Hypercalcaemia and primary hyperparathyroidism

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Abstract

Hypercalcaemia is most commonly caused by primary hyperparathyroidism (PHPT) or malignancy. PHPT is common, affects more women than men, and is usually due to a solitary parathyroid adenoma. Nowadays, the most common presentation is an incidental finding on blood testing. The only curative treatment is parathyroidectomy. In 2009 the Third International Workshop on the management of asymptomatic primary hyperparathyroidism updated their guidance on management of asymptomatic PHPT. They recommend surgery in: all symptomatic patients; asymptomatic patients with hypercalcaemia above the upper limit of the reference range by more than 0.25 mmol/litre, evidence of end-organ damage, including impaired renal function, and reduced bone mineral density; and patients under 50 years old. In other patients, conservative management with regular monitoring is an acceptable management strategy. Defining 'asymptomatic' is not always easy and there is growing awareness of the prevalence of reduced quality-of-life scores among patients with 'asymptomatic' PHPT, but there is a lack of definitive evidence showing benefit in these domains following parathyroidectomy. Therefore, careful clinical decision-making is required in this group of patients.

Keywords cinacalcet; hypercalcaemia; parathyroidectomy; primary hyperparathyroidism; vitamin D

What's new?

- The guidelines updated in 2009 by the Third International Workshop on the management of asymptomatic primary hyperparathyroidism (PHPT), on which groups of patients with asymptomatic PHPT should undergo parathyroidectomy, now have a firmer evidence base, particularly with respect to the sequelae of reduced renal function on skeletal disease in PHPT, and regarding improvements in bone mineral density and fracture risk following parathyroidectomy
- There is still a role for clinical judgement when assessing the risks and benefits of parathyroidectomy in the 'no indication for surgery' group, as emphasized by the American Association of Clinical Endocrinologists and the American Association of Endocrine Surgeons in their position statement on the diagnosis and management of primary hyperparathyroidism published in 2005
- Guidelines for the treatment of PHPT in MEN-1 were released in 2012
- There is a growing recognition of the multiple ways in which vitamin D deficiency and PHPT can interact
- Where it is available, and when imaging results concur, minimally invasive parathyroidectomy is becoming the preferred surgical option
- The calcimimetic, cinacalcet, is now licensed for use in PHPT where surgery is inappropriate, along with its original licence for use in secondary hyperparathyroidism in chronic renal disease and for parathyroid carcinoma

Aetiology

Of the numerous causes of hypercalcaemia, primary hyperparathyroidism (PHPT) is the most common in outpatient settings and malignancy is most common amongst inpatients. PHPT is characterized by hypercalcaemia with elevated or inappropriately normal concentrations of parathyroid hormone (PTH) and elevated urinary calcium excretion. The prevalence is 1–3/1000. It is more common in women (3:1) and most commonly presents after the age of 50 years. The main causes of PHPT are outlined in Table 1. PHPT is usually sporadic, but may be associated with inherited syndromes, most commonly multiple endocrine neoplasia (MEN) type 1 and type 2,[1] familial isolated hyperparathyroidism[2] and hyperparathyroidism–jaw tumour syndrome.[3] These inherited forms tend to present at a younger age. Guidelines for the management of PHPT and other clinical features in MEN-1 have been published recently.[4]

Hypercalcaemia due to other causes (Figure 1) is distinguished from PHPT by suppressed PTH concentration.

Clinical features

Patients are commonly asymptomatic at diagnosis, with serum calcium less than 0.25 mmol/litre above the reference range.

Classical symptoms include polyuria, polydipsia, depression, peptic ulcer disease, musculoskeletal aches and pains and renal colic ('moans, bones, stones and groans'). Some reports have linked asymptomatic PHPT to reduced quality-of-life scores but this does not consistently improve after parathyroidectomy.[5,6] Likewise, although an association of PHPT with hypertension has been described, it is not thought consistently to improve following parathyroidectomy.[7] Features of end-organ damage include osteoporosis, osteitis fibrosa cystica, nephrolithiasis and nephrocalcinosis. Classical skeletal changes (Brown tumours, osteitis fibrosa cystica) occur in fewer than 2% of patients, but osteoporosis is a common feature of hyperparathyroidism and predominantly affects cortical bone (e.g. distal radius) more than trabecular bone (e.g. vertebral bodies).

Diagnosis and investigations

Elevated or inappropriately 'normal' plasma PTH with elevated serum calcium (corrected for serum albumin concentration) is

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Aetiology of primary hyperparathyroidism

Cause	Proportion of PHPT cases
Single parathyroid adenoma	80–85%
Multiple parathyroid adenomata; four-gland hyperplasia	15–20%
Parathyroid carcinoma	<0.5%

Table 1

almost diagnostic of PHPT (see Figure 1). The exception is familial hypocalciuric hypercalcaemia (FHH), which can mimic the serum biochemistry of PHPT and is distinguishable only by urine biochemistry. FHH is an autosomal dominant condition caused by inactivating mutations in the calcium-sensing receptor gene. It is characterized by a modest increase in serum calcium with an inappropriately normal plasma PTH (slight elevation in 5–10% of patients).

The calcium:creatinine clearance ratio is used to distinguish PHPT from FHH. This ratio is calculated from simultaneous measurements of urine and serum calcium and creatinine concentrations. A value of less than 0.01 is indicative of FHH.

The interaction of PHPT with vitamin D deficiency has received much attention. Vitamin D deficiency may mask hypercalcaemic PHPT,[8] and may drive the hyperparathyroid state, increasing skeletal disease activity in PHPT.[9] An assessment of vitamin D status should therefore be performed whenever calcium or PTH biochemistry are abnormal.

Elevated PTH with normal calcium, so-called normocalcaemic hyperparathyroidism, is an increasingly common biochemical finding; it is diagnosed by excluding causes of secondary hyperparathyroidism, such as vitamin D deficiency and renal disease, and may represent 'early' PHPT before serum calcium has had time to rise.[10] However, its natural history is not well described.

Management

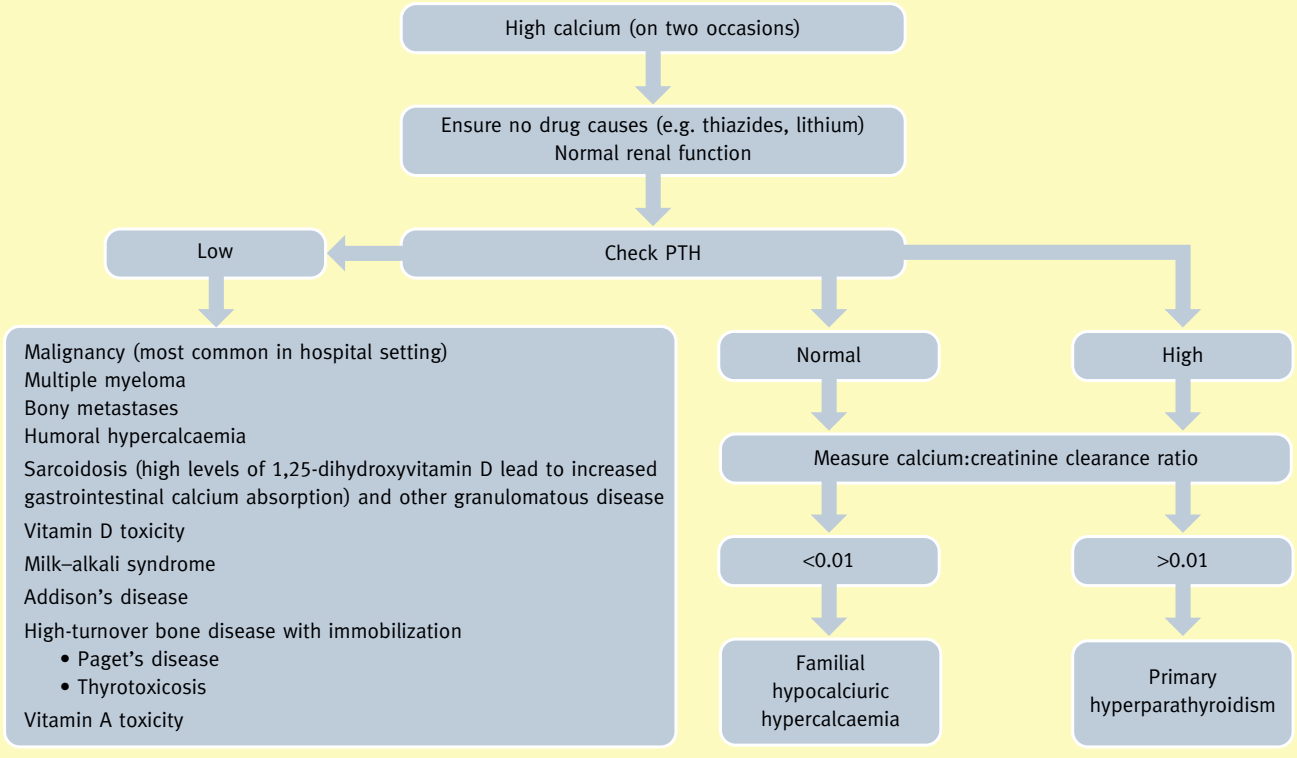
Surgery is the only curative treatment for PHPT, but is not appropriate in all patients; the potential benefits must be weighed against the risks in each case. This process has been simplified by the publication of guidelines from the Third International Workshop on the management of asymptomatic primary hyperparathyroidism (Table 2). However, these guidelines do not apply in the familial PHPT syndromes described above.

Surgery

Surgery is indicated in all symptomatic patients and asymptomatic patients with evidence of end-organ damage, specifically:

- impaired renal function
- age under 50 years (as they are the most likely to progress)

Investigation of hypercalcaemia



PTH, parathyroid hormone.

Figure 1