New perspectives in the management of primary hyperparathyroidism

Ther Adv Endocrinol Metab
(2010) 1(5) 197–205
DOI: 10.1177/2042018810382326

John Ayuk, Mark S. Cooper and Neil J. L. Gittoes

***Abstract*:** Primary hyperparathyroidism (PHPT) is a biochemical syndrome caused by the inappropriate or unregulated overproduction of parathyroid hormone, leading to hypercalcaemia. It was previously considered a relatively rare disorder, with clinical manifestations dominated by renal and/or bone disease. However, in modern times the diagnosis is most frequently recognized coincidentally on biochemical testing in patients evaluated for unrelated complaints. Parathyroidectomy is the only curative treatment for PHPT, with improved outcomes in symptomatic patients following this procedure. However, surgical intervention in patients with no clear clinical features remains controversial. The National Institutes for Health (NIH) have developed consensus guidelines giving specific indications for when surgery is recommended in patients with asymptomatic PHPT. This article examines the impact of treatment on asymptomatic PHPT, focusing on bone disease, neurocognitive function, quality of life, cardiovascular disease and mortality. Medical treatment options, including bisphosphonates and cinacalcet, are also discussed.

***Keywords*:** cinacalcet, hypercalcaemia, parathyroidectomy, primary hyperparathyroidism

Introduction

Primary hyperparathyroidism (PHPT) is a biochemical syndrome caused by the inappropriate or unregulated overproduction of parathyroid hormone (PTH) by one or more of the four parathyroid glands in the absence of a recognized stimulus, leading to hypercalcaemia. Most cases are sporadic and caused by a single parathyroid adenoma (85–95%) or multigland disease (5–10%), with parathyroid carcinoma accounting for <1% [Sitges-Serra and Bergenfelz, 2007].

PHPT was previously considered a relatively rare disorder, with clinical manifestations dominated by renal and/or bone disease. However, the introduction of automated multichannel biochemical analysers in the 1970s has meant that in modern times the diagnosis is most frequently recognized coincidentally on biochemical testing in patients evaluated for unrelated complaints. The annual incidence of PHPT is thought to be around 20 cases per 100,000 [Wermers *et al.* 2006], although the prevalence does vary depending on the populations studied and detection methods used [Fraser, 2009]. Classical skeletal complications (osteitis fibrosa cystica) are now present in <5% of newly presenting patients and the incidence of renal stones has fallen to around 15–20% [Silverberg *et al.* 1990].

Parathyroidectomy is the only curative treatment for PHPT, with experienced surgeons achieving first-time cure rates in >95% of cases [Udelsman, 2002]. Modern imaging techniques to localize parathyroid adenomas (e.g. ultrasound scan/sestamibi) and a radical change in operative techniques (e.g. minimally invasive parathyroidectomy) make surgery a quick, low-morbidity approach to managing PHPT [Udelsman *et al.* 2009]. In symptomatic patients, cohort studies have demonstrated that after parathyroidectomy, fracture rate declines, the incidence of kidney stones declines, cognitive function appears to improve and cardiovascular disease rates and premature death also appear to decrease [Udelsman *et al.* 2009; Mollerup *et al.* 2002; Vestergaard *et al.* 2000; Khosla *et al.* 1999]. For these reasons, if no contraindications exist, all patients with symptomatic PHPT or in whom there is evidence of end-organ disease should be referred for surgical treatment.

However, the clinical profile of PHPT has shifted from a symptomatic disorder with

Correspondence to:
Dr Neil J. L. Gittoes, PhD, FRCP
Department of Endocrinology, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, UK
neil.gittoes@uhb.nhs.uk

John Ayuk, MD, MRCP
Department of Endocrinology, Queen Elizabeth Hospital, Edgbaston, Birmingham B15 2TH, UK

Mark S. Cooper, PhD MRCP
Centre for Endocrinology, Diabetes and Metabolism, University of Birmingham, Edgbaston, Birmingham B15 2TH, UK

hypercalcaemia-related symptoms, kidney stones and overt bone disease, to a fairly mild asymptomatic condition, and there remains controversy concerning surgical intervention in patients with no clear clinical features. Some clinicians believe asymptomatic patients with no complications can be managed nonsurgically, while others believe virtually all patients should undergo parathyroidectomy. This article examines the contemporary management of patients with mild PHPT.

Consequences of untreated asymptomatic PHPT

Developing robust clinical guidelines for the management of asymptomatic PHPT requires a good understanding of the natural history of the disease. However, high-quality data in this area is lacking. A prospective study published in 1999 reported no significant change in serum calcium concentration, urinary calcium excretion and bone mineral density (BMD) after 10 years in 52 patients with asymptomatic PHPT who did not undergo parathyroidectomy [Silverberg *et al.* 1999b]. However, the same group have recently published 15-year follow-up data in the same cohort of patients, reporting a significant increase in serum calcium concentration compared with baseline, along with a 10% decline in BMD at one or more sites, although lumbar spine BMD remained unchanged [Rubin *et al.* 2008]. In addition, there was progression of PHPT in 37% of patients over the 15 years of observation to the point that criteria for surgery were met.

Other studies have examined the impact of asymptomatic PHPT on BMD, renal function, quality of life (QOL), cardiovascular disease and cancer.

The impact of asymptomatic PHPT on BMD and fracture risk

A small number of studies have prospectively examined densitometric changes in treated and untreated asymptomatic PHPT. In a randomized controlled trial of parathyroidectomy *versus* observation, Rao and colleagues found that in 28 patients followed up without surgery, there was loss of BMD at the femoral neck (−0.4% per year) and total hip (−0.6% per year), but not at the spine or forearm [Rao *et al.* 2004]. In 25 patients managed surgically, following parathyroidectomy there was an increase in BMD of the spine, femoral neck, total hip and forearm. Similar findings were reported in two recent randomized controlled trials comprising 191 patients [Bollerslev *et al.* 2007] and 50 patients [Ambrogini *et al.* 2007] with asymptomatic PHPT randomized to surgery or observation. Bollerslev and colleagues reported a significant increase in BMD compared with baseline at the lumbar spine following surgery, with a similar trend at the femoral neck [Bollerslev *et al.* 2007]. BMD remained stable in the observation group. At 1 year, Ambrogini and colleagues observed a statistically significant change in lumbar spine and total hip BMD between the parathyroidectomy and observation groups [Ambrogini *et al.* 2007]. There was no difference in distal radius BMD between the two groups.

The longest study of the natural history of asymptomatic PHPT is a prospective observational study with 15-year follow up [Rubin *et al.* 2008]. A 10% decline in BMD at one or more sites was observed in patients managed without surgery, although lumbar spine BMD remained unchanged. In patients who underwent parathyroidectomy, there was a postsurgical improvement in BMD at all sites (lumbar spine, femoral neck and distal radius). BMD increased and remained above the 10% line for 15 years after surgery.

There are no controlled studies on the risk of fracture in asymptomatic PHPT patients. However, cohort and population studies suggest that fracture risk is increased up to 10 years before diagnosis and treatment of PHPT (relative risk up to 1.8) [Vestergaard and Mosekilde, 2003; Vestergaard *et al.* 2000], suggesting fracture risk may be increased in undiagnosed, asymptomatic PHPT patients. The impact of surgery on this potential increased fracture risk remains to be elucidated.

The impact of asymptomatic PHPT on cardiovascular morbidity and mortality

There is considerable debate regarding the cardiovascular manifestations of PHPT. Population and cohort studies have demonstrated that both serum calcium and PTH are independent risk factors for coronary artery disease in subjects without PHPT [Kamycheva *et al.* 2004; Lind *et al.* 1997].

A number of studies suggest patients with moderate to severe PHPT may have an increased risk of coronary artery disease that appears to decrease after successful parathyroidectomy, but

there are no data in mild PHPT [Nilsson *et al.* 2005; Vestergaard *et al.* 2003]. Left ventricular hypertrophy (LVH) is a strong predictor of cardiovascular mortality and a positive correlation with PTH, independent of hypertension, has been identified in many studies of PHPT [Almqvist *et al.* 2002; Piovesan *et al.* 1999]. Some studies, but not all, have demonstrated a reduction in LVH following successful parathyroidectomy [Almqvist *et al.* 2002; Piovesan *et al.* 1999]. Again, data are lacking in patients with mild PHPT.

Hypertension, cardiac valvular calcification, myocardial calcification, cardiac conduction abnormalities and arrhythmias have all been documented in patients with severe PHPT [Silverberg *et al.* 2009]. However, apart from hypertension, there are no studies demonstrating these features in patients with mild PHPT.

Increased peripheral vascular resistance is an independent marker of cardiovascular risk. A small number of studies have reported increased vascular stiffness in patients with mild PHPT [Rubin *et al.* 2005; Smith *et al.* 2000]. One study demonstrated that 15% of the variance in the difference between the second and first systolic peaks in the pressure waveform of the radial artery was uniquely accounted for by the presence of PHPT [Rubin *et al.* 2005]. PHPT was a stronger predictor of arterial stiffness than traditional risk factors such as age, smoking and hypertension. Interestingly there was a strong positive correlation between PTH and arterial stiffness, suggesting that mild asymptomatic PHPT may represent a prominent risk factor for arterial stiffness, which in turn is a predictor of early cardiovascular pathology. The effect of successful parathyroidectomy on arterial stiffness is unknown.

An increase in cardiovascular mortality has been documented in some studies in patients with severe and moderately severe PHPT [Hedback *et al.* 1990; Palmer *et al.* 1987], but not in patients with mild disease [Wermers *et al.* 1998; Soreide *et al.* 1997]. Hedback and colleagues demonstrated improved survival following surgical intervention [Hedback *et al.* 1990]. The higher mortality rate declined with time from parathyroidectomy, but persisted long after surgical cure, suggesting that PHPT may cause enduring damage to the cardiovascular system [Silverberg *et al.* 2009; Hedback *et al.* 1990].

Mild PHPT and cancer incidence

An almost twofold increased incidence of malignant tumours has been reported in patients with PHPT compared with matched controls [Wajngot *et al.* 1980; Farr *et al.* 1973]. However bias may be present due to a number of factors; some patients may have endocrine tumour syndromes that have PHPT as a feature; in addition, an underlying malignancy is often a prompt for biochemical testing during which incidental PHPT might be detected, and patients with hypercalcaemia detected unexpectedly are likely to undergo detailed assessments for underlying malignancy [Gittoes and Cooper, 2010].

The impact of asymptomatic PHPT on neurocognitive function/QOL

Neurological and neuropsychiatric symptoms have been described in classical PHPT [Coker *et al.* 2005; Fitz and Hallman, 1952], but it remains unclear to what extent they are present in the mild form of PHPT seen commonly today. Neurological and neuropsychiatric symptoms are especially difficult to define and investigate in mild PHPT. Some studies have demonstrated improvements in QOL [Quiros *et al.* 2003; Pasieka *et al.* 2002; Sheldon *et al.* 2002], but others have not [Chiang *et al.* 2005; Brown *et al.* 1987]. Potential reasons for the inconsistent results include the observational nature of many of the studies, small sample sizes, the inclusion of subjects with symptomatic hyperparathyroidism, lack of appropriate control groups and testing at short intervals after parathyroidectomy [Silverberg *et al.* 2009].

In recent years, three randomised studies of surgery *versus* observation, specifically conducted in patients with mild PHPT and addressing aspects of neuropsychiatric function, have been published. In 53 patients randomised to surgery or observation, Rao and colleagues found that QOL scores measured using the Short Form 36-item (SF-36) general health survey showed significant decline in five of the nine domains (social functioning, physical problem, emotional problem, energy and health perception) in patients followed up without surgery, but in only one of the nine domains (physical function) in the patients who had parathyroidectomy [Rao *et al.* 2004]. These findings suggest a modest measurable benefit of parathyroidectomy in social and emotional role function. Psychological function as assessed by the Symptom Checklist 90 (SCL-90) scale did not change significantly in either

group, except for a decline in anxiety and phobia in patients who had surgery in comparison with those who did not. More recently, in a cohort of 191 patients with mild PHPT randomized to medical observation or surgery, Bollerslev and colleagues found significantly lower QOL and more psychological symptoms compared with age- and sex-matched healthy subjects [Bollerslev *et al.* 2007]. Both groups were similar at baseline, and no clinically significant changes in these parameters were seen during the 2-year observation period. Another randomized controlled trial of surgery *versus* observation in 50 patients assessed QOL and psychosocial well-being using SF-36 and SCL-90 at baseline and after 1 year of follow up [Ambrogini *et al.* 2007]. A modest but significant beneficial effect on QOL (bodily pain, general health, vitality and mental health) was observed in the parathyroidectomy group compared with the observation group.

Overall, the findings of these studies are inconsistent and the available data remain incomplete on the precise nature and reversibility of neuropsychological symptoms following surgery for mild PHPT. However, some of the data support a modest beneficial effect of parathyroidectomy on QOL and psychological functioning [Silverberg *et al.* 2009].

The impact of asymptomatic PHPT on survival

A number of large population-based cohort studies have demonstrated that patients with PHPT appear to be at risk of premature death [Hedback and Oden, 1998; Palmer *et al.* 1987], with a 50% increase in mortality, predominantly due to cardiovascular disease. However, these data were not specifically derived from asymptomatic patients. Wermers and colleagues examined outcome in an unselected cohort of patients with predominantly uncomplicated, asymptomatic PHPT [Wermers *et al.* 1998]; overall survival was not reduced, compared with age- and gender-matched controls. Although patients in the highest quartile of serum calcium levels had significantly worse survival than patients in the three lower quartiles, even in this group, compared with age- and gender-matched controls, there was only a trend towards reduced survival in the patients who did not undergo surgery. Based on these data, the authors concluded that the current practice of observing patients with uncomplicated mild PHPT does not compromise survival.

Thresholds for surgery in asymptomatic PHPT

Parathyroidectomy is the only cure for PHPT and should be recommended in all patients with symptomatic PHPT or evidence of end-organ damage such as low BMD or kidney stones. However considerable controversy exists regarding the need for surgery in asymptomatic patients [Silverberg *et al.* 1999a]. New data on the natural history of asymptomatic PHPT have demonstrated a small but significant rise in serum corrected calcium and a significant fall in BMD over time, particularly at sites rich in cortical bone, after 15 years of observation [Rubin *et al.* 2008]. In patients managed surgically there was an initial rise and then maintenance of BMD. Importantly, approximately a third of the 49 initially asymptomatic patients eventually developed conventional indications for surgery. In addition, a number of randomized controlled trials of parathyroidectomy *versus* observation in patients with asymptomatic PHPT have demonstrated improvements in BMD, neurocognitive function and QOL [Ambrogini *et al.* 2007; Bollerslev *et al.* 2007; Rao *et al.* 2004].

The National Institutes for Health (NIH) have developed consensus guidelines, most recently updated in 2009 [Bilezikian *et al.* 2009], giving specific indications for when surgery is recommended in patients with asymptomatic PHPT (Table 1).

The consensus guidelines also recommend a structured conservative follow-up protocol for patients who do not fulfil the guidelines for surgery (Table 2) and advice regarding hydration status and symptom recognition. It is in this situation that the potential benefits of a permanent cure need to be balanced against the risks of surgery. A particular concern is that mild disease will progress to disease fulfilling surgical criteria at a time when the patient's fitness for surgery has decreased.

Medical management of PHPT

Although surgery is the only cure for PHPT, medical treatments can be considered for patients who do not fulfil criteria for surgery or those who are unsuitable for or decline surgery. Bisphosphonates and hormone replacement therapy (HRT) are treatment options for those individuals with PHPT for whom the primary goal is skeletal protection, whilst the calcimimetic cinacalcet effectively lowers serum calcium and PTH levels in PHPT.

Table 1. National Institutes for Health consensus guidelines for surgery in asymptomatic primary hyperparathyroidism. (Adapted from Bilezikian *et al.* [2009]).

Age	<50
Serum calcium	>0.25 mmol/l (>1 mg/dl) above upper limit of normal
Estimated glomerular filtration rate (eGFR) reduced to <60 ml/min	
Bone mineral density (by DEXA)	*T*-score <−2.5 at any site, and/or fragility fracture
Medical follow up	Undesired or impractical

DEXA, dual-energy X-ray absorptiometry; eGFR, estimated glomerular filtration rate.

Table 2. Monitoring protocol for patients with asymptomatic primary hyperparathyroidism. (Adapted from Bilezikian *et al.* [2009]).

Review of symptoms	6–12 monthly
Serum calcium	6–12 monthly
Serum creatinine (and eGFR)	12 monthly
Bone density (hip, spine and forearm)	Every 2 years

eGFR, estimated glomerular filtration rate.

Intravenous and oral bisphosphonates may cause a transient reduction in serum calcium, but are not effective in maintaining lower serum calcium levels in patients with PHPT in the long term [Fraser, 2009]. However, they can prove useful in managing the bone disease associated with PHPT. Alendronate is the most extensively studied bisphosphonate in PHPT and has been shown to significantly increase BMD in the lumbar spine and femoral neck in patients treated for up to 2 years [Fraser, 2009; Chow *et al.* 2003; Parker *et al.* 2002]. The findings of these studies suggest that bisphosphonates, in particular alendronate, may be useful in the treatment of bone disease associated with PHPT when parathyroidectomy is not recommended or possible. However, there are no data demonstrating the BMD changes reflect a reduced fracture risk.

In postmenopausal women with PHPT, HRT has been shown to have beneficial effects on BMD at multiple sites throughout the skeleton, similar to those reported in eucalcaemic women treated with HRT [Grey *et al.* 1996]. These effects are maintained for up to 4 years [Orr-Walker *et al.* 2000]. Two nonrandomized studies have examined the effects of HRT *versus* parathyroidectomy in postmenopausal women with PHPT [Diamond *et al.* 1996; Guo *et al.* 1996]. Both interventions produced similar positive effects on axial BMD. In the time since most of these studies were performed, the Women's Health Initiative (WHI) study has raised concerns about the overall safety profile of HRT [Udell *et al.* 2006], dramatically altering its use as a bone protection agent. HRT would therefore now not normally be considered in this setting, especially given the possible increased risk of cardiovascular disease in patients with PHPT.

Extracellular ionised calcium regulates PTH secretion via the calcium sensing receptor (CaSR). Stimulation of the CaSR results in inhibition of PTH gene transcription, reduced PTH secretion and reduced parathyroid cell proliferation. Cinacalcet is an orally active calcimimetic which acts by modifying the CaSR, causing downstream (calcium-like) effects without having true calcium effects peripherally. By mimicking the action of extracellular calcium on the CaSR, cinacalcet blocks PTH secretion. Studies in humans have demonstrated that cinacalcet lowers PTH levels and improves calcium/phosphate homeostasis in patients with primary and secondary hyperparathyroidism [Block *et al.* 2004; Peacock, 2004]. In a double-blind, randomized, placebo-controlled study, Peacock reported normalization of serum calcium in 73% of patients treated with cinacalcet, compared with 5% of placebo-treated patients [Peacock, 2004]. PTH decreased by 7.6% in the cinacalcet group, but increased by 7.7% in the placebo group. There were no significant differences in 24-hour urinary calcium levels between the cinacalcet- and placebo-treated patients. Some bone turnover markers did increase significantly in the cinacalcet group compared with placebo, but the mean values

remained within the normal range. Hip and forearm BMD were in the osteopaenic range, and remained unchanged throughout the study in both groups. An open-label extension of this study was reported recently, in which 45 subjects from both groups were treated with 30 or 50 mg of cinacalcet twice daily for up to four and a half years [Peacock *et al.* 2009]. Cinacalcet normalized serum calcium in all patients, and maintained eucalcaemia for the duration of the study. Plasma PTH levels reduced substantially, especially in the latter years, but did not normalize. Mean BMD remained in the normal range (*Z*-scores of −1 to +1) for the length of the study with no improvements in BMD observed when expressed as mean change from parent study baseline at the spine, wrist, femoral neck and total femur. A review of studies on the use of cinacalcet in PHPT has confirmed these findings, reporting that cinacalcet effectively lowers serum calcium and PTH levels but does not alter bone turnover or increase BMD [Khan *et al.* 2009].

Despite cinacalcet's beneficial effects on serum calcium and PTH levels in patients with PHPT, no data exist on hard endpoints such as fractures, kidney stones or cardiovascular disease. QOL has been assessed in a study of 17 patients with persistent PHPT after parathyroidectomy or with contraindications to parathyroidectomy that were treated with cinacalcet [Marcocci *et al.* 2009]; using the SF-36 and Medical Outcomes Study (MOS) Cognitive Functioning scales, the authors found that cinacalcet treatment was associated with improved functional status and well being in patients with intractable PHPT. The improvements in the Physical Component Summary and Mental Component Summary scores were comparable with the improvements observed in patients with PHPT following parathyroidectomy. This was a small trial, and the results need corroborating in larger studies. In 2008 cinacalcet was approved by the European Commission for the treatment of hypercalcaemia in patients with PHPT for whom parathyroidectomy is indicated on the basis of serum calcium levels but in whom parathyroidectomy is not clinically appropriate or is contraindicated. However, its high cost and lack of data showing improvements in BMD mean that cinacalcet cannot presently be advocated as an alternative to parathyroidectomy.

Conclusion

Parathyroidectomy offers the only potential cure for PHPT and should be recommended in all patients with symptomatic PHPT or with evidence of end-organ damage, where there is no obvious contraindication. However, considerable controversy exists regarding the need for surgery in asymptomatic patients. Recently published guidelines have outlined criteria for surgery in the management of asymptomatic PHPT, recommending structured follow-up for patients who do not fulfil these criteria.

Presently there is no alternative medical therapy to parathyroidectomy that has proven efficacy in managing all aspects of PHPT. Alendronate has beneficial effects on BMD but has not been shown to reduce fracture risk or significantly lower serum calcium, while cinacalcet normalizes serum calcium but does not alter BMD.

Despite the high success rate, low morbidity and convenience of modern parathyroidectomy, patients need to be assessed on a case-by-case basis and important clinical considerations need to be balanced to determine whether parathyroidectomy is the best option for individual patients with mild asymptomatic PHPT (Table 3).

Table 3. Factors influencing management of patients with mild primary hyperparathyroidism. (Adapted from Gittoes and Cooper [2010]).

Favours conservative management	Favours parathyroidectomy
Old age	Young age
Short life expectancy	Long life expectancy
High operative risk	Low operative risk
Patient preference	Patient preference
Initial low fracture risk	Risk of worsening bone disease
	Risk of worsening renal function
	Neuropsychiatric features

Funding

This article received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

None declared.

References

Almqvist, E.G., Bondeson, A.G., Bondeson, L., Nissborg, A., Smedgard, P. and Svensson, S.E. (2002) Cardiac dysfunction in mild primary hyperparathyroidism assessed by radionuclide angiography and echocardiography before and after parathyroidectomy. *Surgery* 132: 1126–1132.

Ambrogini, E., Cetani, F., Cianferotti, L., Vignali, E., Banti, C., Viccica, G. *et al.* (2007) Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial. *J Clin Endocrinol Metab* 92: 3114–3121.

Bilezikian, J.P., Khan, A.A. and Potts Jr, J.T. (2009) Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. *J Clin Endocrinol Metab* 94: 335–339.

Block, G.A., Martin, K.J., de Francisco, A.L., Turner, S.A., Avram, M.M., Suranyi, M.G. *et al.* (2004) Cinacalcet for secondary hyperparathyroidism in patients receiving hemodialysis. *N Engl J Med* 350: 1516–1525.

Bollerslev, J., Jansson, S., Mollerup, C.L., Nordenstrom, J., Lundgren, E., Torring, O. *et al.* (2007) Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective, randomized trial. *J Clin Endocrinol Metab* 92: 1687–1692.

Brown, G.G., Preisman, R.C. and Kleerekoper, M. (1987) Neurobehavioral symptoms in mild primary hyperparathyroidism: related to hypercalcemia but not improved by parathyroidectomy. *Henry Ford Hosp Med J* 35: 211–215.

Chiang, C.Y., Andrewes, D.G., Anderson, D., Devere, M., Schweitzer, I. and Zajac, J.D. (2005) A controlled, prospective study of neuropsychological outcomes post parathyroidectomy in primary hyperparathyroid patients. *Clin Endocrinol (Oxf)* 62: 99–104.

Chow, C.C., Chan, W.B., Li, J.K., Chan, N.N., Chan, M.H., Ko, G.T. *et al.* (2003) Oral alendronate increases bone mineral density in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 88: 581–587.

Coker, L.H., Rorie, K., Cantley, L., Kirkland, K., Stump, D., Burbank, N. *et al.* (2005) Primary hyperparathyroidism, cognition, and health-related quality of life. *Ann Surg* 242: 642–650.

Diamond, T., Ng, A.T., Levy, S., Magarey, C. and Smart, R. (1996) Estrogen replacement may be an alternative to parathyroid surgery for the treatment of osteoporosis in elderly postmenopausal women presenting with primary hyperparathyroidism: a preliminary report. *Osteoporos Int* 6: 329–333.

Farr, H.W., Fahey Jr, T.J., Nash, A.G. and Farr, C.M. (1973) Primary hyperparathyroidism and cancer. *Am J Surg* 126: 539–543.

Fitz, T.E. and Hallman, B.L. (1952) Mental changes associated with hyperparathyroidism; report of two cases. *AMA Arch Intern Med* 89: 547–551.

Fraser, W.D. (2009) Hyperparathyroidism. *Lancet* 374: 145–158.

Gittoes, N.J. and Cooper, M.S. (2010) Primary hyperparathyroidism—is mild disease worth treating? *Clin Med* 10: 45–49.

Grey, A.B., Stapleton, J.P., Evans, M.C., Tatnell, M.A. and Reid, I.R. (1996) Effect of hormone replacement therapy on bone mineral density in postmenopausal women with mild primary hyperparathyroidism. A randomized, controlled trial. *Ann Intern Med* 125: 360–368.

Guo, C.Y., Thomas, W.E., al-Dehaimi, A.W., Assiri, A.M. and Eastell, R. (1996) Longitudinal changes in bone mineral density and bone turnover in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 81: 3487–3491.

Hedback, G. and Oden, A. (1998) Increased risk of death from primary hyperparathyroidism—an update. *Eur J Clin Invest* 28: 271–276.

Hedback, G., Tisell, L.E., Bengtsson, B.A., Hedman, I. and Oden, A. (1990) Premature death in patients operated on for primary hyperparathyroidism. *World J Surg* 14: 829–835.

Kamycheva, E., Sundsfjord, J. and Jorde, R. (2004) Serum parathyroid hormone levels predict coronary heart disease: the Tromso Study. *Eur J Cardiovasc Prev Rehabil* 11: 69–74.

Khan, A., Grey, A. and Shoback, D. (2009) Medical management of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. *J Clin Endocrinol Metab* 94: 373–381.

Khosla, S., Melton III, L.J., Wermers, R.A., Crowson, C.S., O'Fallon, W. and Riggs, B. (1999) Primary hyperparathyroidism and the risk of fracture: a population-based study. *J Bone Miner Res* 14: 1700–1707.

Lind, L., Skarfors, E., Berglund, L., Lithell, H. and Ljunghall, S. (1997) Serum calcium: a new, independent, prospective risk factor for myocardial infarction in middle-aged men followed for 18 years. *J Clin Epidemiol* 50: 967–973.

Marcocci, C., Chanson, P., Shoback, D., Bilezikian, J., Fernandez-Cruz, L., Orgiazzi, J. *et al.* (2009) Cinacalcet reduces serum calcium concentrations in

patients with intractable primary hyperparathyroidism. *J Clin Endocrinol Metab* 94: 2766–2772.

Mollerup, C.L., Vestergaard, P., Frokjaer, V.G., Mosekilde, L., Christiansen, P. and Blichert-Toft, M. (2002) Risk of renal stone events in primary hyperparathyroidism before and after parathyroid surgery: controlled retrospective follow up study. *BMJ* 325: 807.

Nilsson, I.L., Aberg, J., Rastad, J. and Lind, L. (2005) Maintained normalization of cardiovascular dysfunction 5 years after parathyroidectomy in primary hyperparathyroidism. *Surgery* 137: 632–638.

Orr-Walker, B.J., Evans, M.C., Clearwater, J.M., Horne, A., Grey, A.B. and Reid, I.R. (2000) 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* 160: 2161–2166.

Palmer, M., Adami, H.O., Bergstrom, R., Akerstrom, G. and Ljunghall, S. (1987) Mortality after surgery for primary hyperparathyroidism: a follow-up of 441 patients operated on from 1956 to 1979. *Surgery* 102: 1–7.

Parker, C.R., Blackwell, P.J., Fairbairn, K.J. and Hosking, D.J. (2002) Alendronate in the treatment of primary hyperparathyroid-related osteoporosis: a 2-year study. *J Clin Endocrinol Metab* 87: 4482–4489.

Pasieka, J.L., Parsons, L.L., Demeure, M.J., Wilson, S., Malycha, P., Jones, J. *et al.* (2002) Patient-based surgical outcome tool demonstrating alleviation of symptoms following parathyroidectomy in patients with primary hyperparathyroidism. *World J Surg* 26: 942–949.

Peacock, M. (2004) Clinical effects of calcimimetics in hyperparathyroidism. *J Musculoskelet Neuronal Interact* 4: 414–415.

Peacock, M., Bolognese, M.A., Borofsky, M., Scumpia, S., Sterling, L.R., Cheng, S. *et al.* (2009) Cinacalcet treatment of primary hyperparathyroidism: biochemical and bone densitometric outcomes in a five-year study. *J Clin Endocrinol Metab* 94: 4860–4867.

Piovesan, A., Molineri, N., Casasso, F., Emmolo, I., Ugliengo, G., Cesario, F. *et al.* (1999) Left ventricular hypertrophy in primary hyperparathyroidism. Effects of successful parathyroidectomy. *Clin Endocrinol (Oxf)* 50: 321–328.

Quiros, R.M., Alef, M.J., Wilhelm, S.M., Djuricin, G., Loviscek, K. and Prinz, R.A. (2003) Health-related quality of life in hyperparathyroidism measurably improves after parathyroidectomy. *Surgery* 134: 675–681.

Rao, D.S., Phillips, E.R., Divine, G.W. and Talpos, G.B. (2004) Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. *J Clin Endocrinol Metab* 89: 5415–5422.

Rubin, M.R., Bilezikian, J.P., McMahon, D.J., Jacobs, T., Shane, E., Siris, E. *et al.* (2008) The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. *J Clin Endocrinol Metab* 93: 3462–3470.

Rubin, M.R., Maurer, M.S., McMahon, D.J., Bilezikian, J.P. and Silverberg, S.J. (2005) Arterial stiffness in mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 90: 3326–3330.

Sheldon, D.G., Lee, F.T., Neil, N.J. and Ryan Jr, J.A. (2002) Surgical treatment of hyperparathyroidism improves health-related quality of life. *Arch Surg* 137: 1022–1026.

Silverberg, S.J., Bilezikian, J.P., Bone, H.G., Talpos, G.B., Horwitz, M.J. and Stewart, A.F. (1999a) Therapeutic controversies in primary hyperparathyroidism. *J Clin Endocrinol Metab* 84: 2275–2285.

Silverberg, S.J., Lewiecki, E.M., Mosekilde, L., Peacock, M. and Rubin, M.R. (2009) Presentation of asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. *J Clin Endocrinol Metab* 94: 351–365.

Silverberg, S.J., Shane, E., Jacobs, T.P., Siris, E. and Bilezikian, J.P. (1999b) A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med* 341: 1249–1255.

Silverberg, S.J., Shane, E., Jacobs, T.P., Siris, E.S., Gartenberg, F., Seldin, D. *et al.* (1990) Nephrolithiasis and bone involvement in primary hyperparathyroidism. *Am J Med* 89: 327–334.

Sitges-Serra, A. and Bergenfelz, A. (2007) Clinical update: sporadic primary hyperparathyroidism. *Lancet* 370: 468–470.

Smith, J.C., Page, M.D., John, R., Wheeler, M.H., Cockcroft, J.R., Scanlon, M.F. *et al.* (2000) Augmentation of central arterial pressure in mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 85: 3515–3519.

Soreide, J.A., van Heerden, J.A., Grant, C.S., Yau, L.C., Schleck, C. and Ilstrup, D.M. (1997) Survival after surgical treatment for primary hyperparathyroidism. *Surgery* 122: 1117–1123.

Udell, J.A., Fischer, M.A., Brookhart, M.A., Solomon, D.H. and Choudhry, N.K. (2006) Effect of the Women's Health Initiative on osteoporosis therapy and expenditure in Medicaid. *J Bone Miner Res* 21: 765–771.

Udelsman, R. (2002) Six hundred fifty-six consecutive explorations for primary hyperparathyroidism. *Ann Surg* 235: 665–670.

Udelsman, R., Pasieka, J.L., Sturgeon, C., Young, J.E. and Clark, O.H. (2009) Surgery for asymptomatic primary hyperparathyroidism: proceedings of the third international workshop. *J Clin Endocrinol Metab* 94: 366–372.

Vestergaard, P., Mollerup, C.L., Frokjaer, V.G., Christiansen, P., Blichert-Toft, M. and Mosekilde, L.

(2000) Cohort study of risk of fracture before and after surgery for primary hyperparathyroidism. *BMJ* 321: 598–602.

Vestergaard, P., Mollerup, C.L., Frokjaer, V.G., Christiansen, P., Blichert-Toft, M. and Mosekilde, L. (2003) Cardiovascular events before and after surgery for primary hyperparathyroidism. *World J Surg* 27: 216–222.

Vestergaard, P. and Mosekilde, L. (2003) Fractures in patients with primary hyperparathyroidism: nationwide follow-up study of 1201 patients. *World J Surg* 27: 343–349.

Wajngot, A., Werner, S., Granberg, P.O. and Lindvall, N. (1980) Occurrence of pituitary adenomas and other neoplastic diseases in primary hyperparathyroidism. *Surg Gynecol Obstet* 151: 401–403.

Wermers, R.A., Khosla, S., Atkinson, E.J., Achenbach, S.J., Oberg, A.L., Grant, C.S. *et al.* (2006) Incidence of primary hyperparathyroidism in Rochester, Minnesota, 1993–2001: an update on the changing epidemiology of the disease. *J Bone Miner Res* 21: 171–177.

Wermers, R.A., Khosla, S., Atkinson, E.J., Grant, C.S., Hodgson, S.F., O'Fallon, W.M. *et al.* (1998) Survival after the diagnosis of hyperparathyroidism: a population-based study. *Am J Med* 104: 115–122.