'Understanding and Managing Primary Hyperparathyroidism – Anything New?'

Proceedings of a Satellite Symposium

Held during the 12th European Congress of Endocrinology on 26 April 2010, Prague, Czech Republic

Abstract

The endocrine disorder primary hyperparathyroidism (PHPT) is characterised by increased parathyroid hormone (PTH) in association with elevated serum calcium levels. Over the past 30 years, there has been a shift in the clinical presentation of PHPT in the most developed Western countries from a disorder associated with overt skeletal and renal disease, to an asymptomatic form. The latter form has hypercalcaemia and elevated PTH levels, often only detected through routine biochemical screening, sometimes inadvertently. Despite exhibiting few 'traditional' symptoms, some studies suggest that the quality of life of these PHPT patients may be reduced. Subtle neuropsychological and cardiovascular concerns in PHPT, even prior to diagnosis, have a significant impact both on the patients themselves and on the economy through increased time off work. Although asymptomatic, PHPT may remain stable for at least 10 years without intervention. Parathyroidectomy offers the only definitive solution in the longer term. Successful surgery improves bone mineral density and the neurological and psychological symptoms of PHPT; however, it is not always clinically indicated. Medical management is seen as a viable alternative for interim treatment prior to surgery, or for patients unsuitable for, or unwilling to undergo, surgery. Vitamin D supplements, antiresorptives and calcimimetics redress the biochemical imbalances of PHPT – stabilising bone turnover, serum calcium and PTH levels. Targeted pharmacological therapy increases quality of life in patients under non-surgical follow-up and improves general disease management.

Keywords

Asymptomatic primary hyperparathyroidism, medical management, parathyroidectomy, parathyroid hormone, bone disease, quality of life

Speakers: John Bilezikian, Professor of Medicine and Pharmacology, College of Physicians and Surgeons, Columbia University, Chief, Division of Endocrinology and Director, Metabolic Bone Diseases Program, Columbia University Medical Center; Jens Bollerslev, Professor of Endocrinology, University of Oslo, Head of Endocrinology, Rikshospitalet, Oslo University Hospital; and Claudio Marcocci, Associate Professor of Endocrinology and Director, Unit of Endocrinology and Bone Metabolism, University of Pisa.

Disclosure: These proceedings were prepared by Liz Bennett of medcept Ltd, Switzerland, supported by a grant from Amgen (Europe). The symposium was supported by an educational grant from Amgen (Europe), Switzerland.

Received: 18 June 2010 **Accepted:** 30 August 2010 **Citation:** *European Endocrinology*, 2010;6(2):55–8 *DOI: 10.17925/EE.2010.06.02.55*

Support: The publication of this article was funded by Amgen (Europe).

Classic Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is an endocrine disorder characterised by inappropriately high serum levels of parathyroid hormone (PTH) accompanied by hypercalcaemia. PHPT occurs as a direct (primary) consequence of underlying pathologies, e.g. single benign parathyroid adenoma (approximately 80% of cases), hyperplasia (~15–20%) or carcinoma (<1%) of the parathyroid glands.[1] The incidence, up to one in 1,000 individuals, is highest in post-menopausal women and increases with age in both sexes.[1–3] PHPT is a leading cause of hypercalcaemia in the general population.[1] In more severely affected individuals, PHPT is linked to a variety of complications, such as: cardiovascular calcification, bone disease and pathological fractures, kidney stones and damage, gastrointestinal and central nervous system disturbances.[1,4]

Modern Primary Hyperparathyroidism

Once described as a disease of 'bones, stones and psychic groans', PHPT today frequently presents as hypercalcaemia without overt symptoms.[5,6] 'Asymptomatic' PHPT is most often diagnosed through biochemical screening.[5,7–9] Although earlier diagnosis and treatment could be expected to slow PHPT progression, studies on the natural history of the disease suggest that even patients diagnosed and monitored without intervention for a decade or more rarely go on to develop the 'classic' symptoms.[6] This suggests the emergence of a novel PHPT disorder with similar end-organ involvement but different, yet recognisable, manifestations.[6] While PHPT is most frequently diagnosed in the context of asymptomatic hypercalcaemia, it is important to recognise that classic symptomatic PHPT is still prevalent in some parts of the world.[6] Bilezikian et al. described this classic symptomatic presentation in a study comparing two large PHPT-patient cohorts in New York and Beijing.[9] The Beijing patients were younger and much more symptomatic (mean age 37 years, 97% with bone/stone symptoms) than the US subjects (mean age 55 years; 18.4% with bone/stone symptoms). Mean biochemical parameters were far beyond the normal range in the Beijing patients (see *Table 1*), who were also severely vitamin D depleted, aggravating their PHPT symptoms since this leads to even higher PTH levels.[9]

Non-traditional Features of Mild Asymptomatic Primary Hyperparathyroidism and Impact on Quality of Life

Although the 'modern' PHPT phenotype is termed asymptomatic to

Table 1: Divergent Biochemical Profiles of Primary Hyperparathyroidism Patients in Two Cities

Biochemical Parameter	New York	Beijing
Parathyroid hormone (fold increase over normal)	2	21
Calcium (mg/dl)	10.7±0.1	12.4±1.1
Urinary calcium (% over normal)	38	51
Phosphorous (% under normal)	25	60
Alkaline phoshatase (% over normal)	40	80
25-hydroxyvitamin D (ng/ml)	21.0±1.0	8.8±7.2

Source: Bilezikian et al., 2000.[9]

Table 2: Summary of Consensus Guidelines from the 2008 Third International Workshop on Hyperparathyroidism – Criteria for Parathyroidectomy Surgery in Asymptommatic Primary Hyperparathyroidism and Suggested Monitoring Schedule in the Case of Non-surgical Follow-up

Measurement	Parathyroid Surgery	Non-surgical Follow-up[a]
Serum calcium	1.0mg/dl (0.25mmol/l) above upper limit of normal	Annually
24-hour urinary calcium	Not indicated[b]	No longer recommended
Creatinine clearance	Reduced to <60ml/minute	No longer recommended
Serum creatinine	NA	Annually
Bone mineral density	T-score <-2.5 at any site[c] and/or previous fracture fragility[d]	Every 1–2 years 3 sites[e]
Abdominal X-ray (± ultrasound)	NA	No longer recommended
Age (years)	<50	NA

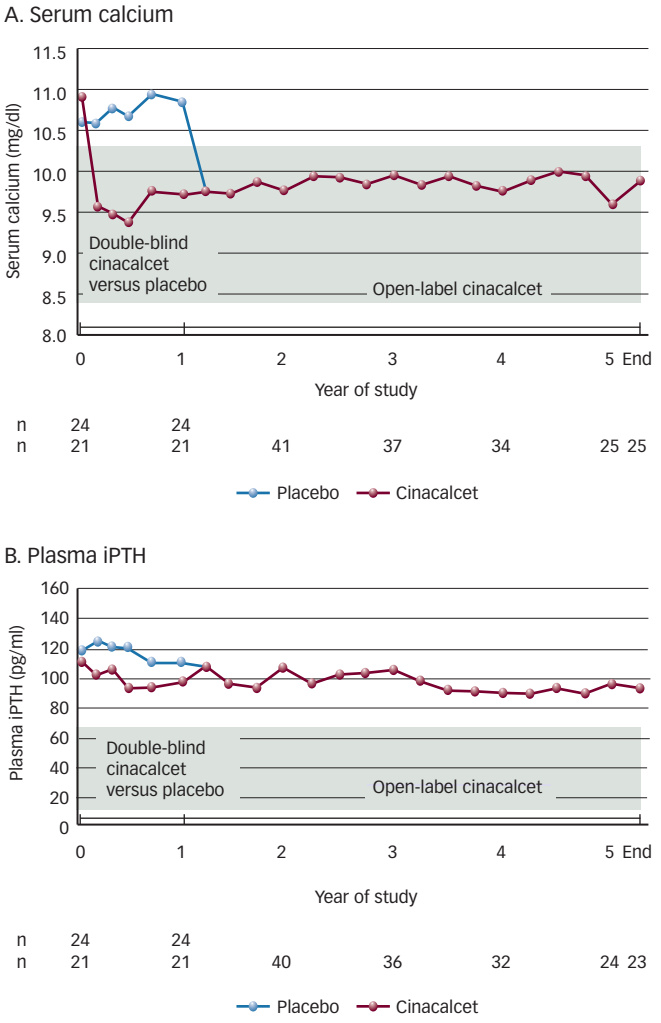
a: Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible; b: Some physicians still regard 24-hour urinary calcium excretion >400mg as an indication for surgery; c: Lumbar spine, total hip, femoral neck or one-third radius site. This recommendation is made recognising that other skeletal features may contribute to fracture risk in primary hyperparathyroidism (PHPT) and that the validity of this cut-off point for any site vis-à-vis fracture risk prediction has not been established in PHPT; d: Consistent with the position established by the International Society for Clinical Densiometry, the use of Z-scores instead of T-scores is recommended in evaluating bone mineral density in pre-menopausal women and men below 50 years of age; e: Three of lumbar spine, total hip, femoral neck or one-third radius. This acknowledges country-specific advisories as well as the need for more frequent monitoring if the clinical situation is appropriate.
NA = not applicable.
Source: Bilezikian et al., 2009.[18]

Table 3: Results from Four Studies Investigating Quality of Life, Neuropsychological and Cognitive Improvements Following Parathyroidectomy in Asymptomatic Primary Hyperparathyroidism

Study	Post-parathyroidectomy Neuropsychological and Cognitive Improvements
Ambrogini et al.[23]	Bodily pain (p=0.001), general health (p=0.008), vitality (p=0.003), mental health (p=0.017)
Bollerslev et al.[24]	None observed
Rao et al.[21]	Social-role function (p=0.007), emotional-role function (p=0.012), anxiety (p=0.003), phobia (p=0.024)
Walker et al.[25]	Depressive symptoms (p=0.024), non-verbal abstraction (p=0.036), immediate/delayed verbal logical memory* (p=0.003/0.009)

**Contextually related material.*

Figure 1: Serum Calcium and Plasma Intact Parathyroid Hormone Levels with Cinacalcet over an Initial One-year Randomised, Placebo-controlled Trial and a 4.5-year Open-label Extension



Pre-dose serum calcium and plasma intact parathyroid hormone (iPTH) levels during the initial trial and the open-label extension (cinacalcet 30mg twice daily).
A: Serum calcium levels (mean ± SE). Shaded region represents normal serum calcium (8.4–10.3mg/dL). B: Plasma iPTH levels (mean ± SE). Shaded region represents normal plasma iPTH (10–65pg/ml). Number of subjects (n) followed during each year of the study is shown in each panel for the placebo (upper row) and cinacalcet-treated groups (lower row). Adapted from Peacock et al., 2009.[35]

differentiate it from the classic symptomatic presentation, the contemporary disease is in fact often associated with neurocognitive problems, e.g. fatigue, irritability, weakness and depression.[4,10] Such non-specific complaints are hard to assess, presenting in other chronic conditions – and also in healthy individuals. These non-traditional features may impact on quality of life (QoL), as well as having a measurable clinical and economic impact. One Swedish study indicated that even prior to diagnosis, PHPT is associated with longer sick leave and almost twice as many health-related retirements as in healthy subjects.[10,11] Morbidity factors must therefore be considered in treatment decisions.

Marked hypercalcaemia in symptomatic PHPT patients has been linked to hypertension and increased mortality.[4] A community-based Scandinavian study, the Uppsala Longitudinal Study of Adult Men, reported a clear association between higher plasma PTH and increased risk of cardiovascular mortality.[12] Currently, adequately

powered and controlled data exploring cardiovascular involvement in mild, asymptomatic PHPT are minimal. Despite this, there is some evidence for subtle cardiovascular changes, including left ventricular hypertrophy, carotid-artery intimal thickening and vascular stiffening.[4,13–16]

Natural Progression of Asymptomatic Primary Hyperparathyroidism

Rubin et al. followed 116 asymptomatic PHPT patients for 15 years with and without parathyroidectomy (PTx).[17] Biochemical and densitometric data from non-surgical patients indicate stability for around a decade; however, this is not indefinite.[17] Deterioration was observed within 15 years, with bone loss particularly apparent at the femoral neck and distal one-third radius, highlighting the importance of regular monitoring (see guidelines in *Table 2*).[17,18] The observational nature of the study and low number of patients completing the 15-year period means that the results require cautious interpretation.[4,17] Currently, there are insufficient data to comment on the natural progression and management of the recently described normocalcaemic PHPT (i.e. PHPT presenting with normal serum calcium levels).[4,18,19]

Treatment during the Asymptomatic Phase

Asymptomatic PHPT brings with it new challenges, particularly in terms of treatment strategies. The aim of PHPT treatment remains to normalise serum calcium and PTH levels and improve any symptoms of disease. In symptomatic patients, PTx is the only definitive treatment for PHPT.[18] While it is reasonable to consider PTx in all patients,[20] advocating surgery in patients who are outwardly healthy and symptom-free is less straightforward.[21]

PTx can successfully normalise biochemical markers in up to 95% of patients.[22] Bone mineral density (BMD) increases at the distal radius, lumbar spine and hip have been shown to persist 15 years later.[17] Several studies also support psychological improvements (measured using either the Symptom Checklist 90 or the Comprehensive Pathological Rating Scale) and increased QoL (measured with a 36-question health survey) following PTx.[18,21,23–25] Despite this, no correlation between test parameters and serum calcium/PTH levels was reported (see *Table 3*).[18,21,23–25]

While growing evidence supports the reversal of skeletal and psychological PHPT symptoms after PTx, the results of other studies are contradictory.[26] These inconsistencies and the limited data available mean that alteration of treatment guidelines is not yet warranted.[27]

Targeted Medical Management

Where PTx is not a clear option, non-surgical follow-up can be sustained for up to eight years with appropriate biochemical and densitometric monitoring (for a recommended follow-up schedule and PTx criteria see *Table 2*).[4,18] In other patients, surgery may be contraindicated or the patient may not consent. Such patients must likewise be frequently monitored and dietary intake of vitamin D and calcium managed.[18] In a short pilot study, vitamin D supplementation was shown to reduce PTH levels and decrease bone turnover without exacerbating hypercalcaemia.[28] More specifically targeted medical management addresses the pathophysiological features of PHPT, including antiresorptives or calcimimetics.[18]

Antiresorptives provide skeletal protection, counteracting damage due to bone loss caused by PHPT. For example, hormone-replacement therapy is effective at increasing BMD in post-menopausal women with PHPT and limits the damaging effects of osteopenia.[29] Alendronate is another widely-used, potent, antiresorptive bisphosphonate. It inhibits osteoclast-mediated bone resorption and suppresses bone turnover.[30] In a two-year placebo-controlled trial, patients with asymptomatic PHPT (n=44) receiving alendronate treatment showed sustained gains in BMD at the lumbar spine and hip compared to baseline.[31]

An additional target for the medical management of PHPT is the modulation of calcium homeostasis.[18] The calcimimetic cinacalcet is the only therapy approved in Europe for the reduction of hypercalcaemia in patients with PHPT who are unsuitable candidates for PTx, despite meeting clinical criteria.[32] As an allosteric modulator of the calcium-sensing receptor, cinacalcet increases the intracellular calcium concentration, thereby reducing PTH release by the parathyroid gland.[33] Cinacalet has been shown in a placebo-controlled clinical study to achieve long-term reduction in serum calcium and PTH levels in patients with mild PHPT compared with placebo (see *Figure 1*).[34] BMD was unchanged by cinacalcet; however, serum levels of bone turnover markers increased ($p<0.05$).[34] These results have been maintained for up to 5.5 years of treatment.[35]

Conclusions

Asymptomatic PHPT poses new therapeutic challenges and further research is warranted. Optimal treatment strategies are supported by comprehensive and regularly updated consensus guidelines for both surgical intervention and the increasingly available pharmacological options. ■

John Bilezikian is a Professor of Medicine and Pharmacology at the College of Physicians and Surgeons, Columbia University, and Chief of the Division of Endocrinology and Director of the Metabolic Bone Diseases Program at Columbia University Medical Center. His major research interests include the clinical investigation of metabolic bone diseases, particularly osteoporosis and primary hyperparathyroidism. He is Senior Associate Editor of the *Journal of Bone and Mineral Research*.

Jens Bollerslev is Head of Endocrinology at Rikshospitalet at Oslo University Hospital and Professor of Endocrinology at the University of Oslo. His scientific interests include bone metabolism, monogenetic disorders of bone metabolism and neuroendocrinology, especially acromegaly and growth hormone deficiency. For many years he has been interested in the treatment of borderline primary hyperparathyroidism and he initiated a randomised Scandinavian study on the effect of surgery versus conservative observation. The first results from this study have recently been published.

Claudio Marcocci is an Associate Professor of Endocrinology in the Department of Endocrinology and Metabolism at the University of Pisa and Director of the Unit of Endocrinology and Bone Metabolism at the University Hospital of Pisa. His major research interests are parathyroid and thyroid diseases, particularly primary hyperparathyroidism and Graves' orbitopathy.

1. Rubin MR, Silverberg SJ, Editorial: HRPT2 in parathyroid cancer: a piece of the puzzle, *J Clin Endocrinol Metab*, 2005;90:5505–7.
2. Lundgren E, Lind L, Palmer M, et al., Increased cardiovascular mortality and normalized serum calcium in patients with mild hypercalcemia followed up for 25 years, *Surgery*, 2001;130:978–85.
3. Adami S, Marcocci C, Gatti D, Epidemiology of primary hyperparathyroidism in Europe, *J Bone Miner Res*, 2002;17 (Suppl 2):N18–23.
4. Silverberg SJ, Lewiecki EM, Mosekilde L, et al., Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop, *J Clin Endocrinol Metab*, 2009;94:351–65.
5. Albright F, Reifenstein EC, *The Parathyroid Glands and Metabolic Bone Disease*, Williams and Wilkins Co, Baltimore, 1948.
6. Silverberg SJ, Bilezikian JP, The diagnosis and management of asymptomatic primary hyperparathyroidism, *Nat Clin Pract Endocrinol Metab*, 2006;2:494–503.
7. Wermers RA, Khosla S, Atkinson EJ, et al., The rise and fall of primary hyperparathyroidism: a population-based study in Rochester, Minnesota, 1965-1992, *Ann Intern Med*, 1997;126:433–40.
8. Wermers RA, Khosla S, Atkinson EJ, et al., Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993-2001: an update on the changing epidemiology of the disease, *J Bone Miner Res*, 2006;21:171–7.
9. Bilezikian JP, Meng X, Shi Y, et al., Primary hyperparathyroidism in women: a tale of two cities-New York and Beijing, *Int J Fertil Womens Med*, 2000;45:158–65.
10. Lundgren E, Ljunghall S, Akerström G, et al., Case-control study on symptoms and signs of 'asymptomatic' primary hyperparathyroidism, *Surgery*, 1998;124:980–5.
11. Lundgren E, Szabo E, Ljunghall S, et al., Population based case-control study of sick leave in postmenopausal women before diagnosis of hyperparathyroidism, *BMJ*, 1998;317:848–51.
12. Hagström E, Hellman P, Larsson TE, et al., Plasma parathyroid hormone and the risk of cardiovascular mortality in the community, *Circulation*, 2009;119:2765–71.
13. Fallo F, Camporese G, Capitelli E, et al., Ultrasound evaluation of carotid artery in primary hyperparathyroidism, *J Clin Endocrinol Metab*, 2003;88:2096–9.
14. Piovesan A, Molineri N, Casasso F, et al., Left ventricular hypertrophy in primary hyperparathyroidism. Effects of successful parathyroidectomy, *Clin Endocrinol (Oxf)*, 1999;50:321–8.
15. Rubin MR, Maurer MS, McMahon DJ, et al., Arterial stiffness in mild primary hyperparathyroidism, *J Clin Endocrinol Metab*, 2005;90:3326–30.
16. Walker MD, Fleischer J, Rundek T, et al., Carotid vascular abnormalities in primary hyperparathyroidism, *J Clin Endocrinol Metab*, 2009;94:3849–56.
17. Rubin MR, Bilezikian JP, McMahon DJ, et al., The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years, *J Clin Endocrinol Metab*, 2008;93:3462–70.
18. Bilezikian JP, Khan AA, Potts JT, Jr, Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop, *J Clin Endocrinol Metab*, 2009;94:335–9.
19. Bilezikian JP, Rubin M, Silverberg SJ, Asymptomatic primary hyperparathyroidism, *Arq Bras Endocrinol Metabol*, 2006;50:647–56.
20. Khan AA, Bilezikian JP, Potts JT Jr, The diagnosis and management of asymptomatic primary hyperparathyroidism revisited, *J Clin Endocrinol Metab*, 2009;94:333–4.
21. Rao DS, Phillips ER, Divine GW, et al., Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism, *J Clin Endocrinol Metab*, 2004;89:5415–22.
22. Hedbäck G, Odén A, Recurrence of hyperparathyroidism; a long-term follow-up after surgery for primary hyperparathyroidism, *Eur J Endocrinol*, 2003;148:413–21.
23. Ambrogini E, Cetani F, Cianferotti L, et al., Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial, *J Clin Endocrinol Metab*, 2007;92:3114–21.
24. Bollerslev J, Jansson S, Mollerup CL, et al., Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective, randomized trial, *J Clin Endocrinol Metab*, 2007;92:1687–92.
25. Walker MD, McMahon DJ, Inabnet WB, et al., Neuropsychological features in primary hyperparathyroidism: a prospective study, *J Clin Endocrinol Metab*, 2009;94:1951–8.
26. Hedback G, Tisell LE, Bengtsson BA, et al., Premature death in patients operated on for primary hyperparathyroidism, *World J Surg*, 1990;14:829–35.
27. Udelsman R, Pasieka JL, Sturgeon C, et al., Surgery for asymptomatic primary hyperparathyroidism: proceedings of the third international workshop, *J Clin Endocrino Metab*, 2009;94:366–72.
28. Grey A, Lucas J, Horne A, et al., Vitamin D repletion in patients with primary hyperparathyroidism and coexistent vitamin D insufficiency, *J Clin Endocrinol Metab*, 2005;90:2122–6.
29. Orr-Walker BJ, Evans MC, Clearwater JM, et al., Effects of hormone replacement therapy on bone mineral density in postmenopausal women with primary hyperparathyroidism: four-year follow-up and comparison with healthy postmenopausal women, *Arch Intern Med*, 2000;160:2161–6.
30. Chesnut CH 3rd, McClung MR, Ensrud KE, et al., Alendronate treatment of the postmenopausal osteoporotic woman: effect of multiple dosages on bone mass and bone remodeling, *Am J Med*, 1995;99:144–52.
31. Khan AA, Bilezikian JP, Kung AW, et al., Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial, *J Clin Endocrinol Metab*, 2004;89:3319–25.
32. Amgen, *Mimpara Summary of Product Characteristics (SmPC)*, EMEA, 2010.
33. Marcocci C, Chanson P, Shoback D, et al., Cinacalcet reduces serum calcium concentrations in patients with intractable primary hyperparathyroidism, *J Clin Endocrinol Metab*, 2009;94:2766–72.
34. Peacock M, Bilezikian JP, Klassen PS, et al., Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism, *J Clin Endocrinol Metab*, 2005;90:135–41.
35. Peacock M, Bolognese MA, Borofsky M, et al., Cinacalcet treatment of primary hyperparathyroidism: biochemical and bone densitometric outcomes in a five-year study, 2009;94:4860–7.