Primary hyperparathyroidism (PHPT) is diagnosed when there is a raised adjusted calcium level with an inappropriately raised parathyroid hormone (PTH) level (ie, in the upper half or higher than the reference range)\(^1\). Although prevalence figures for PHPT range from 0.1–0.5 per cent in the general population, this increases with age to two per cent above 70 years\(^2\). This may be an underestimate as vitamin D insufficiency can lead to a fall in the calcium level into the reference range, even though PHPT is present\(^3\). In 80–85 per cent of cases PHPT is caused by a solitary adenoma.

The remainder are due to multiple adenomas or hyperplasia of all four glands. Parathyroid gland carcinoma accounts of less than 0.5 per cent of cases\(^4\). The classic symptoms of ‘stones, bones, abdominal groans and psychic moans’ due to hypercalcaemia are becoming less common when PHPT is diagnosed. The vast majority of patients diagnosed with PHPT are asymptomatic or have vague complaints such as generalised weakness, fatigue, sleep disorders and reduced social interaction. However, 24 per cent still experience nephrolithiasis and 38 per cent have evidence of osteoporosis\(^5\).

**The role of surgery**

Few would disagree that the best management for patients with obvious symptoms, associated conditions of PHPT or profound hypercalcaemia, is parathyroidectomy. A complete review of current surgical technique is beyond the scope of this article, but it is worth noting that minimally invasive parathyroidectomy under local anaesthesia is an option for some patients following pre-operative localisation scanning.

One institution that used a handheld gamma probe during surgery, described a case series of 98 patients over the age of 70 years who underwent either open or minimally invasive surgery. The cure rate was 98 per cent in the minimally invasive group compared with 84 per cent in open surgery. The complication rate of five per cent was the same in both groups\(^6\). Complications of parathyroid surgery include compression of the trachea due to haematoma, vocal cord paresis and hypocalcaemia, which can be transient or prolonged. Published cure, morbidity and mortality rates are similar in younger and older patients with PHPT\(^7\), so therefore age alone should not be a barrier for the consideration of surgery in a patient with PHPT.

There is much debate surrounding the issue of whether asymptomatic patients or those with mild symptoms should undergo surgery. When counselling a patient about surgery, it is vital to know the possible consequences if surgery is not
performed. A Danish non-randomised retrospective analysis of 3,123 PHPT patients revealed those patients who had surgery had less fractures and gastric or duodenal ulcers and a lower mortality rate, albeit by 7.2 months compared to those treated conservatively. Otherwise there was no difference between the two groups. Selection bias could have influenced the results, therefore this study should be interpreted cautiously.

Supporting the notion that surgery helps to avoid bone loss and its complications are the results of a prospective study of 121 PHPT patients. There were increments in bone mineral density (BMD) of 12–15 per cent in those who underwent parathyroidectomy, mostly occurring within the first two years. Nevertheless, only 25 per cent of those treated conservatively experienced progressive bone loss. Some authors have also shown the vague symptoms of PHPT do improve following surgery.

The 2002 United States National Institute of Health Workshop on Asymptomatic Primary Hyperparathyroidism concluded that surgery is indicated in the following situations:

- Serum calcium concentration of ≥1.0mg/dL (0.25mmol/L) above the upper limit of the normal 2.20mmol/l–2.60mmol/l — in this case, surgery would be indicated if an adjusted calcium level of 2.85mmol/l;
- Hypercalciuria (urinary calcium excretion >400mg/day [10mmol/day] while eating their usual diet);
- Creatinine clearance that is ≤30 per cent than that of age-matched normal subjects;
- Bone density at the hip, lumbar spine or distal radius that is >2.5 standard deviations below peak bone mass (T score <−2.5);
- Where periodic follow-up will be difficult.

Therefore, if surgery is to be considered in an asymptomatic patient with PHPT, it is important to perform a dual x-ray absorptiometry (DXA) scan and 24 hour urine collection to ascertain if the patient fulfills the above criteria.

### Medical approach to management

There are few non-surgical treatment alternatives for patients who fail surgery, have contraindications to surgery, do not wish to have surgery or do not meet current guidelines for surgery. General measures in managing PHPT include keeping well hydrated, and avoiding immobilisation and thiazide diuretics. There are conflicting schools of thought as to whether dietary calcium intake is important in the management. Regular blood and DXA checks are also important. Various medications have been researched in treating PHPT patients, mainly by using an increase in BMD as one of the primary outcomes, due to the perceived risk that untreated PHPT can lead to osteoporosis.

### Hormone replacement therapy (HRT)

Oestrogens oppose the action of PTH in bone and a study using HRT for four years showed a four to eight per cent gain in BMD at both cortical and trabecular sites, however those patients with PHPT still lost more bone than age-matched controls without PHPT. HRT has been shown to give equivalent results in increasing BMD when compared to surgery with calcium supplementation.

### Raloxifene

Raloxifene is a selective oestrogen receptor modulator, which among its various actions acts as an oestrogen agonist on bone and lipid metabolism. Raloxifene has been shown to increase BMD in patients with PHPT, but any benefit is soon lost after treatment is stopped.

### Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption and may be useful in the long-term control of osteopenia in PHPT patients. The only randomised placebo-controlled trial with a bisphosphonate in patients with PHPT was carried out over a two-year period. Forty-four patients, who had an adjusted calcium level less than 3.12µmol/l and did not have an indication for surgery or refused surgery, were split in two groups, with one receiving 10mg alendronate per day and the other placebo. After one year the placebo group then received the same dose of alendronate.

The trial showed that alendronate increased BMD by 4.92 per cent compared to placebo, but the effect on BMD was greatest in the first 12 months as by the end of the two years both groups had similar BMD. Bone biochemical markers and PTH levels did not change in either of the two groups following treatment and there were no fractures in either group. The study group concluded the alendronate is effective in increasing BMD, but without any difference in
fractures between the two groups, it is difficult to state from this trial whether alendronate offers any clinical advantage. Perhaps, if the trial period between alendronate and placebo had been longer than one year, significant clinical differences may have become apparent.

The only published randomised control trial contrasting bisphosphonates and parathyroidectomy is a study of 22 patients that compared surgery to disodium etidronate. BMD was increased by 20 per cent at the lumbar spine in the surgery cohort compared to 10 per cent in the bisphosphonate group, however total BMD did not change with either treatment\textsuperscript{17}.

Bisphosphonates have also been studied in the acute management of patients with PHPT and a calcium level greater than 2.6mmol/l. A retrospective study of 25 patients found that an infusion of pamidronate or clodronate improved motor function as measured by the functional independence measure (FIM) when the calcium level was at its nadir, but this improvement was short lived and there was no difference between the treatment and control groups at discharge.

It was postulated that a bisphosphonate infusion could be used to determine which patients would benefit from surgery, by observing whose function improved when the serum calcium level returned to normal\textsuperscript{18}. Bisphosphonates lower calcium levels by inhibiting osteoclastic bone resorption, which increases serum calcium levels in response to a rise in PTH levels. They prevent the recruitment of osteoclasts to the surface of bone, their adherence to the bony surface and impede osteoclasts producing the protons necessary for continued bone resorption.

**The future**

PTH glands respond to changes in the calcium level through the calcium sensing receptor. Calcimimetics are a group of compounds that increase the sensitivity of this receptor to calcium and thus could lower calcium and PTH levels. Two compounds, teocalcet and cinacalcet have been studied in small trials in patients with PHPT\textsuperscript{1}. The latest trial involving cinacalcet was a 52-week randomised double-blind placebo-controlled study in patients with mild to moderate PHPT\textsuperscript{19}. In this trial, 78 adult patients with PHPT, aged between 27 and 83 years, with a serum calcium level between 2.57mmol/l and 3.12mmol/l were randomised to receive cinacalcet or placebo.

During the maintenance phase, 73 per cent of the cinacalcet group achieved the primary endpoint of a normal serum calcium level and a decrease from baseline of 0.12mmol/l compared
Key points

- Parathyroid adenoma is the most common cause of primary hyperparathyroidism in the elderly.
- Surgery should be considered in all cases as it is the only curative treatment.
- Bisphosphonates offer short term improvement in motor function and are useful in preventing bone mineral density loss.
- Calcimimetics are a possible alternative to manage these patients medically, but further trials are required.
- At present cinacalcet is only licensed in the UK for the treatment of secondary hyperparathyroidism in renal disease and hypercalcaemia of parathyroid carcinoma.

References


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