested in most symptomatic patients.[1] In the case of 4-gland hyperplasia, a 3.5-gland (subtotal) parathyroidectomy is performed.
- Guidelines for the management of PHPT advise surgery if:
    - Age is under 50.
    - Serum albumin-adjusted calcium is more than 0.25 mmol/L (1 mg/dL) above the upper limit of normal (local laboratory reference).
    - Creatinine clearance is <60 ml/minute.
    - There is development of a kidney stone, either clinically or by imaging.
    - Bone mineral density T score is less than -2.5 (at any site) or there is a significant reduction in bone mass density.
    - There is a vertebral fracture.
- Patient request is also an appropriate indication, especially if follow-up is unlikely.
- While there is subtle evidence that patients with PHPT may have cardiovascular dysfunction, there is no evidence that surgery for PHPT affects cardiovascular endpoints .
- Minimally invasive parathyroidectomy in combination with pre-operative localisation investigations is increasingly being used. These investigations include ultrasound, MRI, computerised axial tomography and technetium ^{99m} Tc-labelled sestamibi single-photon emission CT. However, they play no part in the diagnosis of PHPT.[7]
- Parathyroid surgery should only be performed by highly experienced surgeons .
- Intraoperative measurement of PTH may also help to see if the abnormal gland(s) has been removed. The PTH level drops by 50% within 10-15 minutes of the hyper-functioning parathyroid tissue being removed.

Medical treatment[2]

Medical management is used for those who opt against hyperparathyroid surgery or who do not meet the criteria for surgery.[8]

- Parathyroidism treatment is aimed at improving bone mineral density and achieving calcium homeostasis.
- Calcinet:

  consider for people with primary hyperparathyroidism if surgery has been unsuccessful (off-label), is unsuitable or has been declined, and their albumin-adjusted serum calcium is either:

- - 2.85 mmol/L or above with symptoms of hypercalcaemia; **or**
  - 3.0 mmol/L or above with or without symptoms of hypercalcaemia.
- If the initial albumin-adjusted serum calcium level is 2.85 mmol/L or above with symptoms of hypercalcaemia, base decisions on whether to continue treatment with cinacalcet on how well it reduces symptoms.
- If the initial albumin-adjusted serum calcium level is 3.0 mmol/L or above, base decisions on whether to continue treatment with cinacalcet on how well it reduces either symptoms or albumin-adjusted serum calcium level.
- Consider a bisphosphonate to reduce fracture risk for people with primary hyperparathyroidism and increased fracture risk.
- Do not offer bisphosphonates for chronic hypercalcaemia of primary hyperparathyroidism.

Complications after surgery

These include:

- Hypocalcaemia - due to 'hungry bone syndrome'. Calcium and phosphorus are rapidly deposited in bone. There is hypoparathyroidism and transient, sometimes severe, hypocalcaemia until the normal glands regain sensitivity. If hypoparathyroidism persists, calcium and vitamin D supplements are required.

- Recurrent laryngeal nerve injury - suspect this if a patient develops new hoarseness postoperatively. Immediate laryngoscopy is indicated.
- Haematoma formation - if this occurs in the pre-tracheal space, urgent evacuation is required before airway obstruction occurs.

Outcome after surgery [5]

- Successful parathyroid surgery leads to improved bone density, reduction in fracture incidence and fewer kidney stones, in those who have previously had them.
- There may be improvements in some neurocognitive symptoms but this has not been confirmed with controlled trials.

Secondary hyperparathyroidism

Secondary hyperparathyroidism causes

- Secondary hyperparathyroidism (SHPT) is most commonly seen in the setting of chronic kidney disease (CKD).
- The parathyroid glands become hyperplastic after long-term stimulation in response to chronic hypocalcaemia.
- Secondary hyperparathyroidism is seen in almost all patients with dialysis-dependent CKD. Most patients with CKD stage 5 develop SHPT .
- Several studies have documented that PTH levels are increased in CKD (stages 3 and 4) before there are changes in calcium and phosphate. [9]
- Secondary hyperparathyroidism can, however, occur in any condition with chronic hypocalcaemia such as deficiency in vitamin D or malabsorption.

For specific details on vitamin D deficiency, CKD and its management and gastrointestinal malabsorption, see the separate Vitamin D Deficiency including Osteomalacia and Rickets, Chronic Kidney Disease (CKD) and Gastrointestinal Malabsorption articles.

Presentation

- Almost all patients with CKD have SHPT to some degree, so the clinical presentation is often that of kidney disease.
- SHPT causes skeletal and cardiovascular complications in CKD patients. [10]
- If SHPT is due to vitamin D deficiency, the symptoms are mainly due to the vitamin deficiency (eg, osteomalacia with increased fracture risk, myopathy, etc).
- In severe SHPT, bone pain may be present.
- Calcium levels are low-normal; therefore, the symptoms related to hypercalcaemia seen with PHPT are absent.

Investigations

- Findings:
    - Low-normal calcium.
    - Raised PTH.
    - Phosphate levels depend on aetiology (eg, high in renal disease, low in vitamin D deficiency).
- Radiology can show evidence of bone disease and vascular and visceral calcification.

Treatment

- Medical management is the mainstay of treatment.
- The underlying condition needs to be treated - for example, correcting vitamin D deficiency.

- Treatment in CKD includes:
    - Calcium supplementation.
    - Correction of vitamin D deficiency.
    - Phosphate restriction ± phosphate binders.
    - Vitamin D analogues.
    - Calcimimetics (eg, cinacalcet) may also be helpful.
- The National Institute for Health and Care Excellence (NICE) only recommends the use of cinacalcet for those with end-stage kidney disease whose SHPT is refractory to other treatment and in whom surgery is not suitable as a treatment. [11]
- Trials indicate that early intervention in stages 3 and 4 of CKD can correct PTH levels and could prevent renal bone disease, reduce cardiovascular complications and prolong patient survival. [9]
- Parathyroidectomy may be considered in severe cases refractory to medical treatment.
- There is a 10% risk of recurrent or persistent disease after parathyroidectomy.

Tertiary hyperparathyroidism

Causes

- Tertiary hyperparathyroidism (THPT) usually occurs after prolonged SHPT.
- The glands become autonomous, producing excessive PTH even after the cause of hypocalcaemia has been corrected.
- This results in hypercalcaemia.
- Long-standing kidney disease is the most common cause. [1]
- It can persist after a renal transplant.

Presentation

- Symptoms and signs are due to hypercalcaemia so presentation can be similar to PHPT.
- There are important health risks, particularly concerning bone density and the cardiovascular system.

Investigations

- Findings:
    - Raised calcium.
    - Raised PTH.
    - Phosphate often raised.

Treatment

- Cinacalcet may be used in THPT. [12]
- Total or subtotal parathyroidectomy is the recommended treatment. [13]
- Autotransplantation of parathyroid tissue in an easily accessible site, such as the forearm, is also commonly carried out. [1]

Consider a bisphosphonate to reduce fracture risk for people with primary hyperparathyroidism and increased fracture risk.

1.5.5Do not offer bisphosphonates for chronic hypercalcaemia of primary hyperparathyroidism.

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