# Focus on Primary Hyperparathyroidism – Diagnosis, Management and the Role of Calcimimetics

Satellite Symposium: 'Optimal Management of Primary Hyperparathyroidism: What Is the Latest Evidence?'

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## Abstract

Primary hyperparathyroidism (HPT) is an endocrine disorder characterised by increased serum calcium and inappropriately high parathyroid hormone (PTH). Although identified historically by overt bone disease and kidney stones, following the introduction of routine calcium screening, many patients are now asymptomatic or mildly symptomatic at diagnosis. Diagnosis and management of asymptomatic primary HPT has been addressed by recent guidelines, which note the importance of excluding other potential aetiologies and also present updated surgical criteria for parathyroidectomy. Calcimimetics, such as cinacalcet, are a new option for patients in whom parathyroidectomy is not clinically appropriate or is contraindicated. Clinical trials have shown that cinacalcet can achieve sustained reductions in serum calcium levels in patients with primary HPT. An improved understanding of the pathophysiology of this disorder and new guidelines and pharmacological options have greatly improved the prospects for successful management.



## Keywords

Calcimimetics, calcium-sensing receptor, cinacalcet, Third International Workshop, parathyroid, parathyroidectomy, primary hyperparathyroidism



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## Primary Hyperparathyroidism – An Evolving Disorder

Primary hyperparathyroidism (HPT) is a common endocrine disease characterised by inappropriately high serum levels of parathyroid hormone (PTH) and elevated calcium.[1,2] Indeed, it is the leading cause of hypercalcaemia in outpatients.[3] Depending on severity, it may be accompanied by hypercalcaemic symptoms, nephrolithiasis, hyperparathyroid bone disease, loss of bone mineral density (BMD) and neuromuscular weakness.[1,2,4–6] The main pathologies underlying the disorder are parathyroid adenoma (~85%), hyperplasia (~15%) or carcinoma (~<1%).[2] Data suggest that the incidence of primary HPT increases with age in both sexes, with a peak occurring in women after 50 years of age.[5]

The introduction of routine biochemical screening in the 1970s had a substantial impact on the presentation of primary HPT, changing the clinical profile from kidney stones and overt bone disease to a less defined, more asymptomatic state in those regions where routine screening is available (see *Figure 1*).[1,6] Rates of detection have increased correspondingly, with an initial five-fold rise in the number of patients diagnosed with primary HPT, reflecting the identification of this more mildly symptomatic patient group.[5] However, the term 'asymptomatic' may be misleading as many patients identified through routine screening can have non-specific symptoms such as fatigue, depression and poor general health.[1] Thus, physicians have been faced with several challenges in this disease in recent years, including the initial increase in numbers of patients with primary HPT and questions regarding the optimal management of individuals with asymptomatic/mildly symptomatic disease.

## Treatment Guidelines – An Update

Guidelines for the diagnosis and management of asymptomatic primary HPT from the Third International Workshop have recently been published in the *Journal of Clinical Endocrinology and Metabolism*.[7]

### Diagnosis

When diagnosing patients with primary HPT, multiple factors should be considered, including choice of PTH assay and exclusion of other disorders. While second- and third-generation PTH assays are thought to be similarly effective for the diagnosis of primary HPT, the interpretation of these tests can be complicated by vitamin D insufficiency or deficiency.[7,8] Patients with normal serum calcium and persistent elevations in serum PTH may be diagnosed with normocalcaemic primary HPT, although other conditions such as secondary HPT must be excluded.[4] Once elevations in serum PTH and calcium have been confirmed, other causes of hypercalcaemia, including genetic causes such as familial hypocalciuric hypercalcaemia (FHH), multiple endocrine neoplasias type 1 (MEN1), MEN2 and hyperparathyroidism jaw-tumour syndrome, should be considered. Genetic testing is not recommended on a regular basis; however, it may be beneficial when such causes are suspected.[8] Imaging techniques are unlikely to aid diagnosis.[9]

**Table 1: Comparison of Guideline Indications for Surgery in Asymptomatic Primary Hyperparathyroidism Patients[a,7]**

| Measurement | 1990 | 2002 | 2008 |
|---|---|---|---|
| Serum calcium (>upper limit of normal) | 1–1.6mg/dl (0.25–0.4mmol/l) | 1.0mg/dl (0.25mmol/l) | 1.0mg/dl (0.25mmol/l) |
| 24-hour urine for calcium | >400mg/day (>10mmol/day) | >400mg/day (>10mmol/day) | Not indicated[b] |
| Creatinine clearance (calculated) | Reduced by 30% | Reduced by 30% | Reduced to <60ml/min |
| BMD | Z-score <-2.0 in forearm | T-score <-2.5 at any site[c] | T-score <-2.5 at any site[c] and/or previous fracture fragility[d] |
| Age (years) | <50 | <50 | <50 |

*a. Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible.*
*b. Some physicians still regard 24-hour urinary calcium excretion >400mg as an indication for surgery.*
*c. Lumbar spine, total hip, femoral neck or 33% radius (1/3 site). This recommendation is made recognising that other skeletal features may contribute to fracture risk in primary HPT and the validity of this cut-point for any site vis-à-vis fracture risk prediction has not been established in primary HPT.*
*d. Consistent with the position established by the International Society for Clinical Densitometry, the use of Z-scores instead of T-scores is recommended in evaluating BMD in pre-menopausal women and men under 50 years of age.*
*BMD = bone mineral density; HPT = hyperparathyrodism.*
*Source: Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop,* J Clin Endocrinol Metab, *2009;94:335–9.*


**Figure 1: Changing Presentation of Primary Hyperparathyroidism**

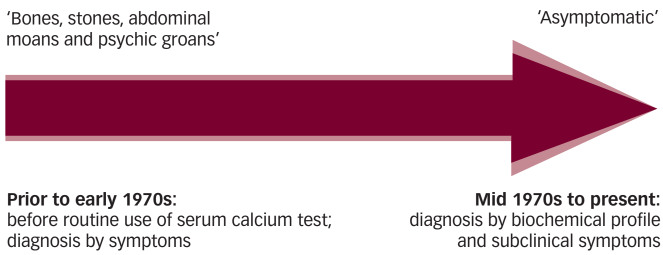
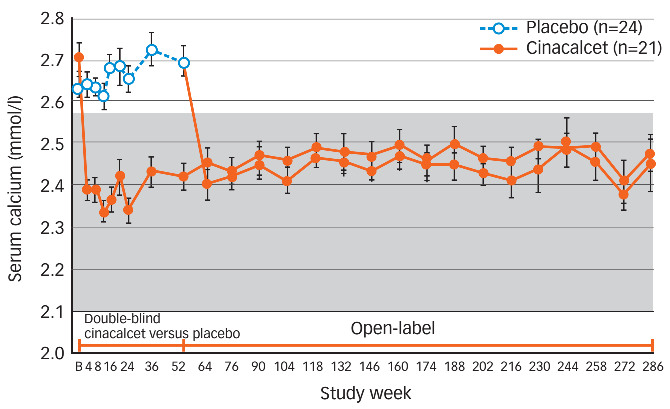



**Table 2: Management Options for Patients with Asymptomatic Primary Hyperparathyroidism[7]**

| Surgery or No Surgery | Recommendations 1990/2002/2008 |
|---|---|
| If no surgery | Monitoring strategy |
| Medical options | Bisphosphonates |
| | HRT and SERMs |
| | Calcimimetics |

*HRT = hormone replacement therapy; SERMs = selective oestrogen receptor modulators.*

**Figure 2: Sustained Reductions in Serum Calcium with Cinacalcet Compared with Placebo[16]**




*B = baseline of initial double-blind study.*
*Normal range (2.1–2.575mmol/l) shaded. n represents the number of subjects at baseline; 30 subjects completed ≥5 years.*
*Reproduced from* J Bone Miner Res, *2006;21:S38, with permission of the American Society for Bone and Mineral Research.*

## Management of Primary Hyperparathyroidism

It is generally accepted that most patients with biochemically confirmed symptomatic primary HPT should undergo parathyroidectomy.[9] This approach may also be beneficial for some patients with asymptomatic primary HPT, particularly as data suggest positive effects on BMD and neurocognitive symptoms following surgery.[9] The guidelines from the Third International Workshop include modified surgical criteria for asymptomatic individuals, with changes from the 2002 guideline including exclusion of 24-hour urine calcium as an indication for surgery (as 24-hour urine calcium is a poor predictor of kidney stones in these patients, is highly variable and is dependent on kidney function, vitamin D status, race and sex),[4,7] amending the creatinine clearance to <60ml/min and adding previous fracture fragility to the BMD indication. Age-based criteria and serum calcium levels remained unchanged (see *Table 1*).[7] Those asymptomatic patients who do not meet the criteria for surgery should be monitored in accordance with the guidelines, or in some cases considered for medical management.[7,10]

## Current Treatment Options

The primary aim of management in primary HPT is to normalise serum calcium levels and reduce excessive PTH levels, leading to improvements in any associated symptoms. It is treated primarily by parathyroidectomy,[9] which is usually curative. However, there are few alternative treatment options for patients who are ineligible for, or unwilling to undergo, surgery and those in whom parathyroidectomy has failed. Current options include bisphosphonates, selective oestrogen receptor modulators (SERMs) and hormone replacement therapy (HRT; off-label use), which inhibit bone resorption and increase BMD without altering calcium, and the recently approved calcimimetic cinacalcet, which reduces serum calcium levels without major changes in BMD (see *Table 2*).[7,10–12]

## Calcimimetics – A New Approach for Primary Hyperparathyroidism

The calcium-sensing receptor (CaSR) is a G-protein-coupled receptor found on various tissues in the human body, including the parathyroid glands.[13] The CaSR plays a key role in regulating extracellular calcium levels by controlling PTH secretion.[14] Calcimimetics, such as cinacalcet, are allosteric regulators of the CaSR, acting to sensitise this receptor to extracellular calcium,[14] therefore representing a logical new approach for the management of primary HPT.

Cinacalcet has been found to be effective in reducing or normalising serum calcium levels in several groups of primary HPT patients, including those with mild to moderate disease, intractable disease and parathyroid carcinoma.[15–18] In a multicentre, randomised, double-blind study in 78 patients with mild to moderate primary HPT,[15] normocalcaemia (serum calcium ≤2.57 mmol/l [10.3mg/dl]) plus a reduction of at least 0.12mmol/l (0.5mg/dl) from baseline was achieved by 73% of patients in the cinacalcet group compared with only 5% of placebo recipients ($p<0.001$). This effect was sustained, with constant serum calcium maintained once steady state was reached. Mean pre-dose serum PTH levels were reduced by approximately 8% in the cinacalcet group but not into the normal range and increased by 8% in the placebo arm. Markers of bone turnover increased slightly in the cinacalcet group, but BMD remained unchanged overall between the treatment arms. Cinacalcet was generally well tolerated with a similar adverse event profile to the placebo group.

A four-year open-label extension study found that cinacalcet was well tolerated and provided long-term control of serum calcium levels. Eighty per cent of patients had serum calcium levels within the normal range at study end (see *Figure 2*), while serum PTH was reduced slightly (9%).[16] Although BMD did not increase, there was no excess bone loss and no evidence that parathyroid gland mass increased. Of particular interest, the dose of cinacalcet remained stable at 30mg twice daily.

In patients with intractable primary HPT (Ca >3.1mmol/l [12.5mg/dl] with no other treatment options),[17] cinacalcet (30mg twice daily, titrated to a maximum of 90mg four times a day) induced marked decreases in serum calcium, with 15 of 17 patients achieving reductions of ≥0.25mmol/l (≥1mg/dl). Importantly, health-related quality of life (HRQoL) also improved.[17] These results led to cinacalcet being approved by European regulatory authorities in 2008 for the treatment of patients with primary HPT for whom parathyroidectomy would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom parathyroidectomy is not clinically appropriate or is contraindicated.[19]

In addition, cinacalcet has been shown to be effective in patients with inoperable parathyroid carcinoma (n=29).[18] Sixty-two per cent of patients had reductions in serum calcium (≥1mg/dl) at the end of the titration period, with the greatest reductions noted in those patients with the highest baseline calcium.[18]

These data indicate that cinacalcet may be of benefit in a wide range of patients with primary HPT, offering a novel alternative option for those who are not able to undergo parathyroidectomy despite meeting the clinical criteria.

## Conclusions

Optimal management of primary HPT is an evolving challenge for physicians, with the changing presentation of this disease leading to questions regarding the most appropriate choice of treatment. The advent of new management guidelines for individuals with asymptomatic primary HPT, as well as novel pharmacological options such as cinacalcet, heralds a positive new era for this patient group. ■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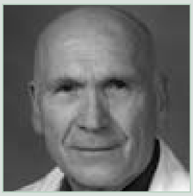

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