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Primary hyperparathyroidism – is mild disease worth treating?

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ABSTRACT – Most patients with primary hyperparathyroidism (PHPT) are asymptomatic at presentation. This presents the dilemma whether to treat surgically or manage by conservative follow-up. This article covers the risks of managing mild PHPT conservatively. Some of these risks are well established, for example worsening of bone disease and increased risk of nephrolithiasis. Others, such as effects on cardiovascular function or the risk of malignancy are more controversial. These factors are critical to decisions relating to surgical or conservative management of mild PHPT.

KEY WORDS: hypercalcaemia, parathyroidectomy, primary hyperparathyroidism

Introduction

The association of primary hyperparathyroidism (PHPT) with 'bones, stones, abdominal groans and moans' bares little relevance to contemporary patients with PHPT. Introduction of automated multichannel biochemical analysers in the 1970s has largely put pay to the textbook presentation of PHPT. 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%.[1] Instead, PHPT has emerged as a disease most frequently recognised coincidentally on biochemical testing (hypercalcaemia with inappropriately high parathyroid hormone (PTH) secretion) in patients evaluated for unrelated complaints. Few patients with PHPT detected this way will volunteer symptoms or have evidence of end organ damage but when questioned in detail, some may complain of non-specific symptoms such as fatigue, weakness, poor memory and difficulty concentrating. It is the management of this group of 'mild asymptomatic' patients with PHPT that forms the focus of this discussion.

Contemporary management of PHPT

Surgery is the only cure for PHPT and experienced surgeons frequently achieve >95% first time cure rates.[2] Imaging techniques to localise parathyroid adenomas (eg ultrasound scan/sestamibi) and operative techniques (eg minimally invasive parathyroidectomy) have evolved in recent years, making surgery a quick, low morbidity approach to managing PHPT.[3] There is unequivocal evidence that successful parathyroidectomy (PTx) reduces the risk of renal stones in symptomatic individuals, causes rapid and sustained increases in bone mineral density (BMD) and reduces fracture risk.[4,5] Surgery is therefore appropriate in patients with symptomatic PHPT and where there is evidence of end organ disease but there remains controversy concerning surgical intervention in patients with no clear clinical features. There are published consensus guidelines on thresholds for surgical intervention (Table 1), the most widely adopted from the National Institutes for Health (NIH) (updated 2009).[6,7] These are followed to varying extents according to local perceptions and practice.

Patients who do not fulfil these guidelines for surgery are offered a structured conservative follow-up protocol (Table 2) and advice regarding hydration status, and how to recognise possible symptoms. It is in this situation that the potential benefits of a permanent cure of their underlying disease need to be balanced against the risks and inconvenience of surgery. The potential benefits from surgery will depend on the impact untreated mild PHPT has on an individual (both through worsening of health and the need for continuing disease monitoring) and the risk that this will develop into symptomatic/severe PHPT. A particular concern is that a patient with mild disease will develop progressive disease at a time when their fitness for surgery has decreased.

Table 1. National Institutes for Health consensus guidelines for surgery in primary hyperparathyroidism.

Symptomatic disease:	
Renal stones	
Polyuria/polydipsia	
Pancreatitis	
Neuropsychiatric disorder	
Florid bone disease eg osteitis fibrosa cystica	
Previous hypercalcaemic crisis	
Asymptomatic disease:	
Age	<50
Serum calcium	>0.25 mmol/l above upper limit of normal (~>2.9 mmol/l)
Estimated glomerular filtration rate	reduced to <60 ml/min
Bone mineral density (by DXA)	T-score <−2.5 at any site, and/or fragility fracture
Medical follow-up	undesired or impractical

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What are the potential consequences of treating mild PHPT conservatively?

It would be helpful to know the natural history of untreated PHPT and how this is modified by PTx or medical treatment. However, data in this area are suboptimal. Rubin *et al* recently reported 15-years follow-up data in an observational cohort of patients with conservatively managed PHPT in the USA.[8] Of 49 initially asymptomatic patients, there was a significant, albeit small, rise in serum corrected Ca^{2+} at 13 and 15 years compared with baseline (Table 3). The other biochemical parameters did not change significantly over this timeframe. Those not undergoing PTx had a significantly greater than expected fall in BMD over time, particularly at sites rich in cortical bone. In those that had PTx there was an initial rise and then maintenance of BMD. Importantly, approximately a third of patients eventually developed conventional indications for surgery. Unfortunately, the small numbers make the results difficult to generalise.

There have been three recent randomised controlled trials that explored the impact of PTx on BMD, renal function and quality of life (QOL) in patients with mild PHPT.[9–11] The number of patients randomised varied between 50 and 191. All studies found a beneficial effect of PTx on BMD at one or more skeletal sites. Two studies found a significant benefit on self-reported measures of QOL whereas the largest study failed to show such an effect. These results have to be tempered by the understandable fact that the non-surgical groups did not receive a sham operation. It is feasible that the surgical procedure itself accounted for some of the differences in QOL. The follow-up times were also relatively limited at up to two years. These studies do support a role for PTx in the prevention or treatment of bone disease and a possible role in reducing neuropsychiatric symptoms/improving QOL.

Above and beyond these recognised risk factors, there is also growing support for the view that PHPT is an independent risk factor for cardiovascular morbidity and mortality and perhaps even malignancy. These are critical issues since such factors, especially if reversed by PTx, would dramatically alter the risk/benefit assessment in patients with mild PHPT.

Table 2. Conservative follow-up plan.

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

Previous recommendations included regular assessment of 24-hour urinary calcium and imaging for renal stones but these are not now generally recommended.

eGFR = estimated glomerular filtration rate.

Cardiovascular risk and mild PHPT

PHPT in its most severe form is associated with cardiac and valvular calcification.[12] Population data from Scandinavia demonstrate a significant increase in cardiovascular mortality in moderate to severe (symptomatic and/or calcium >3.0 mmol/l) PHPT that reduces over time after PTx.[13] Whether mild, asymptomatic, PHPT is a risk factor for cardiovascular pathology and mortality is far less clear.

Cardiovascular mortality in mild PHPT

Studies in patients with mild PHPT have revealed discrepant results; one demonstrating a significant reduction in expected cardiovascular deaths in patients with PHPT.[14] Other studies have demonstrated increased cardiovascular mortality with more severe hypercalcaemia. Hedback and Oden[15] showed that hypertensive PHPT patients (some with severe, albeit asymptomatic, hypercalcaemia) had a 50% higher mortality than normotensive PHPT patients and that the reduction in mortality after PTx was greater in the hypertensive group (a decrease of 2.4% versus 1.3% per year).

Cardiovascular morbidity and mild PHPT

There are limited data pertaining to the influence of mild PHPT on hypertension. Even in symptomatic disease, hypertension rarely reduces following PTx.[16] Both serum calcium and PTH are independent risk factors for coronary artery disease

Table 3. Biochemical changes in asymptomatic patients followed up without parathyroidectomy (n=49). Adapted from Reference 8.

Variable	Baseline (n=49)	Year 5 (n=25)	Year 10 (n=11)	Year 13 (n=9)	Year 15 (n=6)
Serum calcium (mmol/l)	2.62±0.02	2.67±0.02	2.7±0.05	2.75±0.05*	2.78±0.05*
PTH (ng/l)	122±10	119±12	123±14	124±16	121±18
Serum creatinine (mol/l)	76±8	76±8	76±8	76±15	61±8
Urinary calcium (mmol/l)	5.25±0.05	5.5±0.5	5.5±0.75	5.25±0.75	4.75±1

Values shown are mean±SE. To convert values for PTH to pmol/l divide by 9.5. *$p<0.01$ for the comparison with the individual baseline values for these groups.

PTH = parathyroid hormone.

(CAD).[17,18] However, these data are derived from the normal population and not patients with PHPT and are thus not necessarily generalisable to the disease state. Patients with moderate/severe PHPT may have an increased risk of CAD that appears to decrease after successful PTx but there are no data in mild PHPT.[19] Left ventricular hypertrophy (LVH) is a predictor of cardiovascular mortality and in most studies of PHPT, a positive correlation with PTH has been identified.[20,21] Some studies have demonstrated a reduction in LVH following successful PTx whereas others have not.[20–22] Again data are lacking in patients with mild PHPT.

A study of 39 patients with mild PHPT and 134 controls examined the relationship between severity of PHPT and peripheral vascular resistance (an independent predictor of cardiovascular risk).[23] They found that 15% of the variance in arterial stiffness was mediated by the presence of PHPT. 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 and a strong negative correlation between T-score at distal radius (a site rich in cortical bone that is preferentially lost in PHPT) and arterial stiffness. Thus this study suggests 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 PTx on arterial stiffness is unknown.

Cancer and mild PHPT

An increased risk of cancers has been reported in patients with PHPT.[24,25] This risk has been estimated to be approximately double that expected in matched controls. A small contribution to this might be from endocrine tumour syndromes such as multiple endocrine neoplasia that have PHPT as a feature. It must also be borne in mind, however, that there may be important biases in these studies. An underlying malignancy is often a prompt for biochemical testing during which incidental PHPT might be detected. Furthermore, patients with hypercalcaemia detected unexpectedly on a biochemical profile are likely to receive detailed assessments for underlying malignancy, which may account for an apparent increase in malignancy in this group.

Is there a medical alternative to PTx for mild asymptomatic PHPT?

Although surgery is the only cure for PHPT, if there were effective medical therapies to reduce risks in PHPT these might be alternatives to PTx. Medical treatments have attempted to prevent/reverse the skeletal effects of PHPT and to reduce the PTH level itself.

Bisphosphonates

Oral bisphosphonates do not cause clinically significant long-term reductions in serum calcium in patients with PHPT but they can be considered for the associated bone disease. Alendronate is the most extensively studied bisphosphonate in PHPT.[26–28] It reduces bone turnover and increases BMD, probably to a similar extent to that seen in patients after PTx. Despite these positive changes, there are no data demonstrating a reduced fracture risk.

Hormone replacement therapy

Two non-randomised studies have examined the effects of hormone replacement therapy (HRT) versus PTx in post-menopausal women with PHPT.[29,30] Both interventions produced similar positive effects on axial BMD. The use of HRT as a bone protection agent has changed dramatically since these studies and would now not normally be considered in this setting. This is especially so given the possible increased risk of cardiovascular disease in patients with PHPT.

Cinacalcet

The central regulator of PTH secretion is extracellular ionised calcium, which activates and signals 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. Molecular characterisation of the CaSR has allowed development of agents known as calcimimetics that allosterically modify the CaSR causing downstream (calcium-like) effects without having true calcium effects peripherally. Studies in humans have identified a role for the calcimimetic cinacalcet in states of primary and secondary hyperparathyroidism.[31,32]

Studies on the use of cinacalcet in PHPT have recently been reviewed in detail.[33] Most studies have used twice daily cinacalcet in patients with relatively mild PHPT and have shown rapid and sustained reductions in serum calcium, with 80% attaining normalisation during a one-year randomised study with four-year open-label extension.[31] Increases in BMD were not observed, neither was a reduction in urinary calcium excretion. In the UK cinacalcet is now licensed for use in PHPT in patients in whom PTx is inappropriate and is a potentially valuable therapy in patients presenting with life-threatening hypercalcaemia associated with PHPT. However, the absence of hard clinically relevant endpoint data and its high cost mean that cinacalcet cannot presently be advocated as an alternative to PTx in PHPT.

Cost-effectiveness of intervention for mild asymptomatic PTPH

There have been several high-quality cost-effectiveness analyses for mild asymptomatic PHPT.[34–36] All have found pharmacological/medical therapy to be less cost effective than monitoring or surgery. This is partly because surgery for PHPT has changed dramatically over the last decade from a multiple day admission to often a day case procedure. Monitoring is

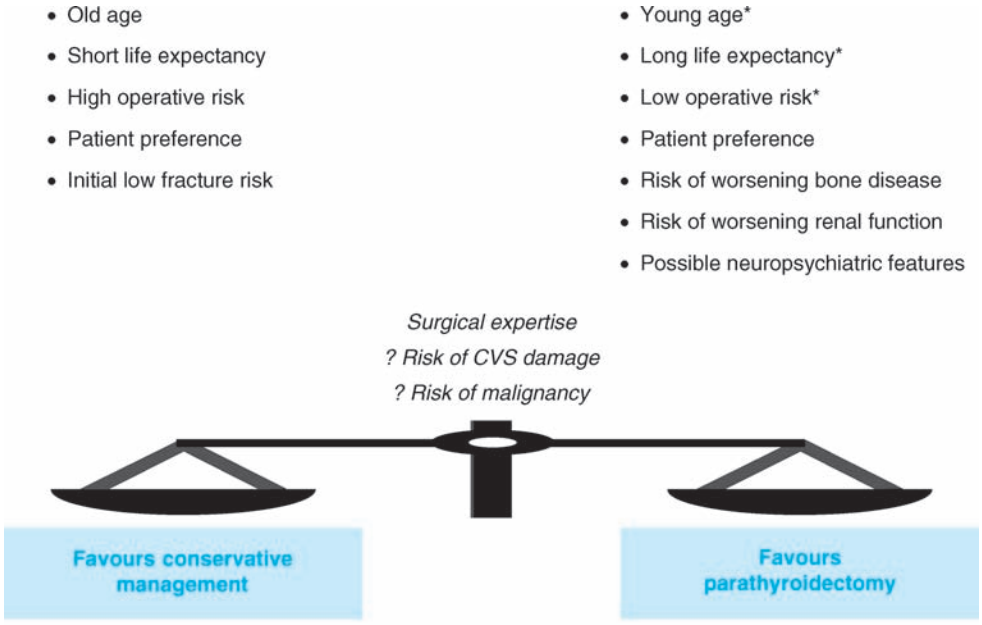

Fig 1. Factors influencing management of patients with mild primary hyperparathyroidism.

cheaper than surgery but is less effective. The importance of life expectancy has been examined in detail and Zanocco and Sturgeon[36] identified that PTx was cost effective for patients with a predicted life expectancy of >5 years (day case PTx) or >6.5 years (inpatient PTx). In essence, published data support PTx as a cost-effective treatment strategy for mild asymptomatic PHPT.

Conclusions

Figure 1 demonstrates the important clinical considerations that need to be balanced to determine whether PTx is the best option for individual patients with mild asymptomatic PHPT. A recent consensus workshop recommended that asymptomatic patients who do not meet surgical criteria can be followed safely without surgery, accepting that further research into cardiovascular manifestations, neurocognitive dysfunction and long-term stability of BMD may change this threshold in the future. When PTx is not carried out due to patient choice, clinician determined or contraindications to PTx, monitoring is critical (Table 2) to determine disease progression and reconsideration for PTx.

Presently there is no alternative medical therapy to PTx that has proven efficacy in managing all aspects of PHPT. Alendronate has beneficial effects on BMD but no data showing a reduction in fracture risk. Alendronate does not cause clinically meaningful reductions in serum calcium. The theoretically appealing approach of using cinacalcet is promising for the future. Current data demonstrate impressive reductions in serum calcium but with no significant changes in BMD. In patients in whom PTx is contraindicated/not feasible, alendronate and cinacalcet may be considered.

Given the high success rate, low morbidity and convenience of modern PTx, coupled with emerging data on potential cardiovascular risk and neurocognitive dysfunction associated with mild PHPT, the threshold for surgical intervention has significantly reduced. Although some centres adopt a blanket policy for PTx in all patients with biochemical PHPT, available data and our local practice is to individually assess each patient and based on merits (as identified in Fig 1), determine whether it is in the patients best interests to be referred for PTx.

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