Hyperparathyroidism

Hyperparathyroidism (HPT) results when there is excessive secretion of parathyroid hormone (PTH). PTH is secreted by the four parathyroid glands, located in the neck behind the thyroid gland. It 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.

HPT 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.
- PTH:
  - 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
- Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder.
- it is most common in postmenopausal women.

Causes
- Excess PTH is produced by one or more of the parathyroid glands, due to:
  - A single parathyroid gland adenoma (85% of cases).
  - 4-gland hyperplasia (10-15%).
  - Double adenomas (3-5%).
  - Parathyroid carcinoma (less than 1%).

- The aetiology of adenomas or hyperplasia is largely unknown.
- There may be an association with ionising radiation.
- 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
- 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:
PHPT is the most common cause of hypercalcaemia in many studies.[1]

If someone presents with hypercalcaemia:
- Look for any obvious drug causes (eg, lithium, thiazide diuretics).
- Repeat plasma albumin-adjusted calcium levels.
- Ensure renal function is normal.
- Measure PTH, which will be raised in PHPT.

Findings:
- Hypercalcaemia.
- Raised PTH.
- Hypophosphataemia.
- Mild-to-moderate increase in 24-hour urinary calcium excretion.

Other tests:
- 25-hydroxyvitamin D (25(OH)D) should be measured if PTH raised; there is evidence that HPT is more active when patients are vitamin D-depleted.[1] There is also evidence that raised PTH levels can reduce when low 25(OH)D levels are corrected. See also 'Secondary hyperparathyroidism', below.
- Dual-energy X-ray absorptiometry (DEXA) scan can show any skeletal involvement in PHPT.
- Pathognomonic X-ray changes include salt and pepper degranulation in the skull and subperiosteal bone resorption in the phalanges in severe cases.
- Imaging of renal tract (X-ray, ultrasound) can demonstrate renal calculi.
- A biopsy may be performed if carcinoma is suspected.

Treatment:
See also separate Hypercalcaemia article.

Mild, asymptomatic disease[2]
- Surveillance can be used in patients with mildly elevated calcium levels and close to normal renal and bone status.[3]
- 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 PHT. However there is controversy over what constitutes 'asymptomatic', as the symptoms of PHT can be nonspecific and subtle, such as fatigue, weakness and muscle pains.[4]
- Check serum creatinine level and calcium levels every six months.
- 3-site DEXA 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[2]

- 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.[4]
- 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

- Medical management is used for those who opt against surgery or who do not meet the criteria for surgery.[5]
- Treatment is aimed at improving bone mineral density and achieving calcium homeostasis.
- HRT and raloxifene may be used in postmenopausal women. They have been shown to reduce calcium levels as well as improve bone density.[1] However, because of the risks associated with oestrogen replacement, it should not be used purely to treat PHPT.
- Bisphosphonates (particularly alendronate) may be a useful treatment.[1]
- Cinacalcet reduces both serum calcium and PTH levels and raises serum phosphorus. Cinacalcet does not, however, reduce bone turnover or improve bone mineral density.[5]

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[2]

- 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

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.
- It 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.[6]
- It 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 separate Vitamin D Deficiency including Osteomalacia and Rickets, Chronic Kidney Disease 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.[7]
- 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 (e.g., 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 people with end-stage kidney disease whose SHPT is refractory to other treatment and in whom surgery is not suitable as a treatment. [8]
- 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. [6]
- 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.[9]
- Total or subtotal parathyroidectomy is the recommended treatment.[10]
- Autotransplantation of parathyroid tissue in an easily accessible site, such as the forearm, is also commonly carried out.[1]

Further reading & references


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