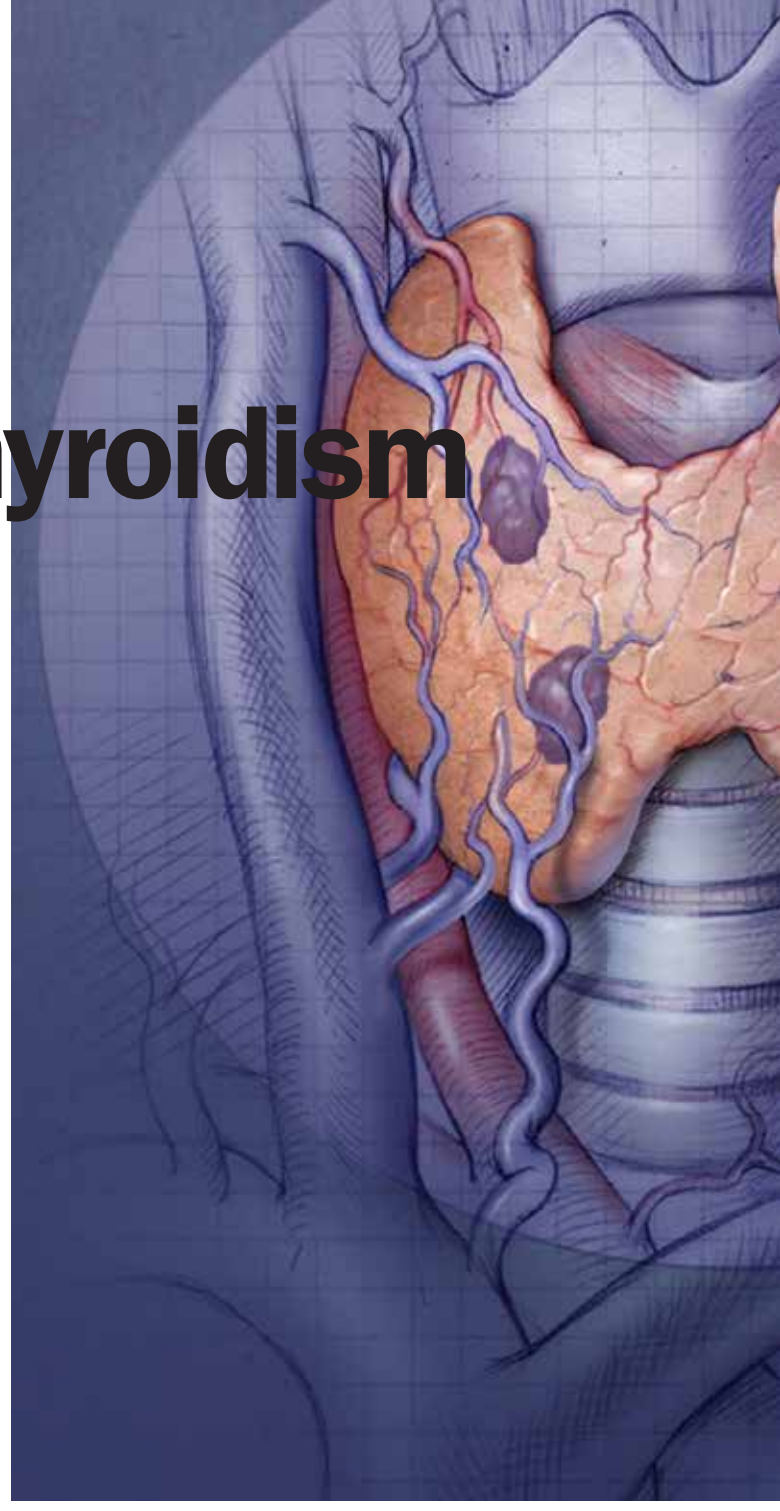
Primary hyperparathyroidism

Who, when, why and how to manage



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Primary hyperparathyroidism is typically diagnosed as an incidental finding in patients who are still asymptomatic. Management is usually by parathyroidectomy, ideally by focused minimally invasive surgery, but medical therapeutic options exist if surgery is not indicated.

Primary hyperparathyroidism (PHPT) is a relatively common disorder accounting for up to 90% of presentations of persistent hypercalcaemia in primary care.[1] Today, PHPT is typically diagnosed as an incidental finding when patients are still asymptomatic and often during investigation for osteoporosis.[2] The spectrum of presentation ranges from normocalcaemic hyperparathyroidism without symptoms through to severely symptomatic disease with hypercalcaemic crisis, nephrolithiasis, osteitis fibrosa cystica, muscular weakness and neuropsychiatric disturbance.

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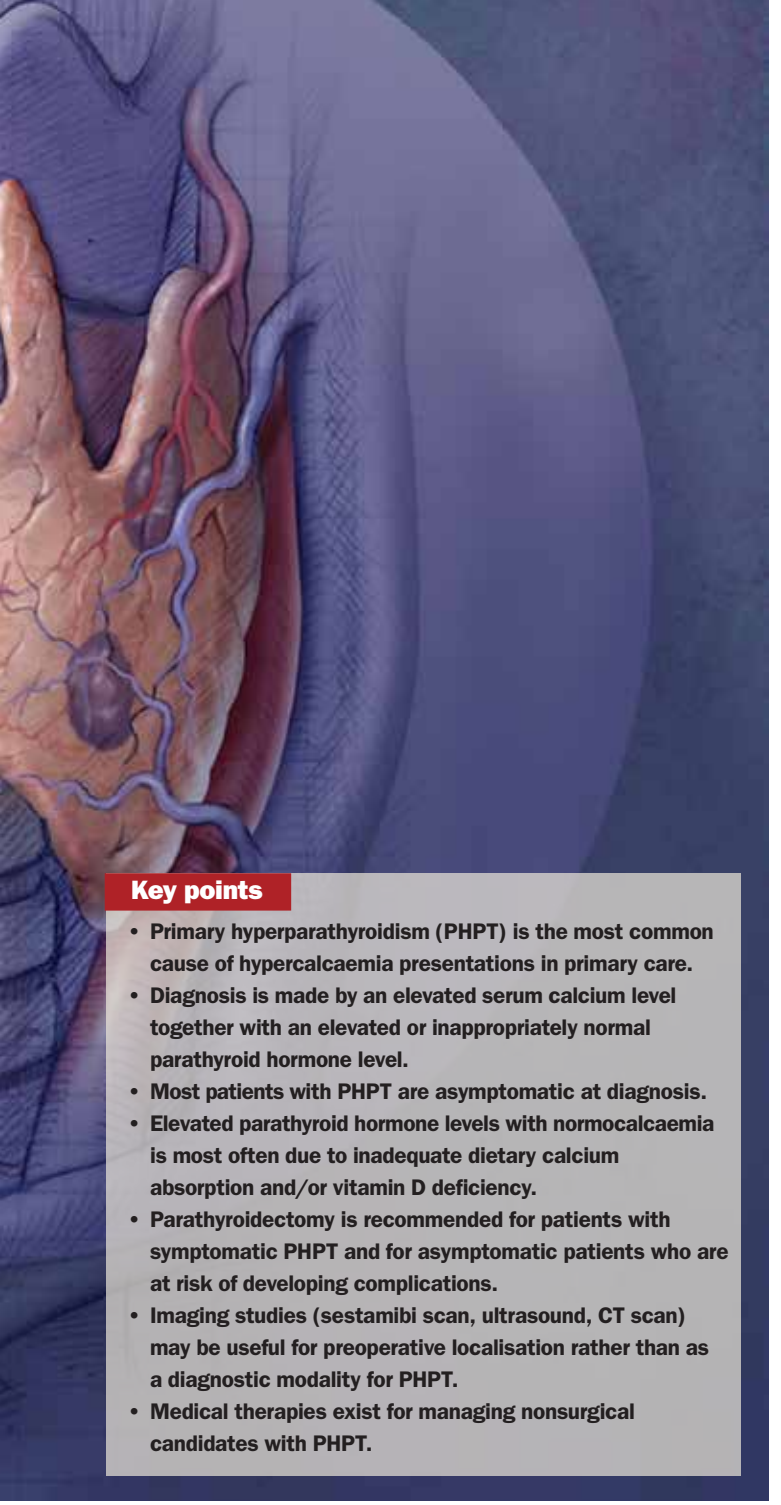
Aetiology

Parathyroid hormone (PTH) along with calcitriol (1,25-dihydroxyvitamin D) are the two major hormonal regulators of calcium homeostasis. PTH is secreted almost instantaneously in response to very small reductions in serum calcium concentrations, which are sensed by the calcium-sensing receptors located on parathyroid cells and renal tubular cells. PTH elevates serum calcium levels by the following three main mechanisms:

- increasing bone resorption
- decreasing urinary calcium excretion
- increasing intestinal absorption indirectly through conversion of 25-hydroxyvitamin D to calcitriol.



Key points

- **Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcaemia presentations in primary care.**
- **Diagnosis is made by an elevated serum calcium level together with an elevated or inappropriately normal parathyroid hormone level.**
- **Most patients with PHPT are asymptomatic at diagnosis.**
- **Elevated parathyroid hormone levels with normocalcaemia is most often due to inadequate dietary calcium absorption and/or vitamin D deficiency.**
- **Parathyroidectomy is recommended for patients with symptomatic PHPT and for asymptomatic patients who are at risk of developing complications.**
- **Imaging studies (sestamibi scan, ultrasound, CT scan) may be useful for preoperative localisation rather than as a diagnostic modality for PHPT.**
- **Medical therapies exist for managing nonsurgical candidates with PHPT.**

The most frequent causes of hypercalcaemia in the primary care setting include primary and tertiary hyperparathyroidism, diuretic or lithium use, and malignancy (see Box 1).[3]

PHPT is most often caused by a single parathyroid adenoma (85 to 90%), multiple adenomas (5 to 15%), multiple gland hyperplasia (5 to 15%) and, rarely, parathyroid carcinoma (<1%).[4,5] Long-term lithium therapy and prior head and neck irradiation have been associated with a higher prevalence of hyperparathyroidism.[6,7] A number of somatic mutations have been identified in various genes such as *PRAD1*, *Rb*, *MEN1* and *CDC73*; however, the aetiology of sporadic PHPT still remains largely unknown.[8] Multigland disease should raise suspicion for a familial syndrome (discussed in more detail below).

Epidemiology

The estimated prevalence of PHPT varies widely from one to seven cases per 1000 adults and has continued to increase over the past three decades, largely attributable to the accumulation of cases diagnosed through routine calcium testing.[1] The incidence peaks in the seventh decade of life and is 2.5 times more common in women than in men.

Diagnosis

The diagnosis of PHPT is usually made in the presence of hypercalcaemia with an elevated or inappropriately normal serum PTH level and normal renal function. Measurement of ionised calcium levels can be useful in patients with hyperalbuminaemia, thrombocytosis and myeloma because total serum calcium level can be artefactually elevated in these patients. Measurement of ionised calcium may also help to diagnose hyperparathyroidism in patients with low serum albumin levels (e.g. in people with malabsorption/coeliac disease).[3] Hypercalcaemia with elevated PTH levels can also occur with tertiary hyperparathyroidism in the setting of end-stage renal failure, prolonged chronic vitamin D deficiency, and long-term use of thiazide diuretics or lithium. A suggested approach to the clinical assessment of patients with PHPT is shown in Box 2.

The most common clinical presentation of PHPT is that of asymptomatic hypercalcaemia. Prolonged PTH excess can lead to the classic symptoms of nephrolithiasis, and kidney stones are still the most common complication of PHPT. Bone loss (more obvious at cortical-rich bone) is generally more evident when estimated glomerular filtration rate is reduced to below 60 mL/min/1.73^2.[9] Other nonspecific symptoms may include weakness, fatigue and neuropsychiatric complaints of depression, decreased attention and increased sleep requirements. Subtle cardiovascular effects have been noted during assessment of vascular reactivity, left ventricular function and carotid intimal thickness; however, these assessments are not routinely recommended for the clinical work up of PHPT. PHPT increases the risk of death from cardiovascular causes, and a recent observational study suggested that mortality associated with PHPT increased with serum PTH levels above 8.5 pmol/L.[10] PHPT also increases the risk of the metabolic syndrome. Data to show improved survival of patients with PHPT following parathyroid surgery are inconclusive.

Hypercalcaemia associated with low serum PTH levels should raise the suspicion of malignancy and specialist referral of the patient is advised. Except for myeloma, malignancy is usually clinically evident by the time hypercalcaemia develops. Other causes of PTH-independent hypercalcaemia, such as sarcoidosis or the milk-alkali syndrome, are rare. Further investigations include measurement of serum and urine immunofixation/electrophoresis, PTH-related peptide and 1,25-dihydroxyvitamin D levels, and imaging studies (such as CT of the chest, abdomen and pelvis), whole body gallium scan (for sarcoidosis) or bone scan in selected circumstances.

Normocalcaemic primary hyperparathyroidism

Increased PTH concentration in the absence of hypercalcaemia is often encountered in patients evaluated for low bone density. The

1. Causes of hypercalcaemia[3]

Parathyroid hormone-mediated
- Primary hyperparathyroidism
- Tertiary hyperparathyroidism (renal failure)
- Familial (see Table)

Parathyroid hormone-independent
- Malignancy
- Excess calcitriol (sarcoidosis and other granulomatous disorders)
- Medications (thiazide diuretics, lithium, teriparatide, calcitriol)
- Other (hyperthyroidism, cortisol deficiency, acromegaly, phaeochromocytoma, immobilisation, milk-alkali syndrome)

underlying cause of this hyperparathyroidism is not completely understood, but it usually turns out to be secondary to one or more factors – for example, inadequate dietary calcium, reduced absorption associated with vitamin D deficiency, hypercalciuria or renal impairment. If secondary hyperparathyroidism is excluded, then a subset of patients with normocalcaemic hyperparathyroidism will have an underlying parathyroid adenoma and will progress to become hypercalcaemic in time. Measurement of serum calcium and PTH levels is recommended annually along with dual energy x-ray absorptiometry assessment every one to two years (MBS item number 12315). It remains controversial whether carefully selected patients with normocalcaemic hyperparathyroidism benefit from parathyroidectomy under certain circumstances, such as decreasing BMD and/or fracture, renal stone disease or nephrocalcinosis.[9]

Familial hypocalciuric hypercalcaemia: an important differential diagnosis

An uncommon mimic of PHPT is familial hypocalciuric hypercalcaemia (FHH), and this is worth recognising because patients with FHH almost never require nor respond to surgery. FHH is an autosomal dominant condition due to a mutation of the calcium-sensing receptor gene. It is characterised by mild to moderate hypercalcaemia (<3.0 mmol/L) and usually normal or mildly elevated PTH levels. It should be routinely excluded in patients who are being considered for parathyroid surgery.

Recent consensus guidelines suggest measuring fasting spot urinary calcium:creatinine ratio in patients suspected of having FHH. If less than 0.01, this raises the possibility of FHH providing the patient is not taking a thiazide diuretic; however, some patients with PHPT will also have a low spot urinary calcium:creatinine ratio and in this case we would recommend confirmation with a 24-hour urine sample. Fractional excretion of calcium (calculated as [24-hour urinary calcium x serum creatinine] / [serum calcium x 24-hour urinary creatinine]) less than 0.01 is highly suggestive of FHH, whereas a value of more than 0.02 is consistent with PHPT. Genetic testing for FHH according to clinical discretion and after appropriate genetic counselling is performed if fractional calcium excretion is less than 0.01 and may also be required if values are between 0.01 and 0.02.[11,12]

2. Suggested approach to the patient with primary hyperparathyroidism

Clinical assessment of severity
- History of renal colic or renal stone disease; polyuria or polydipsia
- History of bone pain or fracture
- History of poor concentration, low mood, fatigue, myopathy
- Medications (thiazide, lithium, calcitriol, calcium supplements)
- Family history of calcium and/or parathyroid disease

Laboratory assessment of severity
- Serum calcium level (ionised calcium if albumin-adjusted calcium is normal)
- Serum parathyroid hormone level
- Creatinine, estimated glomerular filtration rate
- 25-hydroxyvitamin D level
- Urinary calcium level (ideally 24-hour sample)
- Bone mineral density by dual energy x-ray absorptiometry (MBS item #12315)

Imaging studies (if parathyroidectomy contemplated)
- Sestamibi scan and ultrasound
- 4D CT scan, if above negative
- Parathyroid hormone venous sampling (rarely needed)

Treatment

Patients with hyperparathyroidism presenting with severe hypercalcaemia (serum calcium level >3.50 mmol/L, or >3 mmol/L with symptoms) warrant prompt referral to hospital for rehydration and medical treatment to lower the serum calcium level before definitive therapy by parathyroidectomy.

Parathyroidectomy is usually recommended for patients with symptomatic disease or asymptomatic disease when other features that predict increased risk of complications are present (Box 3). Consensus guidelines have been proposed for both parathyroid surgery and monitoring in patients with asymptomatic PHPT (see Boxes 3 and 4).[13] It should be noted that these guidelines are based primarily on expert consensus opinion. In randomised trials, parathyroidectomy has been shown to increase hip and spine BMD and to improve quality of life.[14-16] BMD of the distal radius may be the most sensitive and specific region affected by PHPT. Observational data suggest that parathyroidectomy also improves a wide spectrum of symptoms, reduces risk of renal stones and reduces risk of fracture.[17]

Surgery

Parathyroidectomy is the recommended treatment for PHPT. Traditionally, the operation of choice has been via a collar incision, with exposure of all four parathyroid glands and removal of the adenoma. Focused minimally invasive parathyroidectomy via lateral neck incision has now become the procedure of choice in Australia because of reduced morbidity without compromising surgical cure rates. Focused surgery relies on accurate preoperative localisation of the adenoma by a sestamibi scan and high-resolution ultrasonography.

3. Consensus guidelines for parathyroid surgery in asymptomatic patients with primary hyperparathyroidism[13]

Serum calcium
- >0.25 mmol/L (above upper limit of normal)

Renal
- Estimated glomerular filtration rate <60 mL/min/1.73^2
- Kidney stone by clinical development or imaging (x-ray, CT scan or ultrasound)
- 24-hour urinary calcium level >400 mg/day (10 mmol/day) plus other urinary biochemical indices of increased stone risk

Skeletal
- T-score less than –2.5 at any site
- Vertebral fracture

Age
- Under 50 years

Note: Only one of the above criteria needs to be met for surgery to be advised.

4. Consensus guidelines for monitoring patients with asymptomatic primary hyperparathyroidism[13]

Serum calcium
- Measurement taken annually

Renal
- Estimated glomerular filtration rate measured annually
- Stone risk profile (24-hour urine for analysis of biochemical stone risk factors – Ca, PO_4, SO_4, uric acid), if clinically indicated
- Abdominal imaging (x-ray, CT scan or ultrasound), if clinically indicated

Skeletal
- Dual energy x-ray absorptiometry every one or two years
- CT scan or vertebral fracture assessment, if clinically indicated (e.g. back pain, height loss)

When both localisation studies are concordant, then surgical cure is achieved in 98% of appropriately selected cases.[18] These localisation studies can also identify patients in whom a focused approach would be inappropriate (see Figures 1a and b).

Medical treatment

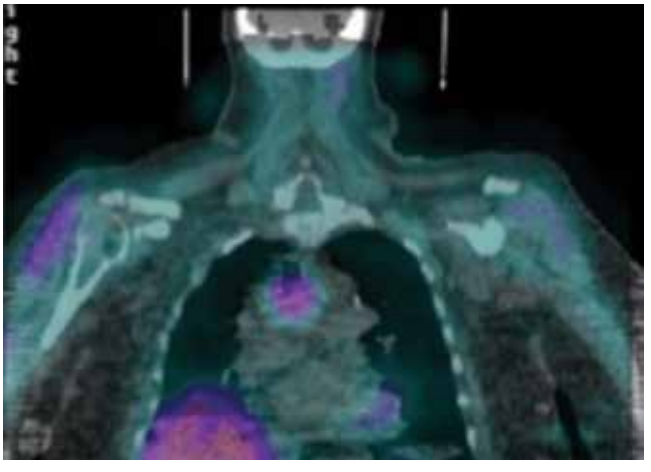
Medical treatment of PHPT is indicated acutely to reduce serum calcium levels before surgery, and also chronically for management of comorbidities associated with PHPT, in particular for patients not undergoing surgery.

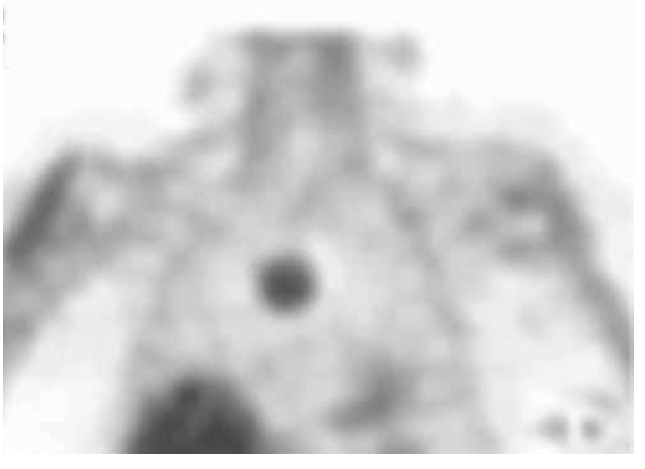
Acute medical management

Acute medical management of patients with hypercalcaemia (serum calcium level >3.5 mmol/L or >3.0 mmol/L with symptoms) should occur in hospital and includes saline rehydration and administration of intravenous bisphosphonate (e.g. zoledronic acid or pamidronate). Cinacalcet, an oral calcimimetic (agonist of the calcium-sensing receptor), may also be helpful short term to reduce serum calcium levels, although it is not PBS listed for this indication. Denosumab has also been used for hypercalcaemia of malignancy, but is not approved for the treatment of hypercalcaemia.

Long-term medical management

Long-term medical management of patients with PHPT is indicated for those with osteoporosis who are unwilling or unable to undergo parathyroidectomy. Randomised trials have shown that use of oral alendronate improves BMD in patients with PHPT.[19,20] Oestrogen replacement[21] and raloxifene[22] have been shown to increase BMD and marginally reduce serum calcium levels; however, the benefits of these therapies need to outweigh the risks. Cinacalcet is approved (but not PBS listed) for the chronic treatment of moderate to severe hypercalcaemia associated with PHPT in nonsurgical candidates and is the drug of choice in individuals with parathyroid cancer and severe hypercalcaemia.[23-25]





Figures 1a and b. Parathyroid sestamibi study showing a mediastinal parathyroid adenoma in a 61-year-old woman presenting with acute severe hypercalcaemia after previous negative neck exploration. The large parathyroid adenoma was successfully removed via a median sternotomy approach and the patient made an excellent recovery.

Table. Syndromes of familial hyperparathyroidism

Disorder	Responsible gene	Parathyroid gland pathology	Associated clinical features
Multiple endocrine neoplasia (MEN) type 1	*MEN1, CDKN1B*	Multigland hyperplasia/adenoma	Pituitary adenomas Pancreatic neuroendocrine tumours Adrenocortical tumours Gastric and thymic neuroendocrine tumours
MEN type 2A	*RET*	Single or multigland adenomas/ hyperplasia	Medullary thyroid cancer Phaeochromocytoma
MEN type 4	*CDKNB1*	Single or multigland adenoma	Pituitary adenomas
Hyperparathyroidism-jaw tumour syndrome	*CDC73*	Single or double gland adenoma Carcinoma in 10 to 15%	Mandible/maxillary fibromas Renal/uterine tumours
Familial isolated hyperparathyroidism	*MEN1, CDC73, CDKN1B*	Single or multigland adenoma	
Neonatal severe primary hyperparathyroidism	*CASR*	Mildly enlarged/markedly hyperplastic parathyroid glands	Marked hypercalcaemia, hypotonia, respiratory distress
Familial hypocalciuric hypercalcaemia	*CASR, GNA11, AP2S1*	Normal or hyperplasia	Relative hypocalciuria Rarely pancreatitis

Vitamin D replacement

Vitamin D deficiency is more common in patients with PHPT because of conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D and accelerated catabolism of 25-hydroxyvitamin D, which often exacerbates the condition. Vitamin D deficiency has been associated with higher calcium and PTH levels and more severe bone disease. Furthermore, postparathyroidectomy hypocalcaemia and hungry bone syndrome are more common in patients with vitamin D deficiency.

Although vitamin D repletion poses the theoretical risk of worsening hypercalcaemia and hypercalciuria, recent meta-analyses have shown vitamin D replacement in mild PHPT (serum calcium level <3.0 mmol/L) to be safe and followed by a decrease in PTH levels.[26] There are insufficient data on the effect of vitamin D treatment on bone turnover and BMD in PHPT. Serum calcium levels and urinary excretion of calcium should be monitored during repletion.[26] Treatment with calcitriol and calcium is important in the postsurgical setting if hungry bone syndrome is evident.

Rare familial hyperparathyroid syndromes

The presence of a family history of hyperparathyroidism, and/or the discovery of multigland or recurrent disease, should prompt consideration of an underlying familial syndrome (see Table). The presence of a heritable genetic condition is discovered in about 10 to 15% of patients with PHPT who are younger than 50 years;[27,28] conversely, familial hyperparathyroidism rarely presents *de novo* after this age. Genetic counselling and testing is appropriate for adequate follow up of the index case with respect to additional syndromic features and for counselling and predictive testing of family members.

Conclusion

Management of patients with asymptomatic PHPT remains contentious; however, longitudinal data on the natural history as well as cardiovascular, neurocognitive and bone abnormalities are emerging to aid decision making. Guidelines are generally shifting towards a position that 'surgery is indicated unless it is contraindicated'.

The manifestations of PHPT are more severe with coexisting vitamin D deficiency. A number of recent studies suggest that vitamin D supplementation is safe in people with PHPT if serum calcium level is less than 3.0 mmol/L, although urinary calcium may need monitoring if definitive therapy with parathyroidectomy is delayed in this situation.

Preoperative localisation followed by focused minimally invasive parathyroidectomy is the treatment of choice for patients with PHPT, and in expert centres achieves surgical cure in more than 97% of cases. Short-term medical therapy is sometimes used to control severe hypercalcaemia before surgery. Long-term medical therapy may be required for patients if surgery cannot be performed and, in particular, coexisting osteoporosis should be assessed and treated on its own merits. **ET**

References

A list of references is included in the website version (www.medicinetoday.com.au).

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