

Mild Asymptomatic Hyperparathyroidism

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Citation

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Abstract

According to consensuses, the term “asymptomatic primary hyperparathyroidism” should be reserved for “the clinical profile of patients with documented PHP without symptoms or signs commonly attributable to the disease”. Therefore the term “asymptomatic” is a misnomer in fact and sometimes causes confusion. We think that the term “mild PHP” may be best defines those without overt symptoms and those who do not meet NIH criteria. Surgery is the only curative therapy of PHP. Many authors recommend PTX to almost all cases while some prospective studies failed to show new onset symptoms and complications (5). PTX is a cost effective procedure under age 50 and when life expectancy exceeds 5 years. (48,49). It is prudent to observe the patient if life expectancy is shorter. For the mild “asymptomatic” disease the issue has not been settled down and larger, long term studies are needed to suggest PTX .

INTRODUCTION

Primary hyperparathyroidism (PHP) is a disease of excessive parathormone (PTH) secretion in the absence of known stimuli (1). In 80-85% of cases the cause is a benign parathyroid adenoma (2). PTH promotes intestinal calcium absorption, renal calcium reabsorption, and release of calcium from bones (3). PHP is the most common cause of hypercalcemia (4). It is a quite common disease with a prevalence of 1-21/1000 (1,5). The prevalence rises up to 7% in the elderly population (6). It is more prevalent among postmenopausal women. After the introduction of multichannel screening, the incidence and clinical presentation changed a great deal (7). Currently intact PTH (1-84) measurement using second and third generation tests allows for more precise diagnosis (8).

The clinical picture was originally described as “bones (osteitis fibrosa cystica), kidney stones, abdominal groans and psychic moans” (9). The classical picture is not seen as frequent as once it has been. The radiographic evidence of bone disease is rare (10). Bone disease in PHP presents as decreased bone density that leads to fracture instead of the rare characteristic finding osteitis fibrosa cystica. Psychosis, gait disturbance, proximal muscle weakness, atrophy, and hyperreflexia are classic neuromuscular abnormalities in PHP and currently are more rare. Renal stone disease occurs in 20% of cases and may be asymptomatic (10,11). On the other hand, ultrasonography may not be reliable due to artifacts and stones less than 5 mm diameter may be missed

(11). Eighteen to 40% of patients have hypercalciuria (4,11). Not only the prevalence but also the size of the calculi decreased since 1950s (11).

SUMMARY OF THE CONSENSUSES

In 1990 the National Institutes of Health (NIH) Consensus Development Conference on the Diagnosis and Management of Asymptomatic Primary Hyperparathyroidism was held (12). Parathyroidectomy (PTX) was recommended for the “symptomatic” patients (kidney stones, overt bone disease, and specific neuromuscular disease) and to those who met certain biochemical criteria (Table 1) (12). The remaining patients were defined as “asymptomatic” and advised to get regular check-ups for progression of the disease (Table 2).

Figure 1

Criteria	Consensus 1990	Consensus 2002	Consensus 2008
Serum calcium above upper normal limit	1-1.6 mg/dl	1.0 mg/dl	1.0 mg/dl
24-hour urinary calcium	>400 mg	>400 mg	Not a criterion any more
Creatinine clearance	Decrease by 30%*	Decrease by 30%*	<60 ml/min per 1.73 m ² **
Age	<50	<50	<50
Bone mineral density by DXA	Z-score <-2.0 (forearm)	T-score <-2.5 (any site)	T-score <-2.5 (any site) for peri- and postmenopausal women and men over 50 years of age Z-score <-2.5 (any site) for premenopausal women and men under 50 years of age
Medical surveillance	impossible or unwanted	impossible or unwanted	impossible or unwanted

*estimated by 24-hour urinary collection or by Cockcroft Gault equation. **estimated by MDRD equation.

Measurement	Consensus 1990	Consensus 2002	Consensus 2008
Serum calcium	Every 6 month	Every 6 month	Annually
24-hour urinary calcium	Annually	Not recommended	Not recommended
Creatinine clearance	Annually	Not recommended	Not recommended
Serum creatinine	Annually	Annually	Annually
Bone density	Annually (forearm)	Annually (all 3 sites)	Every 1-2 years (all 3 sites)
Abdominal X-ray /ultrasound	Annually	Not recommended	Not recommended

* Modified from reference 13.

In 2002 the recommendations for treatment and follow-up were updated (Table 1 and 2) (13). The Third International Workshop on Primary Hyperparathyroidism was held in

2008 (14). In three of the workshops age is a determinant in surgery decision. Since the majority of patients under 50 years of age develop at least one new indication for surgery during follow-up, age is picked up as a criterion. Three main changes exist in the last consensus:

1- Urinary calcium has no longer accepted as a criterion in surgery decision (Table 1). Urinary calcium excretion over 400 mg/day was a criteria for PTX both in 1990 and 2002 consensuses. The rationale was kidney stone formation in hypercalciuric patients (15). But hypercalciuria is only one of the six factors (urinary volume, oxalate excretion, citrate excretion, uric acid, and pH) in stone formation (15). Hypercalciuric patients do not necessarily develop stones. Calcium excretion also varies with age, gender, race, dietary calcium intake, and vitamin D status (15). Twenty-four hour urinary collection is not always precise. Therefore in the last workshop, it has been suggested that urinary calcium should not be used as a sole criterion for surgery in the absence of stone formation (15).

2- Glomerular filtration rate (GFR) calculated according to Cockcroft-Gault formula or from direct measurement in 24 hour urine collection were abandoned (16). The National Kidney Foundation Kidney Disease Outcomes Quality Initiative (KDOQI) does not recommend the use of 24-h urinary collections to estimate creatinine clearance. Modification of Diet in Renal Disease (MDRD) study and the Cockcroft-Gault equation are both recommended. The Cockcroft-Gault equation takes into account age, weight, gender, and serum creatinine whereas the MDRD equation takes into account age, gender, race, serum creatinine, albumin, and urea nitrogen. GFR estimated from 24-h urinary collection or by the Cockcroft-Gault equation tend to overestimate GFR relative to the MDRD equation. In the last workshop on PHP, the use of the MDRD equation is recommended because this is a more accurate estimate of GFR than the Cockcroft-Gault equation. The KDOQI recommends using stages of chronic kidney disease; stage 3 corresponds with a GFR of 60 ml/min per 1.73m² and would be a suitable threshold for further renal compromise. PTH begins to rise below this cutpoint in chronic kidney disease in the absence of PHP (16,17). Even in mild renal insufficiency (serum creatinine <1.4 mg/dl in women and <1.5 mg/dl in men) bone density decreases significantly and the decrease is more pronounced in patients with a creatinine clearance rate less than 70 ml/min (18). There is concern that GFR below this level may worsen PHP (16,17). This cut off may be an arbitrary point instead of being a precise level.

Furthermore GFR declines with age and whether surgery improves GFR afterwards is still unknown. In a study done by Tassone et al showed that only severely decreased GFR present with significant PTH increase (17).

3- The absolute bone mass density (BMD) T-score below -2.5 was revised (15). In accordance with the Official Positions of the International Society for Clinical Densitometry (ISCD), BMD should be reported as T-scores in peri- and postmenopausal women and in men age 50 and older, and as Z-scores in premenopausal women and in men under 50 yr of age. In the last 2008 workshop, parathyroid surgery was recommended when the T-score was ≤ 2.5 at the lumbar spine, femoral neck, total hip, or distal one-third radius in peri- and postmenopausal women and in men age 50 and older, and when the Z-score was ≤ 2.5 in premenopausal women and in men under 50 years of age (15).

During follow-up, comparing changes in bone density should not depend on the absolute T or Z scores. According to the Official Positions of the (ISCD), the reproducibility of the measurement, namely precision is not well in dual energy X-ray absorptiometry (DXA) (15). There is an inherent precision error within DXA measurement. Precision is evaluated when 15 patients have 3 measurements or 30 patients have 2 measurements on the same day with the same instrument and repositioning after each measurement. The smallest BMD change that is statistically significant with a 95% level of confidence is termed least significant change (LSC). As a result in the last workshop it has been recommended that PTX should be considered in patients who had a decrease in BMD that is equal to or greater than the calculated LSC (15).

What about the outsiders? Really “asymptomatic”?

Two thirds of PHP present without classic symptoms or vague constitutional and nonspecific symptoms (4,11). Many of the “asymptomatic” patients may define neuropsychological and neuropsychiatric symptoms and may show cognitive impairment if certain questionnaires and scoring are used (19). Other nonspecific manifestations are anorexia, nausea, constipation, vomiting, and abdominal pain (20). Furthermore some patients are unaware of their symptoms before PTX and report that they feel better and their symptoms are retrospectively documented (21).

Among the nonspecific neuropsychogenic symptoms (weakness, easy fatigability, depression, intellectual

weariness, cognitive impairment, loss of initiative, anxiety, irritability, sleep disturbance, and somatization) weakness and easy fatigability takes the lead (4,15). Although rare, type II muscle cell atrophy can be seen (4). Constitutional, psychiatric, and behavioral symptoms can be detected by psychometric tests and may regress after surgery (4,22). Unfortunately the reports about the association are inconsistent (15). Commonly co-existing vitamin D deficiency may contribute to weakness and fatigue (15). Another feature of PHP is daytime sleepiness (23). Daytime sleepiness decreased and quality of sleep improved after surgery in a small sized study. The findings were supported by functional magnetic resonance imaging (MRI). The relation was attributed to circadian rhythm of PTH secretion.

Single-photon emission computed tomography evaluating cerebral blood flow and cortical activation and functional MRI assessing neurocognitive impairment showed subtle changes (2,24). The reversibility after surgery is also inconclusive.

Although the consensus has drawbacks on neuropsychiatric symptoms as a criterion for PTX, International Society of Surgery substantially favours PTX for neuropsychiatric symptoms and improvement of quality of life (19).

Other associations with isolated PHP are dyslipidemia, impaired glucose metabolism, hypertension, peptic ulcer, pancreatitis, hyperuricemia, gout, and pseudogout (4,25-27). The association between hypertension and PHP is pronounced if it is a component of multiple endocrine neoplasia (MEN) syndromes (gastrinoma in MEN1 and pheochromocytoma in MEN2) (4). Renin increases and renin-angiotensin-aldosterone system is impaired (28,29). Hypertension and peptic ulcer disease are unlikely to remit after surgery in isolated PHP (4). The patients with severe and moderately severe PHP have high cardiovascular mortality rates (15). On the contrary, the mortality rate from cardiovascular disease (CVD) is not affected in patients with mild disease (15). The discrepancy in mortality rates between American and European studies may arise from milder disease in American studies (15). The severity of hypercalcemia was related to mortality rate (4).

In a 15 year follow up study of PHP, 19% of nonsurgical patients (nearly half of them meeting surgical criteria and half asymptomatic) died due to CVD (7). They had higher calcium and PTH levels. Many other studies also detected high mortality rate in PHP due to CVD (28).

It has been proposed that vascular calcification causes CVD and hypertension in PHP but the data do not support it (25). In high serum concentrations, calcium deposition occurs in valvular and vascular structure (15,28). It seems unlikely that increased calcium is the culprit factor in CVD of milder PHP.

Arrhythmias and left ventricular hypertrophy are also common in PHP (4). Less ST segment depression, increase in QT interval, and decrease in left ventricular mass after surgery has been documented in some studies (15,28). Diastolic dysfunction has also been detected. (15,28). But these findings are not consistent in all studies.

Carotid intima-media thickness was shown to be associated with serum calcium levels in some studies (15,30,31). In Rubin's study, arterial stiffness measured at the radial artery increased in PHP and the increase was irrelevant to the established cardiovascular risk factors. (30). In a recent study done by Tordjman et al, arterial stiffness measured by noninvasive methods including the method used by Rubin did not yield any significant difference between control group and both hypercalcemic and normocalcemic groups (32). The groups also did not differ in established cardiovascular risk factors. Some studies showed impaired endothelial vasodilatory response in PHP (15).

PHP also is a strong predictor of increased aortic stiffness (15). Both in vivo and in vitro studies showed increased chronotropy and inotropism in PHP (28). An interesting study done by Farahnak et al showed no significant changes in cardiovascular functions evaluated by Doppler echocardiography. They studied patients who were referred for surgery. The patients neither had any CVD including hypertension nor diabetes mellitus. Their body mass index were under 28 kg/m². They reassessed cardiovascular functions after approximately one year and did not observe any deterioration (33). In a small size study coronary artery calcification was evaluated in mild asymptomatic hypercalcemia by tomographic coronary scoring. (34). The hypertensive patients had higher scores than normotensive ones and control subjects. It was proposed that mild asymptomatic PHP carry risk for coronary atherosclerosis only in the presence of other cardiovascular risk factors.

According to the last consensus, despite deleterious cardiovascular consequences of marked hypercalcemia, data on the extent and nature of cardiovascular involvement are limited to suggest PTX and routinely search clinical and imaging clues of CVD in PHP (15).

There is 2-4 fold increase in diabetes (26). The prevalence of impaired glucose tolerance also increases (26,35). Increased insulin resistance may cause other metabolic and cardiovascular disturbances (26). Phosphate has important functions in intracellular glucose metabolism and decreases tissue sensitivity to insulin (26). Likewise glucose metabolism is impaired in hypophosphatemic states other than PHP (29). In one study amylin secretion along with insulin was also blamed for impaired glucose metabolism (29). Insulin resistance was shown in small euglycemic insulin clamp test studies in PHP (26). There are some in vitro studies showing a relation between glucose metabolism and calcium metabolism parameters, but clinical studies do not (26). Yet the data are inconclusive to draw a conclusion that impaired glucose metabolism should be a criteria for surgery in PHP.

Increased intracellular calcium in adipocytes causes insulin resistance and inhibits lipolysis. PTH also effects adipocyte differentiation (25). This interaction may lead to weight gain and resultant obesity related complications. Weight gain antedates PHP (25). Weight gain has also been blamed for cardiovascular morbidity and mortality in PHP (25). Increased gallstone disease and cancer (female reproductive system, kidney, gastrointestinal system and breast) in association with PHP may also be due to increased weight (25).

The dyslipidemia profile in PHP includes decreased HDL and increased VLDL and triglyceride levels (36).

Dyslipidemia may be more prevalent among patients with PHP independent of coexisting diseases associated with dyslipidemia. Dyslipidemia may normalize after surgery and those who do not get surgery show a deteriorating lipid profile (36).

Despite these workshops and studies, the question of who should be treated and what happens if not is still a debate of discussion. Other than classic signs of PHP, the course of mild PHP may determine the indication for surgery. There are few long-term follow up studies (5,7,10,37,38).

In one study after a up-to-10 years of follow-up of 23 postmenopausal patients with PHP, only 19 met consensus 2002 criteria. Ionized serum calcium, urinary calcium ve creatinine levels stayed stable and few complications occurred. Unfortunately the number of cases was small to reach a conclusion. The point of this study was ionized calcium. It remained stable whilst total and corrected calcium levels increased throughout the study. Furthermore

ionized calcium was high in all patients in whereas only 6 has elevated corrected calcium levels. It was proposed that ionized calcium reflected serum levels best and should be used for diagnosis and follow-up (5).

Silverberg and his colleagues studied 121 patients with PHP (10). Seventeen percent had classic symptoms. PTX was recommended for those who were symptomatic and those who met NIH 1990 criteria; but not all patients accepted operation. Fourty nine asymptomatic patients who met NIH criteria and 12 symptomatic patients had surgery. During follow-up they had normalized biochemical values and BMD improved. Kidney disease did not progress. The remaining 60 patients did not undergo surgery. Disease progression, which was defined as development of at least one indication of PTX, was observed in 27% of asymptomatic patients (n=14) and in all symptomatic disease (n=8).

This study was extended to 15 years and mixed model analysis was applied (7). Fifty asymptomatic patients who met consensus criteria and 9 symptomatic patients had surgery. During follow-up disease progression was observed in 37% (n=18) of asymptomatic patients who did not undergo surgery (n=49) and in all symptomatic disease (n=8). Seven of those asymptomatic patients met consensus criteria at baseline, but refused operation. Therefore 35% (n=7) of asymptomatic patients who met consensus criteria at baseline had disease progression, whereas 38% (n=11) of asymptomatic patients without criteria had disease progression. Meeting PTX criteria at baseline did not predict worse outcome in patients who were observed instead of PTX. This result caused suspicion about the reliability of consensus criteria in making decision about surgery. In these studies it was also stressed that increased BMD did not necessarily mean decreased fracture risk, improved bone quality, and bone strength. BMD is not the only influential factor that determines the risk of fracture (39,40). In vitro studies showed that 70% of bone strength came from mineral content (40). Both bone quality and quantity determines bone strength (39). There is also an overlap in bone density values between those with and without fractures (39). In addition, periosteal apposition provoked by increased endosteal reabsorption may result in increased bone size which may mislead to increased BMD with DXA. But increased bone size may provide biomechanical protection. The microarchitecture is generally well preserved and even improved in cancellous bones. So how the balance between bone resorption and counteracting protective

mechanisms effect the incidence of fracture should be elucidated with other prospective studies (4). The bone disease is more pronounced in those with concomitant vitamin D deficiency because of the loss of regulatory effects of 1,25 (OH) vitamin D on PTH gene (41,42). Co-existing vitamin D deficiency may cause normocalcemic PHP (41).

Both studies showed that cancellous bone (lumbar spine) density improved after surgery but cortical bone (femur neck and distal one third radius) density did not. On the other hand although most cases who did not undergo surgery had stable disease in cancellous bone, cortical bone density decreased over time. It was proposed that catabolic effects of PTH was partially reversible.

Over age 50, there is a marked increase in risk of fractures (40). The fracture risk is especially high in older female patients (43). This finding contradicts to the age criteria (<50 years of age). Following surgery bone turnover markers return to normal within six months and the fracture risk returns to control levels within one year after PTX (43,44). Resorption markers diminish before formation markers (44). This reduction reflects as increased BMD over three years (44). In a small size study, the patients with a high preoperative resorption marker N-telopeptide got the highest vertebral bone mass gain after surgery (45).

There is a 10-12% gain in bone density at lumbar spine and femoral neck after a successful surgery (4). The gain is exaggerated in young patients. Most of the increase is observed within 3-4 years of PTX (4). All sites of skeleton are vulnerable to deleterious effects of PTH to a different extent according to bone content. Therefore bone density profile is not consistent in every case of PHP. The hip is a mixture of both cortical and cancellous bone (4). The vertebrae consists of nearly 25% cortical bone whereas distal third radius is almost 100% cortical bone (15,43). Vertebral osteopenia may be evident in 15% of PHP at presentation (4). Many studies yielded increased risk of vertebral fractures (43). Increased bone turnover is blamed for fractures at cancellous bone sites (43).

Many cases of vertebral fractures (VF) are clinically silent (46). Clinically silent VFs bear the same risk of additional vertebral and nonvertebral fractures as symptomatic VFs. VFs can be detected by plain X-ray films. Instead DXA can be used to evaluate both bone densitometry and make vertebral fracture assessment (VFA). Vignali et al (46). showed that both symptomatic and asymptomatic PHP had

higher rates of VF than postmenopausal control group. Although insignificant, VF rate was higher in symptomatic PHP than asymptomatic PHP and in asymptomatic who met NIH criteria than those without. But VF rate in asymptomatic PHP group who did not meet NIH criteria was not increased. These findings support NIH consensus for surgery. In that study many patients with VFs were also demonstrated to have higher T-scores than -2.5. The cut-off for surgery may need to be validated. It has been postulated that decreased anabolic growth hormone secretion during the decade preceding menopause may cause accelerated bone mass loss in postmenopausal women with PHP (47). Decreased estrogen may also contribute to greater bone mass loss after menopause in PHP (47).

CONCLUSION

According to consensus, the term "asymptomatic primary hyperparathyroidism" should be reserved for "the clinical profile of patients with documented PHP without symptoms or signs commonly attributable to the disease". Therefore the term "asymptomatic" is a misnomer in fact and sometimes causes confusion. We think that the term "mild PHP" may be best defines those without overt symptoms and those who do not meet NIH criteria.

Surgery is the only curative therapy of PHP. Many authors recommend PTX to almost all cases while some prospective studies failed to show new onset symptoms and complications (5). PTX is a cost effective procedure under age 50 and when life expectancy exceeds 5 years. (48,49). It is prudent to observe the patient if life expectancy is shorter. For the mild "asymptomatic" disease the issue has not been settled down and larger, long term studies are needed to suggest PTX .

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