

## Presentation of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Third International Workshop

Shonni J. Silverberg, E. Michael Lewiecki, Leif Mosekilde, Munro Peacock, and Mishaela R. Rubin

Columbia University College of Physicians & Surgeons (S.J.S., M.R.R.), New York, New York 10032; New Mexico Clinical Research & Osteoporosis Center (E.M.L.), Albuquerque, New Mexico 87106; Department of Endocrinology C (L.M.), Aarhus University Hospital, DK-8000 Aarhus C, Denmark; and Indiana University School of Medicine (M.P.), Indianapolis, Indiana 46202

**Background:** At the Third International Workshop on Asymptomatic Primary Hyperparathyroidism (PHPT) in May 2008, recent data on the disease were reviewed. We present the results of a literature review on issues arising from the clinical presentation and natural history of PHPT.

**Methods:** Questions were developed by the International Task Force on PHPT. A comprehensive literature search for relevant studies was reviewed, and the questions of the International Task Force were addressed by the Consensus Panel.

**Conclusions:** 1) Data on the extent and nature of cardiovascular involvement in those with mild disease are too limited to provide a complete picture. 2) Patients with mild PHPT have neuropsychological complaints. Although some symptoms may improve with surgery, available data remain inconsistent on their precise nature and reversibility. 3) Surgery leads to long-term gains in spine, hip, and radius bone mineral density (BMD). Because some patients have early disease progression and others lose BMD after 8–10 yr, regular monitoring (serum calcium and three-site BMD) is essential in those followed without surgery. Patients may present with normocalcemic PHPT (normal serum calcium with elevated PTH concentrations; no secondary cause for hyperparathyroidism). Data on the incidence and natural history of this phenotype are limited. 4) In the absence of kidney stones, data do not support the use of marked hypercalciuria ( $>10$  mmol/d or 400 mg/d) as an indication for surgery for patients. 5) Patients with bone density T-score  $-2.5$  or less at the lumbar spine, hip, or distal one third radius should have surgery. (*J Clin Endocrinol Metab* 94: 351–365, 2009)

At the Second International Workshop on Primary Hyperparathyroidism (PHPT) (1), an evidence-based approach was used to modify the guidelines for surgery in patients with asymptomatic PHPT. Parathyroidectomy was recommended for patients with mild PHPT in whom testing or other information indicates end-organ effects that are likely to be mitigated by intervention (*i.e.* greater renal or skeletal involvement), or a higher likelihood of disease progression (young age). The 2008 Workshop revisited these issues in light of additional data that have become available since that time.

This report focuses on issues arising from the clinical presen-

tation and natural history of PHPT. The first two questions review advances in the understanding of nonclassical manifestations of PHPT, namely those affecting the cardiovascular system and neuropsychiatric/ cognitive function. The third question provides an update on the natural history of PHPT, reviewing data on both typical hypercalcemic and normocalcemic variants. The next questions delve into the 2002 criteria for surgery, reviewing the current evidence for existing cut-points for both levels of hypercalciuria and bone density. Finally, we review available data key to the nonsurgical management of patients with PHPT, assessing what represents a clinically important change in

**TABLE 1.** Literature searches

Search words	Studies found
1. Primary hyperparathyroidism + cardiovascular	104
2. Primary hyperparathyroidism + mortality	110
3. Primary hyperparathyroidism + cerebrovascular	4
4. Primary hyperparathyroidism + neuropsychiatric	16
5. Primary hyperparathyroidism + depression	26
6. PHPT + asymptomatic	500
7. PHPT + natural history	44
8. Primary hyperparathyroidism + normocalcemic	90
9. PHPT + randomized trial	100
10. PHPT + bone density	199
11. PHPT + BMD	93
12. PHPT + calcium	875
13. PHPT + creatinine	89
14. PHPT + urine calcium + renal stone	18

serum calcium, serum creatinine, and bone mineral density (BMD) that might lead to a recommendation of surgery. Consensus responses are offered after the presentation of data and commentary in each area.

## Methods

Electronic literature searches were undertaken. Keywords were combined to find the relevant articles in PubMed (Table 1). The search was conducted on all literature limited to English language and humans published between 1996 and June, 2008. Of these the relevant articles were reviewed in detail. Consensus responses were gleaned after discussion of the available data by panel members. Levels of evidence for studies that contributed to the consensus responses are listed in Table 2.

### Question 1. Are there Cardiovascular Manifestations of Asymptomatic PHPT? Can They be Routinely Detected?

There is considerable debate regarding the cardiovascular manifestations of PHPT, with conflicting data concerning their extent and clinical significance. Many of the inconsistencies in the literature may be related to the evolution of the clinical presentation of PHPT, which has seen a once highly symptomatic disorder become minimally symptomatic in most cases. As a result, studies of the cardiovascular system in PHPT have enrolled populations with varying disease severity, often leading to discrepant findings. Increased serum calcium and PTH, the biochemical hallmarks of PHPT, are both known to affect the cardiovascular system. Studies assessing the effect of PHPT on the cardiovas-

cular system have investigated mortality, hypertension, cardiac and noncardiac vascular abnormalities, as well as more subtle functional changes in the cardiovascular system. This review will highlight available data, with particular attention to asymptomatic disease.

## Mortality

The increase in cardiovascular mortality in patients with severe and moderately severe PHPT has been well documented in studies from Scandinavia (2–5). The higher mortality rate declines with time from parathyroidectomy, but persists long after surgical cure, suggesting that PHPT may cause enduring damage to the cardiovascular system (6). The data on those with asymptomatic PHPT are limited, but several studies of patients with mild disease have not found mortality to be adversely impacted (7, 8). Patients followed for up to 15 yr [mean, 12 yr; calcium, (11.2 mg/dl) 2.81 mmol/liter] did not have decreased survival compared with age- and sex-matched controls (7). PHPT patients diagnosed in Rochester, Minnesota between 1965 and 1992 [mean calcium, (10.9 mg/dl) 2.73 mmol/liter] had no increase in overall mortality. Indeed, a significantly lower than expected cardiovascular death rate was seen in patients with PHPT (relative risk, 0.6) (8). This study did find that higher maximal serum calcium levels were an independent predictor of mortality.

One explanation for these incongruent mortality data is that more patients in the American studies (7, 8) had mild disease, with lower serum calcium levels and fewer symptoms, than patients in the European studies (2–6), where average calcium levels were significantly higher. This hypothesis is supported by data from Nilsson *et al.* (9) who analyzed mortality over a 30-yr period in 10,995 Swedish patients who underwent parathyroidectomy. Although an increased risk of cardiovascular mortality was observed in the overall cohort, this risk dissipated in those enrolled later in the study, when the patients had lower levels of serum calcium. Another study reported that survival after parathyroidectomy improved in those with a more recent calendar year of surgery (10). The decline in death risk paralleled the decrease in mean preoperative serum calcium level over time (10). Hedbäck and Odén (11) found that hypertensive patients had a 50% higher mortality than normotensive patients with PHPT, and the decline in mortality after surgery was significantly higher in the hypertensive individuals (2.4 *vs.* 1.3% per year). This cohort was not typical of those with asymptomatic PHPT (serum calcium levels up to 20 mg/dl). Another case-control study from Denmark of patients from a national hospital registry from 1977–1993 found that diagnosis of PHPT carried with it an increased risk of premature death, primarily from cerebrovas-

**TABLE 2.** Evidence for recommendations

Hierarchy of evidence	Refs.
Level Ia: Systematic review of randomized controlled trials	
Level Ib: Single randomized controlled trials	66–68
Level II: Systematic review of observational studies	
Level III: Single observational studies, case series	8, 9, 12, 20, 24, 44, 54, 57, 59, 60, 74, 76, 78–80, 82–84, 98–100, 104, 105
Level IV: Consensus guidelines	1, 73, 103

cular disease and cancer. Again, the relationship to level of serum calcium is unclear (12).

Although the available data do lend credence to the hypothesis that the decline in mortality in more recent years is due to lower calcium levels, it is also possible that increased cardiovascular mortality in PHPT is reversed by earlier diagnosis and intervention or recent advances in therapy for cardiovascular disease, or that there was a change in the referral pattern for parathyroidectomy. Finally, it must be noted that there are no population studies of mortality in mild PHPT surveying cohorts as large as those studied in patients with more severe disease. However, the reduction in cardiovascular mortality in mild PHPT was striking.

### Hypertension

Hypertension is frequently seen in association with PHPT, even among those with mild disease. The cause of hypertension is obvious in some patients with multiple endocrine neoplasia, in whom hypertension may be due to catecholamine excess and pheochromocytoma resection is curative. In those with sporadic PHPT, a few studies have shown a reduction in blood pressure immediately after parathyroidectomy (13, 14). However, because the majority of studies indicate that hypertension is not reversible with surgical cure, the presence of hypertension in patients with PHPT is not currently an indication for parathyroidectomy (15, 16). There has been no new information in this regard since the 2002 Workshop. However, if recent data suggesting a greater reduction in post-cure mortality in PHPT patients with hypertension were confirmed in a cohort limited to those with mild disease, it could warrant a reconsideration of this conclusion (11).

### The heart

#### Coronary artery disease

Both calcium and PTH have been implicated in the development of coronary disease. Lind *et al.* (17) have found serum calcium, even within the normal range, to be an independent, prospective risk factor for myocardial infarction in middle-aged Swedish men. The recently published Norwegian Tromsø study (18) found serum PTH to be an independent predictor of coronary heart disease. However, because the participants had normal serum calcium levels, it is likely that most patients with higher PTH levels had secondary hyperparathyroidism rather than PHPT and that the higher PTH levels may have been a surrogate for worse renal function or lower 25-hydroxyvitamin D levels.

There are very limited data regarding coronary artery disease in PHPT. The autopsy study of Roberts and Waller (19) concluded that hypercalcemia and PHPT (which affected only half of the patients studied) caused coronary atherosclerosis. The range of calcium in that report was 16.8–27.4 mg/dl (4.21–6.86 mmol/liter), making it impossible to generalize these data to patients with mild hyperparathyroidism. More recently, data from Vestergaard *et al.* (20) support an increased incidence of coronary artery disease in PHPT patients with more moderate hypercalcemia [mean serum calcium, (11.8 mg/dl) 2.96 mmol/liter], although the risk of cardiovascular death was related to tradi-

tional cardiovascular risk factors rather than to features of the hyperparathyroid state. Nilsson *et al.* (21) investigated reversible signs of myocardial ischemia in those with PHPT [mean serum calcium, 11.9 mg/dl (2.98 mmol/liter)] and found less ST-segment depression during exercise after parathyroidectomy. More data regarding the risk of coronary artery disease are needed in patients with mild PHPT before definitive conclusions can be made.

#### Valvular and myocardial calcification

Myocardial and valvular calcifications have clearly been demonstrated in PHPT patients with marked hypercalcemia (22). Studies in patients with more modest increases in serum calcium [(11.1 mg/dl) 2.78 mmol/liter] are limited but indicate no increase in valvular or myocardial calcifications (23), suggesting that this phenomenon is less likely to be seen in those with the milder biochemical phenotype of PHPT so common today.

#### Left ventricular hypertrophy (LVH)

LVH, a strong predictor of cardiovascular mortality, has been associated with PHPT in most, but not all (24, 25), studies across a wide range of calcium levels [(10.5–12 mg/dl) 2.63–3.00 mmol/liter]. Data suggest that LVH is independent of hypertension and is instead associated with PTH level (23, 26, 27). Whether or not LVH is reversible in PHPT is key to determining the management implications of these findings. LVH has been found to regress after parathyroidectomy in some but not all studies (23, 24, 26, 28). A recent study evaluated left ventricular mass index in patients who had surgery in comparison to a second group followed with no intervention for 1 yr. Left ventricular mass index was higher in those who did not have surgery, and extent of elevation was associated with PTH but not serum calcium levels (27). The finding of myocardial perfusion defects in five of 22 PHPT patients without a history of myocardial infarction, angina pectoris, or diabetes (29) represents a small, uncontrolled study that needs to be confirmed.

#### Cardiac conduction abnormalities and arrhythmia

In patients with severe hypercalcemia [calcium, 12.1 mg/dl (3.03 mmol/liter)], serum calcium levels correlated positively with T-wave duration and negatively with QT interval (30). Again, data are limited in asymptomatic patients. A small study in patients with more moderate hypercalcemia [mean calcium, (11.4 mg/dl) 2.85 mmol/liter] confirmed an increase in QT interval after parathyroidectomy but found no increased prevalence of supraventricular or ventricular arrhythmias or high-grade atrioventricular block (31). QT shortening was not observed in the small study of Barletta *et al.* (32) [11.5 mg/dl (2.88 mmol/liter)], but only 14 patients were studied. A recent study, which did not report calcium levels, also found QT shortening and higher sympathetic tone in those with PHPT (33).

#### Cardiac functional abnormalities

Diastolic dysfunction has been documented in most but not all studies, although the interpretation of some data is limited due to higher blood pressure in the PHPT group (23, 24, 27, 34). It is not clear whether diastolic dysfunction, if present, is secondary

to the effects of hypercalcemia or PTH excess. Data on improvement with surgical cure are also conflicting.

### Carotid plaque

Recent population-based evidence from Rubin *et al.* (35) supports an association between serum calcium concentration and carotid plaque thickness, an important predictor of cardiovascular outcomes. Carotid intima-medial thickness, a strong predictor of systemic atherosclerosis and cerebrovascular events, has been studied in patients with severe PHPT (26). Studies in mild disease (showing no effect of PHPT or its cure on carotid intima-medial thickness) have been limited by their small sample sizes, and by technical difficulties (36–39).

### Vascular function

Endothelial dysfunction is thought to be an early and important step in atherogenesis. Three studies in patients with severe PHPT [calcium, 12.0 mg/dl (3.00 mmol/liter)] variously reported normal and abnormal endothelial vasodilatory responses using differing methodologies (36, 40, 41). In those with somewhat lower calcium levels [mean, 11.6 mg/dl (2.90 mmol/liter)], Baykan *et al.* (42) also found impaired flow-mediated (endothelial) dilation that negatively correlated with calcium levels. No data are available in mild disease. Data on markers of endothelial dysfunction in PHPT are preliminary at this time (38). Two studies have reported increased vascular stiffness, an independent marker of cardiovascular risk in patients with mild PHPT [10.7–10.9 mg/dl (2.68–2.73 mmol/liter)] (43, 44). Indeed, PHPT was a stronger predictor of increased aortic stiffness than many traditional cardiovascular risk factors and was associated with the extent of elevation in PTH levels.

### Consensus response

*Despite the strong evidence that PHPT associated with marked hypercalcemia has deleterious cardiovascular consequences, data on the extent and nature of cardiovascular involvement in those with mild disease are too limited to provide a complete picture. There is evidence for subtle cardiovascular manifestations in mild disease, such as changes in endothelial function, increased vascular stiffness, and perhaps diastolic dysfunction, which must be confirmed and extended. It will be important to ascertain, to the extent possible, the association of any cardiovascular abnormalities with hypercalcemia or elevated PTH levels. The implications of subtle cardiovascular manifestations of asymptomatic PHPT, some of which are indirect surrogates for disease outcomes, are unknown at this time. However, demonstration of significant reversible cardiovascular abnormalities in asymptomatic PHPT could change the recommendation for parathyroidectomy.*

## Question 2. Can Neurocognitive Dysfunction be Detected in Asymptomatic PHPT? What is the Evidence for a Causal Relationship?

Classical PHPT had prominent psychological and neurological manifestations. It remains unclear to what extent neuropsychi-

atric symptoms are present in the mild form of PHPT seen commonly today. Many patients do report nonspecific symptoms, including weakness, easy fatigability, depression, intellectual weariness, cognitive impairment, loss of initiative, anxiety, irritability, sleep disturbance, and somatization. However, the 2002 National Institutes of Health Workshop on Asymptomatic PHPT did not add neuropsychiatric symptoms to the list of criteria for parathyroidectomy. The experts who convened at the time concluded that although such symptoms may well be associated with PHPT, there were insufficient data on the precise nature of these symptoms, their association with the disorder in an individual patient, and their reversibility to make these complaints a stand-alone indication for surgical intervention. Using an evidence-based approach, the guidelines for surgery in patients with asymptomatic PHPT were modified to recommend parathyroidectomy for patients with mild PHPT in whom testing or other information indicates end-organ effects that are likely to be mitigated by intervention (*i.e.* greater renal or skeletal involvement), or a higher likelihood of disease progression (young age). We revisit this issue in light of additional data that have become available since that time.

As is the case with cardiovascular manifestations of PHPT, the elevated serum calcium and PTH concentrations that are the hallmarks of the disease clearly have the potential to produce neuropsychiatric symptoms, and there is clear evidence of such involvement in those with severe hypercalcemia. It is also possible that coexisting vitamin D insufficiency, so common in patients with PHPT, could explain some of the weakness and fatigue of patients with the disease. There are, however, no data specifically investigating the association of neuromuscular function with vitamin D deficiency in PHPT. A number of studies have sought to characterize the neuropsychiatric features that may accompany mild PHPT, as well as the reversibility of such features with surgical cure (45). Some, but not all, suggest that there are psychological features of the disease that improve with surgery. Among the issues that have limited widespread acceptance of the conclusions from some of the studies in this area are their observational nature, their small sample sizes, the inclusion of subjects with symptomatic hyperparathyroidism, a lack of appropriate control groups, and testing at short intervals after parathyroidectomy.

Studies have also assessed the more recent concept of Health-Related Quality of Life as a reflection of the physical, social, and psychological effect of a disease state on the individual. Assessment tools have included the Short Form-36 (SF-36), the Medical Outcomes SF-36 (46), and the more disease-specific tool developed by Pasioka *et al.* (56, 57), the Parathyroid Assessment of Symptoms. Since the 2002 Workshop, there have been several observational studies using these assessment tools. Pasioka *et al.* (57) investigated the effect of parathyroidectomy on 203 patients with PHPT in comparison to a thyroid surgery control group and found a significant improvement in global Health-Related Quality of Life after parathyroid but not thyroid surgery. Sheldon *et al.* (58) reported significant improvement after parathyroidectomy in emotional health and energy/fatigue on the SF-36 in 43 “asymptomatic” patients. The study of Quiros *et al.* (59) showed improved perception of health status as well. However, the main



results reflected data obtained only 1 month after surgery, too short an interval to be sure that the effect was isolated from the successful outcome of surgery itself.

In addition to studies investigating psychological manifestations of PHPT, there have been several observational studies examining aspects of cognitive function (45, 51, 53, 54, 60) that have also yielded inconsistent results. Some reports suggest improvement with parathyroidectomy, whereas others do not. This variability may be due to variation in the aspects of cognition that have been investigated, as well as to differences in study design. Some are difficult to evaluate because of the very limited number of patients with PHPT [Cogan (Ref. 61),  $n = 4$ ; Goyal (Ref. 62),  $n = 14$ ], or limited breadth of neuropsychological testing (53, 61, 62). Recently, Chiang *et al.* (60) reported on 20 PHPT patients with an appropriate surgical control group. Although findings may have been obscured by a highly variable follow-up interval (30–380 d in PHPT, and 14–162 d after surgery in controls), they reported no differences between groups on neuropsychological testing in four domains and no within group improvement after surgery. In 2005, Coker *et al.* (63) reviewed all data on neuropsychological assessments in PHPT available since 1978 and concluded that the available data suffers from the small size of most studies, their variable design, the use of a limited number of cognitive tests rather than a battery testing varied domains, and limitation of most data collected to the immediate postoperative period. Potential confounding by coexisting depression is also a concern.

Recently, there have been preliminary reports suggesting possible subtle changes in cerebral function in PHPT. Pilot data suggest disease-specific changes, using single-photon emission computed tomography to study cerebral blood flow and cortical activation (64) and assessing neurocognitive impairment using functional magnetic resonance imaging (65). Extension and confirmation of these studies will be of significant interest.

Because the benefit of surgery in observational studies could be due to baseline differences between the surgical and observation groups or to biases introduced by their nonrandomized designs, more rigorously designed trials were identified as an important goal in 2002. Since that time, the first randomized studies of surgery *vs.* observation specifically conducted in patients with mild hypercalcemia have been published. All three studies have addressed aspects of neuropsychiatric function. The group of Rao and Talpos (66) randomized 53 patients to surgery or observation. They were assessed using the SF-36 general health survey, which determines the degree to which disease affects physical, psychological, and social functioning, and the SCL-90 scale, which quantifies psychological distress in nine dimensions. Within-group changes over time were measured, as were comparisons among the two treatment groups. Surgery was associated with a significant benefit in social functioning and emotional role function. On the SCL-90, surgery was associated with lower anxiety and phobia scores in comparison with those who did not have surgery, whereas there were no differences in the dimensions of depression, somatization, aggression, obsessive-compulsive, interpersonal sensitivity, paranoid ideation, and psychoticism. No significant differences between groups were noted in the three composite scores (Global Severity Index,

Positive Symptom Distress Index, Positive Symptom Total) or in any or the nine individual or three composite scores in the observational group alone over time. It is notable that unlike previous studies, Rao *et al.* (66) found no difference in baseline SF-36 scores between PHPT patients and normal subjects.

In 2007, the results of two randomized controlled trials of parathyroidectomy *vs.* observation in PHPT were published. In the first, Bollerslev *et al.* (67) reported on a large, multinational trial in Scandinavia. Although biochemical and BMD data are included, the end-points of the study were the effect of parathyroidectomy on quality of life and psychiatric symptoms in the 191 patients randomized to medical observation or surgery. The assessment tools included the SF-36 and the Comprehensive Psychopathological Rating Scale, which measures 65 items and can be used to screen for the presence and severity of psychotic, mood, and neurotic disorders. Their report represented an interim analysis, with data available on 191 patients at baseline, 119 at 1 yr, and 99 at 2 yr. In comparison with a large age- and sex-matched reference population at baseline, the patient population scored lower in all psychological domains on the mental component summary of the SF-36. Those with PHPT also had more psychiatric symptoms than controls as determined by the Comprehensive Psychopathological Rating Scale. At 2 yr, SF-36-assessed physical function worsened in the observation group, although this parameter did not improve after parathyroidectomy. Similarly, surgery provided no consistent improvement in psychological domains of functioning or psychiatric symptoms. Thus, although the preliminary results of this study suggest that impaired quality of life and psychiatric symptoms are present in mild PHPT, they do not demonstrate any clear benefit of surgery.

Most recently, Ambrogini *et al.* (68) reported on a randomized controlled trial of surgery *vs.* observation in 50 patients who met none of the National Institutes of Health (NIH) Guidelines for Surgery in asymptomatic PHPT. This study assessed quality of life and psychosocial well-being using the same tools used by Rao *et al.* (SF-36 and SCL-90) before and after 1 yr of follow-up. As in the Rao study but not the Bollerslev report, baseline differences between PHPT and a normal control data were minimal. Randomization resulted in a significantly higher emotional role function score in those undergoing surgery. Emotional role function did not improve after surgery as it did in the Rao study; if anything, a relative improvement was noted in the nonoperated group in whom scores came to resemble those of the operated group by 12 months. Overall, however, a between-group analysis did demonstrate a beneficial effect of parathyroidectomy in the following domains: bodily pain, general health, vitality, and mental health. No differences were noted in any of the other SF-36 or SCL-90 domains between the two groups, and no worsening in the nonoperated group was noted.

In summary, these three studies provide the first randomized controlled trials of surgery on neuropsychological function in mild PHPT. Aspects of the findings are inconsistent, with the larger Bollerslev study but not the others strongly supporting the existence of more psychological symptoms in those with PHPT. The Bollerslev study also differed from the others in not finding an improvement with surgery. Furthermore, the specific do-

mains noted to be abnormal and to improve or worsen over time differed among the studies. Although all the authors raise the possibility of a placebo effect of surgery, noting that the improvements were all in domains affecting social, emotional, and psychological functions, the balance of data in these studies does support a modest beneficial effect of parathyroidectomy on quality of life and psychological functioning.

### Consensus response

*Although patients with mild PHPT clearly have neuropsychological complaints, available data remain incomplete on their precise nature and their reversibility with surgery. However, there are some data supporting a modest beneficial effect of parathyroidectomy on quality of life and psychological functioning. Further efforts to define neuropsychological and cognitive deficits that are specific to PHPT are needed.*

### Question 3. What is the Natural History of Asymptomatic PHPT, and How Can That Knowledge Help to Determine When Surgical Therapy is Appropriate?

In 1968, with the recognition that many patients with PHPT were asymptomatic (69, 70), a prospective 10-yr study was initiated at the Mayo Clinic, although the data that were obtained were not able to predict which patients would ultimately require surgery (71). In another study, Rao *et al.* (72) followed 80 asymptomatic patients for up to 11 yr, during which time no evidence for worsening in biochemical or densitometric indices was found. This information, as well as other data, led to the establishment of guidelines for surgical criteria at the 1990 NIH Consensus Conference on Asymptomatic PHPT (73).

In 2002, a Workshop on Asymptomatic Primary Hyperparathyroidism was convened to review the advances in this disorder. At the time of that Workshop, data were available from a more recent observational study on the 10-yr natural history of the treated and untreated disease (74). These data showed that most asymptomatic patients did well, with no evidence of progressive disease (74). Reassuringly, in most patients who were followed without surgery, the average serum levels of calcium and PTH did not change over a 10-yr period. Average bone mass as measured by dual-energy x-ray absorptiometry (DXA) was typically stable, and hypercalciuria did not worsen. However, approximately 25% of patients had evidence of progressive disease, including worsening hypercalcemia, hypercalciuria, and reductions in bone mass. Only age appeared to be predictive of progression; patients younger than 50 yr of age were approximately three times as likely to have worsening disease (75). In contrast, in the patients who underwent successful surgery, in addition to normalization of serum calcium and PTH levels, BMD improved significantly at the lumbar spine and hip regions (74).

Based on these and other data, the Workshop Panel in 2002 developed conclusions about when surgical therapy is appropriate in asymptomatic PHPT, and the 1990 NIH Guidelines for Surgery were revised. It was suggested that surgery is always an

appropriate course to follow in patients with asymptomatic PHPT, so long as no medical contraindications are present (1). The Panel also agreed that although there are certain patients with asymptomatic PHPT who can be followed safely without surgery, the use of guidelines to decide on surgery can be helpful. Moreover, the Panel recommended that despite the generally benign natural history of PHPT, patients who do not have surgery should be monitored. The Panel also concluded that studies on the natural history of asymptomatic PHPT can be helpful and that secure clinical recommendations for management of this asymptomatic disorder required information about its natural history (1).

Since 2002, important new data on the natural history of asymptomatic PHPT have become available. Specifically, four studies (66–68, 76) have now provided heretofore unknown information about the treated and untreated disorder. Three of the studies (66–68) were randomized controlled trials, ranging in duration from 1 to 3.5 yr. Despite its design limitations, the single observational study is notable for its long duration, lasting 15 yr (76). All four of the studies prospectively addressed the course of biochemical and densitometric indices of PHPT and the extent to which the progression of disease occurred. In addition, they provided data on the safety of long-term medical monitoring as well as the reversibility of biochemical and densitometric indices with successful parathyroid surgery.

#### 1. Henry Ford PHPT Study

In 2004, a randomized controlled trial of parathyroidectomy *vs.* no surgery was reported by Rao *et al.* (66). Fifty-three patients were assigned to either parathyroidectomy ( $n = 25$ ) or observations ( $n = 28$ ) and were followed for at least 2 yr. After parathyroidectomy, there was an increase in BMD of the spine (1.2% per year;  $P < 0.001$ ), femoral neck (0.4% per year;  $P = 0.031$ ), total hip (0.3% per year;  $P = 0.07$ ), and forearm (0.4% per year;  $P < 0.001$ ) and a fall in serum total and ionized calcium, serum PTH, and urine calcium ( $P < 0.001$  for all) (66). In contrast, patients followed up without surgery lost BMD at the femoral neck ( $-0.4\%$  per year;  $P = 0.117$ ) and total hip ( $-0.6\%$  per year;  $P = 0.007$ ) but gained at the spine (0.5% per year;  $P =$  not significant) and forearm (0.2% per year;  $P = 0.047$ ), with no significant changes in biochemical indices of disease (66). Consequently, a significant effect of parathyroidectomy on BMD was evident only at the femoral neck (a group difference of 0.8% per year;  $P = 0.01$ ) and total hip (a group difference of 1.0% per year;  $P = 0.001$ ) but not at the spine (a group difference of 0.6% per year) or forearm (a group difference of 0.2% per year). Quality of life scores as measured by a 36-item SF-36 showed a modest measurable benefit of parathyroidectomy that was evident in social and emotional role function ( $P = 0.007$  and 0.012, respectively). Of note, the enrolled subjects were only 19% of the total number of eligible patients, raising a question about how nonparticipants, who refused to be randomized, might have differed from participants in this study.

#### 2. Scandinavian PHPT Study

In 2007, a randomized controlled trial of parathyroidectomy *vs.* no surgery was conducted by Bollerslev *et al.* (67). Recruited

from three Scandinavian countries, 191 patients were randomized to medical observation or surgery. Baseline, 1 yr ( $n = 119$ ), and 2 yr ( $n = 99$ ) data have been reported (67). Calcium and PTH normalized after surgery. BMD increased in the group randomized to operation, whereas the BMD remained stable in the medical observation group. No change in kidney function (creatinine) or blood pressure was observed longitudinally or between the groups. The two groups were similar at baseline in terms of quality of life (as measured by the SF-36 tool) and psychological symptoms, and no clinically significant changes in these parameters were seen during the observation time. As with the Rao study (66), a large number of eligible patients (enrolled over 7 yr) was necessary to yield the study population, again raising the question about how nonparticipants, who refused to be randomized, might have differed from participants in this study.

### 3. University of Pisa PHPT Study

In 2007, a randomized controlled trial of parathyroidectomy *vs.* observation was reported by Ambrogini *et al.* (68). Fifty subjects were randomly assigned to parathyroidectomy or no parathyroidectomy and were evaluated at 6 months and at 1 yr. At 1 yr, the change in BMD at the lumbar spine was greater after surgery ( $+4.16 \pm 1.13\%$  for surgery *vs.*  $-1.12 \pm 0.71\%$  for no surgery;  $P = 0.0002$ ). The change in BMD at the total hip was also significantly greater in the surgery group ( $+2.61 \pm 0.71\%$  for surgery *vs.*  $-1.88 \pm 0.60\%$  for no surgery;  $P = 0.0001$ ). There was no difference in BMD after 1 yr between both groups at the distal one-third radius site. In comparison with those who did not undergo surgery, the surgical subjects, after 1 yr, showed significant differences in four quality-of-life measures as determined by the SF-36 tool: bodily pain ( $P = 0.001$ ), general health ( $P = 0.008$ ), vitality ( $P = 0.003$ ), and mental health ( $P = 0.017$ ) (68).

### 4. Columbia University PHPT Project

In 1984, Bilezikian and Silverberg initiated a prospective observational study to define the natural history, pathophysiology, densitometric and other skeletal abnormalities of PHPT in the multichannel screening era (73). The 15-yr follow-up of this study, the longest natural history study of this disorder, has been recently reported (76). The longer follow-up period has led to new observations that have implications for decision-making and for management of this disorder.

Although recommendations for surgery or observation were made based upon NIH Guidelines, both groups included patients who were symptomatic and asymptomatic and those who met and did not meet guidelines. At baseline, the surgical and non-surgical groups were generally well matched, with the exception of the surgical group having higher serum calcium and PTH levels and lower lumbar spine and femoral neck Z-scores.

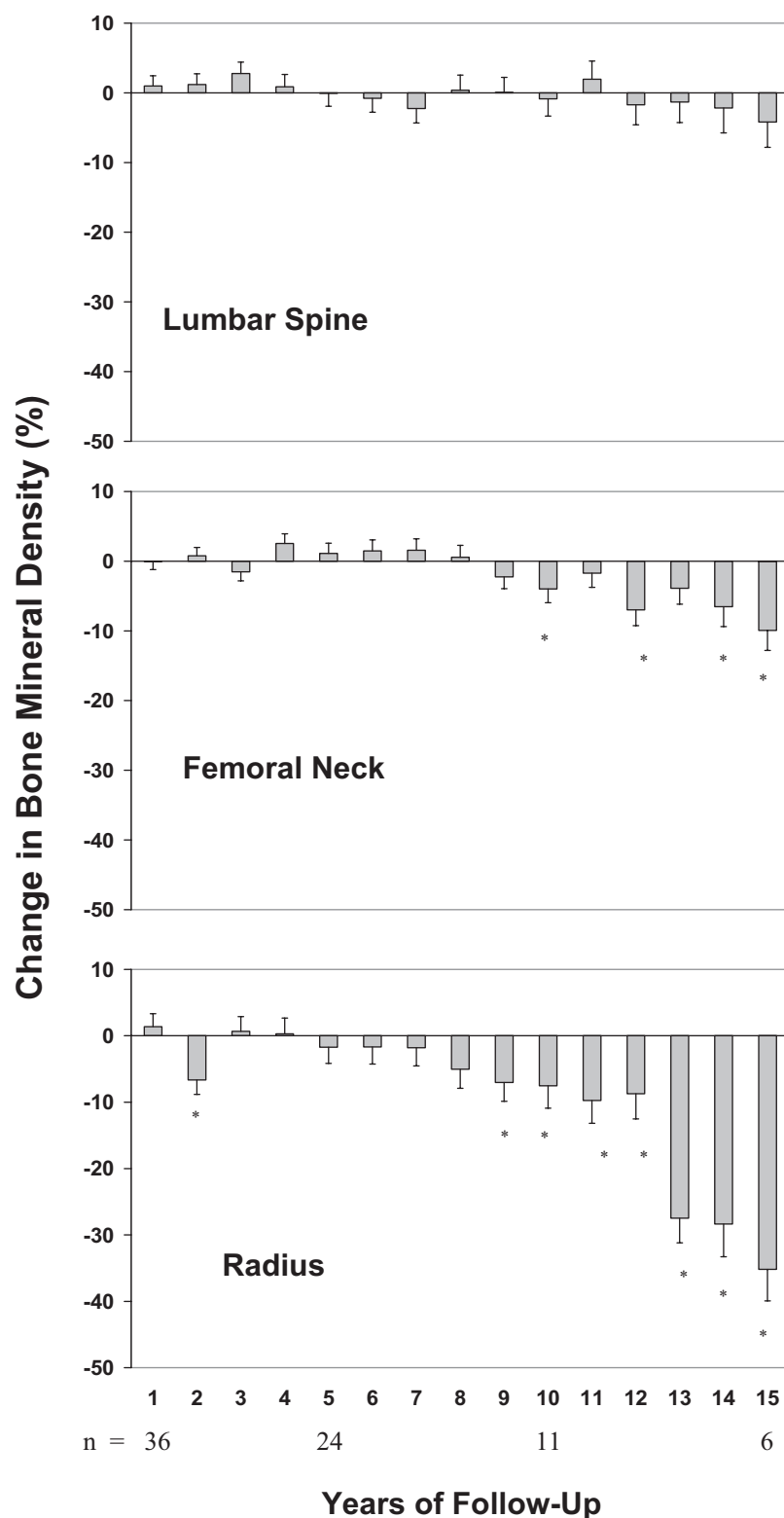
Parathyroidectomy resulted in early and persistent improvement in biochemical and densitometric parameters. After surgery, normalization of biochemical parameters, including serum calcium, PTH, vitamin D levels (25-hydroxy and 1,25-dihydroxy), and 24-h urinary calcium levels, was observed. Even more impressive was the postsurgical improvement in BMD: at all sites (lumbar spine, femoral neck, and distal 1/3 radius), BMD increased and remained above the 10% line for 15 yr after surgery (76) (Fig.

1). The improvements were seen in those who met and did not meet surgical criteria at study entry, confirming the salutary effect of parathyroidectomy in this regard on all patients.

Without parathyroid surgery, biochemistries remained stable for at least 12 yr, with a tendency for the serum calcium level to rise in yr 13–15. Densitometric indices remained stable for the first 8–10 yr of observation at all sites. However, beginning in yr 9, worsening cortical BMD began to be observed. Significant reductions in distal one-third radial BMD began to be seen; a decrease was also observed in femoral neck BMD beginning after yr 10 (76) (Fig. 2). Even more concerning was the observation that nearly 60% of the subjects lost more than 10% of their BMD over the 15 yr of observation. These data suggest that long-term conservative management of PHPT might not always be appropriate.

The group that did not undergo surgery was segregated into two subgroups that did (41%) and did not (59%) meet surgical criteria (1990 NIH Guidelines) at baseline. Surgical criteria included a serum calcium level greater than 12 mg/dl (3.00 mmol/liter), hypercalciuria, reduced cortical bone density, and age less than 50 yr. There was no difference in the proportion of subjects who initially met surgical criteria or did not in terms of ultimate progression of disease (35 *vs.* 38%, respectively). Thus both progression of disease and stable indices were not predicted by whether patients met or did not meet criteria for surgery at baseline. These data suggest that the current surgical guidelines might not be adequately predictive of progressive disease. Eventually, 40% of the subjects who were initially followed without surgery went on to have surgery (76).

There are no controlled studies on the risk of fracture in asymptomatic PHPT patients according to the 2002 criteria (1). However, in undiagnosed PHPT, follow-up studies and register studies suggest that fracture risk is increased up to 10 yr before diagnosis and treatment (relative risk, 1.8) (77, 78). Fracture risk increases with age, but is independent of the preoperative occurrence of kidney stones, whether or not the patients later undergo surgery or, if operated, the weight of the removed parathyroid tissue. These findings suggest that fracture risk may be increased in undiagnosed, free living, and untreated PHPT patients independent of whether they have other symptoms. Furthermore, there are no randomized controlled studies on the effect of surgery on the increased fracture risk in PHPT. However, a controlled nationwide register-based cohort study in 3213 patients with PHPT (mean age, 60.9 yr) evaluated the effect of surgery on fracture risk in patients with and without a prevalent fracture (79). Patients who had surgery ( $n = 1934$ ) were younger (mean age, 58.3 yr) and had higher serum calcium [ $(11.8 \text{ mg/dl})$  2.95 mmol/liter] than those ( $n = 1279$ ) who were not operated upon [mean age, 64.2 yr; 2.74 mmol/liter (11.0 mg/dl)]. Parathyroid surgery decreased the risk of hip and upper arm fracture by 50% (79) and all fractures by 30% after adjustment for sex, age, and previous fracture (80) over up to 20 yr of observation. This effect, which mirrors the effect of surgery on BMD, was also observed in patients without any prevalent fractures at diagnosis, suggesting that surgery may also prevent fractures in less symptomatic patients.



**FIG. 1.** Mean ( $\pm$  SEM) changes in bone mineral density at 3 sites in patients with primary hyperparathyroidism. Data shown are cumulative % changes from baseline at each site in subjects who did not undergo parathyroidectomy after 1–15 years of follow-up. \*,  $P < 0.05$  as compared to baseline.

#### Natural history of normocalcemic PHPT

To make the diagnosis of normocalcemic PHPT, in which the serum calcium is consistently normal but the PTH is consistently

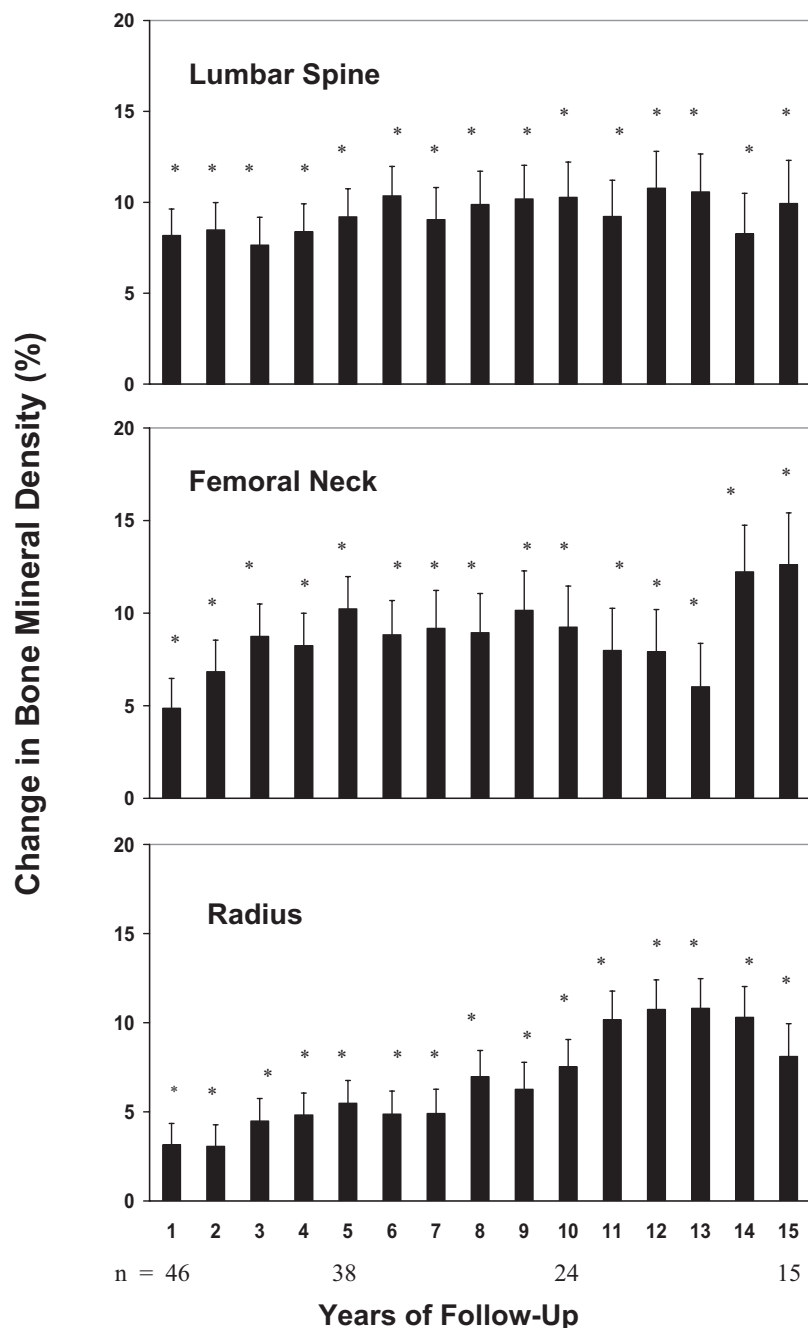
elevated, a rigorous search for causes of secondary hyperparathyroidism must be undertaken. In particular, it is essential to have data on vitamin D nutritional status. Many patients once thought to have normocalcemic PHPT are instead patients with the more usual hypercalcemic PHPT who have coexisting vitamin D deficiency, which lowers their serum calcium levels into the reference range. Such patients will become hypercalcemic when their vitamin D is replaced. In the absence of vitamin D deficiency or other causes of secondary hyperparathyroidism, patients are being seen regularly now that conform to the diagnosis of normocalcemic PHPT. There are limited data on the natural history of normocalcemic PHPT. Information is even more limited on those who meet the diagnostic criteria proposed as a result of this meeting, in which patients have normal serum calcium levels in the presence of elevated PTH concentrations; they must have normal ionized calcium levels, and possible causes of secondary hyperparathyroidism must be eliminated.

A large population-based study screened 5202 postmenopausal women and revisited subjects 8 yr after screening of calcium and PTH levels (81, 82). They identified as normocalcemic PHPT those women with normal serum calcium but frankly elevated PTH levels (consistent with the definition of normocalcemic PHPT) as well as those whose levels of PTH were in the upper half of the normal range ( $\geq 35$  pg/ml) in association with serum calcium concentrations that were high normal [9.9–10.3 mg/dl (2.48–2.58 mmol/liter)]. Over time, some of those in both of these groups did go on to exhibit a biochemical profile typical of hypercalcemic PHPT. Unfortunately, no data on vitamin D assessment were available, raising the possibility that some in the former group had typical hypercalcemic PHPT with coexisting vitamin D deficiency, and that some in the latter group (normal PTH and calcium levels) might not have been hyperparathyroid at all. Although these studies make it clear that some patients with asymptomatic normocalcemic PHPT do progress to typical hypercalcemic disease, they do not allow us to predict progression to hypercalcemia.

Two observational studies of normocalcemic PHPT have followed patients longitudinally. Several of the 32 individuals in one study had vitamin D deficiency and significant hypercalciuria, but PTH levels remained high after these issues were addressed (83). Twelve of the normocalcemic patients underwent surgery. Of the

20 who did not, none became hypercalcemic over a mean of 4 yr (range, 1–13 yr) of follow-up. In another observational study (84), the only report in which alternative explanations for ele-





**FIG. 2.** Mean ( $\pm$  SEM) changes in bone mineral density at 3 sites in patients with primary hyperparathyroidism after parathyroidectomy. Data shown are cumulative % changes from surgery at each site after 1–15 years of follow-up. \*,  $P < 0.05$  as compared to baseline.

vated PTH levels were rigorously assessed, 37 patients were followed for a mean of 3 yr (range, 1–9 yr). Typical hypercalcemic PHPT emerged in only seven (19%) individuals. However, 40% developed evidence of progressive disease, developing kidney stones, fracture, marked hypercalciuria or more than a 10% decline in BMD. Seven patients had successful parathyroidectomy, of whom three were hypercalcemic and the rest met another criteria for surgery. The authors raise the possibility that these patients, who presented to a Metabolic Bone Diseases Unit for evaluation, may not represent an early form of asymptomatic PHPT, and instead may be a variant of symptomatic disease.

### Consensus response

The balance of available evidence suggests that surgery is appropriate in the majority of patients with asymptomatic PHPT. Although there is evidence for biochemical and densitometric stability in the absence of surgery, the only long-term data (which are limited by both its observational nature and a small study group) suggests that the stability is not indefinite. Biochemistries are stable for up to 12 yr, whereas BMD is stable for up to 8 yr. In contrast, after parathyroidectomy, definitive gains ensue. There is normalization of biochemical abnormalities and long-term gains in lumbar spine, hip, and distal radius BMD (9).

However, there are still patients with asymptomatic PHPT for whom a nonsurgical approach is safe at least over the first 8 yr. Because the previously established guidelines for surgery in asymptomatic subjects do not predict who will or who will not show progression of disease, it is essential that monitoring with serum calcium and regular three-site BMD be performed if patients are to be followed without surgery.

In conclusion, a more proactive approach to surgical management should be recommended, although there is still a role for conservative or medical management.

### Consensus response on normocalcemic PHPT

There are insufficient data to comment on the natural history of normocalcemic PHPT. In some but not all patients, there is progression from the normocalcemic hyperparathyroid to the hypercalcemic hyperparathyroid state. Data also suggest that there is clinical heterogeneity in patients identified with this diagnosis, and further research into the various clinical phenotypes and their natural histories is warranted.

### Question 4. Should Hypercalciuria (>10 mmol/d or 400 mg/d) in the Absence of Kidney Stones be Considered an Indication For

#### Surgery?

#### Comment

Urinary calcium is only one of six risk factors affecting the development of kidney stones (the others are urinary volume, oxalate, uric acid, pH, and citrate). In PHPT, those patients who form stones do have a higher urinary calcium excretion than those who do not form stones (85). However, in patients who have not yet formed stones, a high urinary calcium is not associated with the development of stones (1). Urinary calcium excretion has low precision and varies with age, sex, race, dietary

calcium intake, and vitamin D status as well as glomerular filtration rate. Thus, it should not be used as a criterion for parathyroidectomy.

Both the 1990 and the 2002 (1) guidelines for management of PHPT stated that urinary excretion of calcium of greater than 400 mg in a 24-h period, collected at home on a free diet (defined as hypercalciuria), was an indication for parathyroidectomy. The dual rationale underlying this guideline was both that hypercalciuria was *the* major risk factor for urinary calcium stone formation in PHPT and that it reflected the “calcium burden on the kidney.” Both of these assumptions are largely incorrect. The calcium excreted in a 24-h urine collection varies with age, sex, and race, and thus an absolute value of 400 mg has different implications for children, men, and women, and individuals of different racial backgrounds. Finally, because the precision of a 24-h urine calcium collection is poor, one 24-h collection does not capture the large variability in the measurement.

As previously mentioned, urinary calcium concentration is only one of at least six urinary risk factors that determine the urine saturation of the calcium salts that underlie calcium stone formation (86). Urinary pH and volume, as well as levels of oxalate, uric acid, and inhibitors all play key roles in the overall risk of stone formation. Thus, measuring only urine calcium provides at best a poor risk of stone formation. This is supported by data demonstrating that 24-h urinary calcium excretion discriminates poorly between PHPT patients with and without stones.

The “calcium load” to the kidney is the product of the serum ultrafilterable calcium concentration, renal blood flow, and glomerular filtration rate. In patients with normal blood flow and filtration rates, the serum calcium concentration best reflects the renal calcium load. The 24-h urinary calcium excretion, on the other hand, reflects the sum of calcium absorption from the diet and net calcium resorption from bone (87). Daily urine calcium is low during childhood. As the skeleton stops growing and net bone accretion slows, the daily urine calcium increases until adult values are achieved by the second decade. Thereafter, daily calcium excretion is relatively constant until the seventh decade when it starts to decrease due to the combination of reduced dietary calcium and reduced calcium absorption that occurs with aging. Women have an increase in daily calcium excretion in the decade after menopause but have lower urine calcium excretion than men throughout adulthood (88). African-Americans have lower urine calcium levels than Caucasian Americans at all ages.

The low precision of 24-h urinary calcium measurement arises from several sources. The main source is the difficulty of timing the urine collection. Many subjects either overcollect or undercollect. Variation in dietary calcium and its availability for absorption is another source of the low precision.

### Consensus response

*In the absence of kidney stones, hypercalciuria (>10 mmol/d or 400 mg/d) should not be considered an indication for surgery for patients with PHPT.*

### Question 5. What Level of BMD Makes a Recommendation of Surgery Advisable? Is This Still a T-score of –2.5, Especially in Older Women? How Should the Status of the Three Assessed Skeletal Sites (Lumbar Spine, Hip, and Forearm) be Weighed?

Skeletal complications are a recognized consequence of PHPT. Advanced or “classical” PHPT is typically associated with a clinical presentation that includes generalized or focal bone pain, localized swelling of bone (“brown” tumors), and fragility fractures (89). In such cases, parathyroid surgery is indicated (90). With the introduction of autoanalyzers for blood chemistries in the 1970s, routine screening of serum calcium levels in apparently healthy individuals became common practice in Western societies. Now, most patients (about 80%) with PHPT are diagnosed before overt skeletal disease has developed (91). Although bone turnover is increased in PHPT, there are no data suggesting that bone markers are useful in the management of patients with the disease. On the other hand, BMD testing has emerged as a useful clinical tool to evaluate patients with asymptomatic PHPT for the presence of skeletal complications and to assess the risk of fracture. The 2002 Workshop on Asymptomatic Primary Hyperparathyroidism identified a T-score of less than –2.5 at the lumbar spine, hip, or distal one-third radius as an indication for surgery (1). The use of a T-score threshold of –2.5 was consistent with the WHO classification of osteoporosis (92), which was established according to the observed correlation between BMD and fracture risk in postmenopausal Caucasian women. The implication was that men and women with asymptomatic PHPT, regardless of ethnicity, had a similar correlation between BMD and fracture risk. Although it was recognized that PHPT was associated with a catabolic effect on cortical bone that was manifest by low BMD at the distal one-third radius (a skeletal site that is almost 100% cortical bone), BMD at the lumbar spine and hip (skeletal sites with both trabecular and cortical bone) was included in the recommendations for three reasons: 1) a subset of patients with PHPT has BMD that is much lower at the lumbar spine than at other skeletal sites (93); 2) vertebral fracture risk appears to be elevated in patients with PHPT (94); and 3) increases in BMD at trabecular skeletal sites are commonly observed after successful parathyroidectomy (95). The 2002 panel of experts felt that the reference databases used for calculation of T-scores should be matched for sex and ethnicity wherever possible but suggested that when an ethnicity-matched database is not available, a Caucasian reference database be used. The report of the 2002 Workshop included a research agenda to better define the relationship between BMD and fracture risk before and after parathyroidectomy; develop more BMD-, age-, sex-, and ethnicity-matched reference data; define the relationship between bone geometry and fracture risk before and after parathyroidectomy; and evaluate dynamic, structural, and microarchitectural aspects of PHPT before and after parathyroidectomy using micro-computed tomography (CT) and other technologies with bone biopsy specimens (1). At

the 2008 International Workshop on Primary Hyperparathyroidism, the recommendations for surgery based on BMD were reevaluated in the light of new data that have emerged since the previous Workshop.

Conventional two-dimensional bone histomorphometry in patients with PHPT has shown an increase in bone turnover that is consistent with observed increases in biochemical markers of bone turnover (96), with cortical thinning, increased cortical porosity, endosteal resorption, and preservation of trabecular bone volume and connectivity (97). Evaluation of trabecular microarchitecture using new technologies has largely confirmed these findings. In a three-dimensional analysis of transiliac bone biopsies using micro-CT technology in 29 women with PHPT (seven premenopausal, 22 postmenopausal) compared with 20 controls (15 premenopausal, 5 postmenopausal), and in 15 men with PHPT, there was a high correlation with conventional histomorphometry (98). Postmenopausal women with PHPT had higher trabecular bone volume/total volume (TV), higher bone surface area/TV, higher connectivity density, and lower trabecular separation than controls, with smaller age-related declines in trabecular bone volume/TV and connectivity density compared with controls, with no decline in bone surface area/TV. The measured parameters were similar in men and women with PHPT. It was concluded that trabecular bone microarchitecture is preserved in patients with mild PHPT. In another study of 51 patients (16 men, 35 women) with mild PHPT, quantitative backscattered electron imaging was used to evaluate trabecular BMD distribution in iliac crest bone biopsies (66). The observed reduction in average mineralization density and increase in the heterogeneity of the degree of mineralization was consistent with reduced mean age of bone tissue and previous observations of high bone turnover in patients with PHPT.

In a randomized controlled clinical trial of parathyroidectomy ( $n = 25$ ) vs. no parathyroidectomy ( $n = 28$ ) in patients with mild PHPT, parathyroidectomy was associated with a significant BMD increase at the femoral neck and total hip, but not the lumbar spine or forearm, compared with no parathyroidectomy, after at least 24 months of follow-up (99). There was a decrease in biochemical markers of bone turnover after parathyroidectomy. Another study of 11 patients followed for 5 yr after parathyroidectomy reported a significant increase in BMD at the lumbar spine, but not the hip and distal one-third radius compared with baseline, and a decrease in markers of bone turnover (100). To date, the longest prospective observational study of mild PHPT is in 116 patients (25 men, 91 women) followed for up to 15 yr, with and without parathyroidectomy (76). In patients without parathyroidectomy, lumbar spine BMD remained stable, whereas BMD at cortical skeletal sites decreased significantly, by a mean of 10% at the femoral neck and 35% at the one third distal radius in those observed for 15 yr. Over the entire period of follow-up, 37% of patients not having parathyroidectomy showed evidence of disease progression, representing a substantial increase over the 25% rate of progression observed over the first 10 yr (74). In patients having parathyroidectomy, there was a sustained increase in BMD at the lumbar spine, femoral neck, and distal one-third radius.

Geometric properties of bone at skeletal sites other than the iliac crest have been evaluated by quantitative CT in patients with PHPT. In a cross-sectional study of 36 women with PHPT compared with 100 healthy controls, peripheral quantitative CT of the radius showed a significant ( $P < 0.01$ ) 20% reduction in volumetric BMD at a predominantly trabecular region of interest and a significant ( $P < 0.01$ ) 5% reduction at a predominantly cortical region of interest (101). In the same patients, areal BMD by DXA was similar at the lumbar spine but decreased at the distal one-third radius compared with controls. This suggests that PHPT may have a catabolic effect on both trabecular and cortical bone, at least at some skeletal sites, with the effect on trabecular bone not being well captured with measurement of areal BMD by DXA. Compared with controls, the PHPT patients had a significantly greater radial endosteal circumference ( $+11\%$ ;  $P < 0.01$ ) and periosteal circumference ( $+4\%$ ;  $P < 0.01$ ), but significant difference in the polar strength strain index, a measure of stability against bending and torsion. In another study of 52 women with normocalcemic and hypercalcemic PHPT compared with 56 matched controls, peripheral quantitative CT of the tibia showed differences in both trabecular and cortical volumetric BMD consistent with a catabolic effect on both types of bone in both groups of patients with PHPT (102). There was a significantly greater tibial endosteal circumference but no difference in periosteal circumference compared with control.

Review of the literature revealed no new data to clarify the association of BMD and fracture risk in PHPT in women or men of any age category. The Official Positions of the International Society for Clinical Densitometry state that BMD should be reported as T-scores in peri- and postmenopausal women and in men age 50 and older, and that Z-scores should be used in premenopausal women and in men under 50 yr of age. In summary, the data suggest that PHPT is associated with a complex mix of competing effects that may vary according to skeletal site, load-bearing function, bone compartment, and probably other factors. These confounding factors may, in part, explain the apparent discrepancies in the effects of PHPT on trabecular bone in studies evaluating different skeletal sites with different technologies. PHPT appears to have anabolic effects at sites rich in trabecular bone with preservation of geometric properties, and catabolic effects on cortical bone with cortical thinning and endosteal resorption. During 15 yr of observation, over one-third of patients with mild PHPT have evidence of disease progression, whereas parathyroidectomy is associated with improvement in bone turnover and BMD at both cortical and trabecular skeletal sites.

### Consensus response

*We recommend parathyroid surgery when the T-score is  $-2.5$  or less 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 is  $-2.5$  or less in premenopausal women and in men under 50 yr of age.*

### Question 6. For the Management of Hyperparathyroidism in Patients Who Have Not Had Parathyroidectomy, What Represents a Clinically Important Change in Serum Calcium, Serum Creatinine, and BMD, Considering the Long-Term Variability in These Parameters?

Some patients with mild PHPT elect not to undergo parathyroidectomy, even when standard criteria for surgical intervention are met (76). In such cases, BMD and laboratory tests (e.g. serum calcium and creatinine) are typically monitored to assess disease progression. When there is clear evidence of worsening disease or clinical harm from PHPT, then surgery may be the most appropriate intervention. It is therefore instructive to have a thorough understanding of the natural history of PHPT to determine how best to monitor it and when to intervene. The longest observational study of mild PHPT followed 116 patients over up to 15 yr. Of these patients, 59 (51%) underwent parathyroidectomy, and 57 (49%) were followed without surgery (74). BMD at the lumbar spine, femoral neck, and distal one-third radius was measured at baseline and yearly thereafter. Laboratory studies included serum calcium and creatinine. Of the 57 patients not having initial surgery (mean baseline age,  $57 \pm 2$  yr; 32 postmenopausal women, 13 premenopausal women, 12 men), 49 (86%) were asymptomatic. The mean baseline serum calcium was  $10.5 \pm 0.1$  mg/dl (2.63 mmol/liter) and creatinine was  $1.0 \pm 0.1$  mg/dl. During the time of observation, 11 of these patients died. Those who died had baseline serum calcium that was similar to survivors, but they did have higher baseline PTH levels ( $161 \pm 25$  vs.  $107 \pm 8$  pg/ml;  $P < 0.05$ ). During the 15-yr period of observation, almost half (20 of 57) of the patients had successful parathyroidectomy. Of these, one was symptomatic at baseline but declined surgery, six initially met criteria for surgery but declined surgery at that time, six had evidence of disease progression, and seven did not wish to continue without surgery.

In the 49 asymptomatic PHPT patients who were followed conservatively for up to 15 yr, serum calcium rose to levels that were slightly but significantly greater than baseline, beginning at yr 13 [ $11.0 \pm 0.2$  mg/dl ( $2.75 \pm 0.05$  mmol/liter) and  $11.1 \pm 0.2$  mg/dl ( $2.78 \pm 0.05$  mmol/liter) at yr 13 and 15, respectively;  $P < 0.01$  for both compared with baseline]. There was no significant change in serum creatinine. BMD did not change at any measured skeletal site during the first 8 yr of follow-up, and BMD at the lumbar spine was stable for the entire 15 yr of follow-up. However, before the 10-yr observation point, there was a significant decrease in BMD at the femoral neck, a skeletal site with a substantial component of cortical bone, and at the distal one-third radius, which is almost exclusively cortical bone. There was a BMD decline greater than 10% at one or more skeletal sites in the majority (59%) of patients during the 15 yr of observation. Thirteen of the asymptomatic nonsurgical patients received off-protocol antiresorptive therapy at some time during the 15 yr, with a median treatment duration of 4 yr (range, 1 to 11 yr). In these patients, BMD changes were not significantly different than in those who did not receive therapy. Of the 49 asymp-

tomatic patients not having surgery initially, 20 (41%) initially met surgical criteria, 29 (59%) did not, and 18 (37%) developed new criteria for surgery at some time during the 15 yr of observation. Meeting surgical criteria at baseline was not predictive of progression of disease, defined as meeting new surgical criteria in the following 15 yr.

The findings of the 15-yr observation period enhance understanding of the natural history of mild PHPT beyond what was previously reported over 10 yr. Significant increases in serum calcium were first seen at 13 yr, despite stability of serum PTH levels, whereas serum creatinine remained unchanged. BMD at the lumbar spine remained stable over 15 yr, whereas BMD decreases at the femoral neck and distal one-third radius that were observed before 10 yr continued to progress. Because there were no reliable predictors of rising serum calcium or declining BMD at the time of baseline assessment, and because these changes may occur many years after diagnosis of PHPT, patients must receive long-term monitoring for evidence of disease progression.

To quantitatively compare BMD values over time in an individual patient, it is necessary to know the error that is inherent to the measurement itself ("precision error"). This allows the DXA interpreter to distinguish with confidence the difference between a measurement error and a genuine biological change. This is done by precision assessment in patients who are typical of those usually seen at a DXA facility, conducted according to well-recognized standards (103) that have been described in detail in the Official Positions of the International Society for Clinical Densitometry (104). Precision represents the reproducibility of the measurement and is typically calculated by measuring BMD in 15 patients three times or 30 patients two times on the same day with the same DXA instrument, repositioning the patient after each scan. The least significant change (LSC), a value that is derived from the precision calculation, is the smallest BMD change that is statistically significant with a 95% level of confidence. Quantitative comparison of serial BMD tests may be made using the same DXA instrument when the LSC is known, or with different DXA systems if a cross-calibration study (105) has been done. A difference in BMD that is smaller than the LSC may be clinically relevant, but it cannot be known with a high level of confidence that the change is real.

There are no data available on the LSC for serum calcium concentration.

### Consensus response

*We recommend that surgery be considered in patients who have a decrease in BMD that is equal to or greater than the calculated LSC. Serum creatinine does not appear to be a reliable marker of disease progression.*

### Acknowledgments

We appreciate the assistance of Sultan Chaudhry, medical writer, in the preparation of this manuscript.



This paper focuses on issues arising from the clinical presentation and natural history of asymptomatic PHPT, as presented at the Third International Workshop on Primary Hyperparathyroidism.

Address all correspondence and requests for reprints to: Shonni J. Silverberg, M.D., Columbia University College of Physicians and Surgeons, 630 West 168th Street, PH 8W-864, New York, New York 10032. E-mail: sjs5@columbia.edu.

Disclosure Statement: The authors have no conflicts of interest to declare.

## References

- Bilezikian JP, Potts Jr JT, El-Hajj Fuleihan G, Kleerekoper M, Neer R, Peacock M, Rastad J, Silverberg SJ, Udelman R, Wells Jr SA 2002 Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. *J Bone Min Res* 17(Suppl 2): N2-N11, and *J Clin Endocrinol Metab* 87:5353–5361
- Palmer M, Adami HO, Bergstrom R, Akerstrom G, 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
- Ronni-Sivula H 1985 Causes of death in patients previously operated on for primary hyperparathyroidism. *Ann Chir Gynaecol* 74:13–18
- Hedback G, Tisell LE, Bengtsson BA, Hedman I, Oden A 1990 Premature death in patients operated on for primary hyperparathyroidism. *World J Surg* 14:829–835; discussion, 836
- Ljunghall S, Jakobsson S, Joborn C, Palmer M, Rastad J, Akerstrom G 1991 Longitudinal studies of mild primary hyperparathyroidism. *J Bone Miner Res* 6(Suppl 2):S111–S116; discussion, S121–S124
- Hedback G, Odén A, Tisell LE 1991 The influence of surgery on the risk of death in patients with primary hyperparathyroidism. *World J Surg* 15:399–405; discussion, 406–407
- Soreide JA, van Heerden JA, Grant CS, Yau Lo C, Schleck C, Ilstrup DM 1997 Survival after surgical treatment for primary hyperparathyroidism. *Surgery* 122:1117–1123
- Wermers RA, Khosla S, Atkinson EJ, Grant CS, Hodgson SF, O'Fallon M, Melton III LJ 1998 Survival after the diagnosis of hyperparathyroidism: a population-based study. *Am J Med* 104:115–122
- Nilsson IL, Yin L, Lundgren E, Rastad J, Ekblom A 2002 Clinical presentation of primary hyperparathyroidism in Europe—nationwide cohort analysis on mortality from nonmalignant causes. *J Bone Miner Res* 17(Suppl 2):N68–N74
- Hedback G, Odén A 1998 Increased risk of death from primary hyperparathyroidism—an update. *Eur J Clin Invest* 28:271–276
- Hedback GM, Odén AS 2002 Cardiovascular disease, hypertension and renal function in primary hyperparathyroidism. *J Intern Med* 251:476–483
- Øgaard CG, Engholm G, Almdal TP, Vestergaard H 2004 Increased mortality in patients hospitalized with primary hyperparathyroidism during the period 1977–1993 in Denmark. *World J Surg* 28:108–111
- Nainby-Luxmoore JC, Langford HG, Nelson NC, Watson RL, Barnes TY 1982 A case-comparison study of hypertension and hyperparathyroidism. *J Clin Endocrinol Metab* 55:303–306
- Ringe JD 1984 Reversible hypertension in primary hyperparathyroidism—pre- and postoperative blood pressure in 75 cases. *Klin Wochenschr* 62:465–469
- Rapado A 1986 Arterial hypertension and primary hyperparathyroidism. Incidence and follow-up after parathyroidectomy. *Am J Nephrol* 6(Suppl 1):49–50
- Lind L, Jacobsson S, Palmer M, Lithell H, Wengle B, Ljunghall S 1991 Cardiovascular risk factors in primary hyperparathyroidism: a 15-year follow-up of operated and unoperated cases. *J Intern Med* 230:29–35
- Lind L, Skarfors E, Berglund L, Lithell H, 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
- Kamycheva E, Sundsfjord J, Jorde R 2004 Serum parathyroid hormone levels predict coronary heart disease: the Tromsø Study. *Eur J Cardiovasc Prev Rehabil* 11:69–74
- Roberts WC, Waller BF 1981 Effect of chronic hypercalcemia on the heart. An analysis of 18 necropsy patients. *Am J Med* 71:371–384
- Vestergaard P, Møllerup CL, Frøkjær VG, Christiansen P, Blichert-Toft M, Mosekilde L 2003 Cardiovascular events before and after surgery for primary hyperparathyroidism. *World J Surg* 27:216–222
- Nilsson IL, Aberg J, Rastad J, Lind L 2005 Maintained normalization of cardiovascular dysfunction 5 years after parathyroidectomy in primary hyperparathyroidism. *Surgery* 137:632–638
- Stefenelli T, Mayr H, Bergler-Klein J, Globits S, Woloszczuk W, Niederle B 1993 Primary hyperparathyroidism: incidence of cardiac abnormalities and partial reversibility after successful parathyroidectomy. *Am J Med* 95:197–202
- Dalberg K, Brodin LA, Juhlin-Dannfelt A, Farnebo LO 1996 Cardiac function in primary hyperparathyroidism before and after operation. An echocardiographic study. *Eur J Surg* 162:171–176
- Nuzzo V, Tauchmanova L, Fonderico F, Trotta R, Fittipaldi MR, Fontana D, Rossi R, Lombardi G, Trimarco B, Lupoli G 2002 Increased intima-media thickness of the carotid artery wall, normal blood pressure profile and normal left ventricular mass in subjects with primary hyperparathyroidism. *Eur J Endocrinol* 147:453–459
- Nilsson IL, Aberg J, Rastad J, Lind L 2000 Left ventricular systolic and diastolic function and exercise testing in primary hyperparathyroidism—effects of parathyroidectomy. *Surgery* 128:895–902
- Piovesan A, Molineri N, Casasso F, Emmolo I, Ugliengo G, Cesario F, Borretta G 1999 Left ventricular hypertrophy in primary hyperparathyroidism. Effects of successful parathyroidectomy. *Clin Endocrinol (Oxf)* 50:321–328
- Almqvist EG, Bondeson AG, Bondeson L, Nissborg A, Smedgard P, Svensson SE 2002 Cardiac dysfunction in mild primary hyperparathyroidism assessed by radionuclide angiography and echocardiography before and after parathyroidectomy. *Surgery* 132:1126–1132; discussion, 1132
- Stefenelli T, Abela C, Frank H, Koller-Strametz J, Globits S, Bergler-Klein J, Niederle B 1997 Cardiac abnormalities in patients with primary hyperparathyroidism: implications for follow-up. *J Clin Endocrinol Metab* 82:106–112
- Øgaard CG, Søndergaard SB, Vestergaard H, Jakobsen H, Nielsen SL 2005 Myocardial perfusion defects and the left ventricular ejection fraction disclosed by scintigraphy in patients with primary hyperparathyroidism. *World J Surg* 29:914–916
- Lind L, Ridefelt P, Rastad J, Akerstrom G, Ljunghall S 1994 Cytoplasmic calcium regulation and the electrocardiogram in patients with primary hyperparathyroidism. *Clin Physiol* 14:103–110
- Rosenqvist M, Nordenstrom J, Andersson M, Edhag OK 1992 Cardiac conduction in patients with hypercalcaemia due to primary hyperparathyroidism. *Clin Endocrinol (Oxf)* 37:29–33
- Barletta G, De Feo ML, Del Bene R, Lazzeri C, Vecchiario S, La Villa G, Brandi ML, Franchi F 2000 Cardiovascular effects of parathyroid hormone: a study in healthy subjects and normotensive patients with mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 85:1815–1821
- Curione M, Letizia C, Amato S, Di Bona S, Di Fazio F, Minisola S, Mazzuoli G, D'Erasmus E 2007 Increased risk of cardiac death in primary hyperparathyroidism: what is a role of electrical instability? *Int J Cardiol* 121:200–202
- Baykan M, Erem C, Erdogan T, Ersoz HÖ, Gedikli Ö, Korkmaz L, Küçükosmanoglu M, Hacahasanoglu A, Kaplan S, Celik S 2007 Assessment of left ventricular diastolic function and the Tei index by tissue Doppler imaging in patients with primary hyperparathyroidism. *Clin Endocrinol (Oxf)* 66:483–488
- Rubin MR, Rundek T, McMahon DJ, Lee HS, Sacco RL, Silverberg SJ 2007 Carotid artery plaque thickness is associated with increased serum calcium levels: the Northern Manhattan study. *Atherosclerosis* 194:426–432
- Nilsson IL, Aberg J, Rastad J, Lind L 1999 Endothelial vasodilatory dysfunction in primary hyperparathyroidism is reversed after parathyroidectomy. *Surgery* 126:1049–1055
- Kosch M, Hausberg M, Vormbrock K, Kisters K, Rahn KH, Barenbrock M 2000 Studies on flow-mediated vasodilation and intima-media thickness of the brachial artery in patients with primary hyperparathyroidism. *Am J Hypertens* 13:759–764
- Lumachi F, Ermani M, Frego M, Pilon F, Filosa T, Di Cristofaro L, De Lotto F, Fallo F 2006 Intima-media thickness measurement of the carotid artery in patients with primary hyperparathyroidism. A prospective case-control study and long-term follow-up. *In Vivo* 20:887–890
- Fallo F, Camporese G, Capitelli E, Andreozzi GM, Mantero F, Lumachi F 2003 Ultrasound evaluation of carotid artery in primary hyperparathyroidism. *J Clin Endocrinol Metab* 88:2096–2099
- Neunteufl T, Katzenschlager R, Abela C, Kostner K, Niederle B, Weidinger F, Stefenelli T 1998 Impairment of endothelium-independent vasodilation in patients with hypercalcemia. *Cardiovasc Res* 40:396–401
- Kosch M, Hausberg M, Vormbrock K, Kisters K, Gabriels G, Rahn KH, Barenbrock M 2000 Impaired flow-mediated vasodilation of the brachial

- artery in patients with primary hyperparathyroidism improves after parathyroidectomy. *Cardiovasc Res* 47:813–818
42. Baykan M, Erem C, Erdogan T, Hachisanoglu A, Gedikli O, Kiris A, Kucukosmanoglu M, Ersoz HO, Celik S 2007 Impairment of flow mediated vasodilatation of brachial artery in patients with primary hyperparathyroidism. *Int J Cardiovasc Imaging* 23:323–328
  43. Smith JC, Page MD, John R, Wheeler MH, Cockcroft JR, Scanlon MF, Davies JS 2000 Augmentation of central arterial pressure in mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 85:3515–3519
  44. Rubin MR, Maurer MS, McMahon DJ, Bilezikian JP, Silverberg SJ 2005 Arterial stiffness in mild primary hyperparathyroidism. *J Clin Endocrinol Metab* 90:3326–3330
  45. Brown GG, Preisman RC, 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
  46. Burney RE, Jones KR, Christy B, Thompson NW 1999 Health status improvement after surgical correction of primary hyperparathyroidism in patients with high and low preoperative calcium levels. *Surgery* 125:608–614
  47. Caillard C, Sebag F, Mathonnet M, Gibelin H, Brunaud L, Loudot C, Kraimps JL, Hamy A, Bresler L, Charbonnel B, Leborgne J, Henry JF, Nguyen JM, Mirallie E 2007 Prospective evaluation of quality of life (SF-36v2) and non-specific symptoms before and after cure of primary hyperparathyroidism (1-year follow-up). *Surgery* 141:153–159; discussion, 159–160
  48. Dotzenrath CM, Kaetsch AK, Pfingsten H, Cupisti K, Weyerbrock N, Vossough A, Verde PE, Ohmann C 2006 Neuropsychiatric and cognitive changes after surgery for primary hyperparathyroidism. *World J Surg* 5:680–685
  49. Eigelsberger MS, Cheah WK, Ituarte PH, Streja L, Duh QY, Clark OH 2004 The NIH criteria for parathyroidectomy in asymptomatic primary hyperparathyroidism: are they too limited? *Ann Surg* 239:528–535
  50. Joborn C, Hetta J, Lind L, Rastad J, Akerstrom G, Ljunghall S 1989 Self-rated psychiatric symptoms in patients operated on because of primary hyperparathyroidism and in patients with long-standing mild hypercalcemia. *Surgery* 105:72–78
  51. Numann PJ, Torppa AJ, Blumetti AE 1984 Neuropsychologic deficits associated with primary hyperparathyroidism. *Surgery* 96:1119–1123
  52. Pasieka JL, Parsons LL 1998 Prospective surgical outcome study of relief of symptoms following surgery in patients with primary hyperparathyroidism. *World J Surg* 22:513–518; discussion, 518–519
  53. Prager G, Kalaschek A, Kaczirek K, Passler C, Scheuba C, Sonneck G, Niederle B 2002 Parathyroidectomy improves concentration and retentiveness in patients with primary hyperparathyroidism. *Surgery* 132:930–935; discussion, 935–936
  54. Roman SA, Sosa JA, Mayes L, Desmond E, Boudourakis L, Lin R, Snyder PJ, Holt E, Udelsman R 2005 Parathyroidectomy improves neurocognitive deficits in patients with primary hyperparathyroidism. *Surgery* 138:1121–1128; discussion, 1128–1129
  55. Solomon BL, Schaaf M, Smallridge RC 1994 Psychologic symptoms before and after parathyroid surgery. *Am J Med* 96:101–106
  56. Pasieka JL, Parsons LL 2000 A prospective surgical outcome study assessing the impact of parathyroidectomy on symptoms in patients with secondary and tertiary hyperparathyroidism. *Surgery* 128:531–539
  57. Pasieka JL, Parsons LL, Demeure MJ, Wilson S, Malycha P, Jones J, Krzywda B 2002 Patient-based surgical outcome tool demonstrating alleviation of symptoms following parathyroidectomy in patients with primary hyperparathyroidism. *World J Surg* 26:942–949
  58. Sheldon DG, Lee FT, Neil NJ, Ryan Jr JA 2002 Surgical treatment of hyperparathyroidism improves health-related quality of life. *Arch Surg* 137:1022–1026; discussion, 1026–1028
  59. Quiros RM, Alef MJ, Wilhelm SM, Djuricin G, Lovisek K, Prinz RA 2003 Health-related quality of life in hyperparathyroidism measurably improves after parathyroidectomy. *Surgery* 134:675–681; discussion, 681–683
  60. Chiang CY, Andrewes DG, Anderson D, Devere M, Schweitzer I, Zajac JD 2005 A controlled prospective study of neuropsychological outcomes post parathyroidectomy in PHPT. *Clin Endocrinol (Oxf)* 62:99–104
  61. Cogan MG, Covey CM, Arief AI, Wisniewski A, Clark OH, Lazarowitz V, Leach W 1978 Central nervous system manifestations of hyperparathyroidism. *Am J Med* 65(6):963–970
  62. Goyal A, Chumber S, Tandon N, Lal R, Srivastava A, Gupta S 2001 Neuropsychiatric manifestations in patients of primary hyperthyroidism and outcome following surgery. *Indian J Med Sci* 55:677–686
  63. Coker LH, Rorie K, Cantley L, Kirkland K, Stump D, Burbank N, Tembreull T, Williamson J, Perrier N 2005 Primary hyperparathyroidism, cognition and health related quality of life. *Ann Surg* 242:642–648
  64. Mjaland O, Normann E, Halvorsen E, Rynning S, Egeland T 2003 Regional cerebral blood flow in patients with primary hyperparathyroidism before and after successful parathyroidectomy. *Br J Surg* 90:732–737
  65. Perrier ND, Coker LH, Rorie KD, Burbank NS, Kirkland KA, Passmore LV, Tembreull T, Stump DA, Laurienti PJ 2006 Preliminary report: functional MRI of the brain may be the ideal tool for evaluating neuropsychologic and sleep complaints of patients with primary hyperparathyroidism. *World J Surg* 30:686–696
  66. Rao DS, Philips ER, Divind GW, Talpos GB 2004 Randomized controlled clinical trial of surgery versus no surgery in patients with mild PHPT. *J Clin Endocrinol Metab* 89:5415–5422
  67. Bollerslev J, Jansson S, Mollerup CL, Nordenstrom J, Lundgren E, Tørring O, Varhaug J-E, Baranowski M, Aanderud S, Franco C, Freyschuss B, Isaksen GA, Ueland T, Rosen T, on behalf of the SIPH Study Group 2007 Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective, randomized trial. *J Clin Endocrinol Metab* 92:1687–1692
  68. Ambrogini E, Cetani F, Cianferotti L, Vignali E, Banti C, Viccica G, Oppo A, Miccoli P, Berti P, Bilezikian JP, Pinchera A, Marcocci C 2007 Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial. *J Clin Endocrinol Metab* 92:3114–3121
  69. Albright F, Reifenstein EC 1948 The parathyroid glands and metabolic bone disease. Baltimore: Williams, Wilkins
  70. Heath 3rd H, Hodgson SF, Kennedy MA 1980 Primary hyperparathyroidism. Incidence, morbidity, and potential economic impact in a community. *N Engl J Med* 302:189–193
  71. Scholz DA, Purnell DC 1981 Asymptomatic primary hyperparathyroidism. 10-year prospective study. *Mayo Clin Proc* 56:473–478
  72. Rao DS, Wilson RJ, Kleerekoper M, Parfitt AM 1988 Lack of biochemical progression or continuation of accelerated bone loss in mild asymptomatic primary hyperparathyroidism: evidence for biphasic disease course. *J Clin Endocrinol Metab* 67:1294–1298
  73. NIH Conference 1991 Diagnosis and management of asymptomatic primary hyperparathyroidism: consensus development conference statement. *Ann Intern Med* 114:593–597
  74. Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP 1999 A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med* 341:1249–1255
  75. Silverberg SJ, Brown I, Bilezikian JP 2002 Age as a criterion for surgery in primary hyperparathyroidism. *Am J Med* 113:681–684
  76. Rubin MR, Bilezikian JP, McMahon DJ, Jacobs T, Shane E, Siris E, Udesky J, Silverberg SJ 2008 The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. *J Clin Endocrinol Metab* 93:3462–3470
  77. Vestergaard P, Mollerup CL, Frokjaer VG, Christiansen P, Blichert-Toft M, Mosekilde L 2000 Cohort study of risk fracture before and after surgery for primary hyperparathyroidism. *BMJ* 321:598–602
  78. Vestergaard P, Mosekilde L 2003 Fractures in patients with primary hyperparathyroidism: nationwide follow-up study of 1201 patients. *World J Surg* 27:343–349
  79. Vestergaard P, Mosekilde L 2004 Parathyroid surgery is associated with a decreased risk of hip and upper arm fractures in primary hyperparathyroidism: a controlled cohort study. *J Int Med* 255:108–114
  80. Vestergaard P, Mosekilde L 2003 Cohort study on the effect of parathyroid surgery on multiple outcomes in primary hyperparathyroidism. *BMJ* 327:530–534
  81. Lundgren E, Rastad J, Thurfjell E, Akerstrom G 1997 Population based screening for PHPT with serum calcium and PTH values in menopausal women. *Surgery* 121:287–294
  82. Lundgren E, Hagstrom EG, Lundin J, Winnerback K, Roos J, Ljunghall S, Rastad J 2002 Primary hyperparathyroidism revisited in menopausal women with serum calcium in the upper normal range at population based screening 8 years ago. *World J Surg* 26:931–936
  83. Tordjman KM, Greenman Y, Osher E, Shenkerman G, Sern N 2004 Characterization of normocalcemic primary hyperparathyroidism. *Am J Med* 117:861–863
  84. Lowe H, McMahon DJ, Rubin MR, Bilezikian JP, Silverberg SJ 2007 Normocalcemic primary hyperparathyroidism: further characterization of a new clinical phenotype. *J Clin Endocrinol Metab* 92:3001–3005
  85. Odvina CV, Sakhae K, Heller HJ, Peterson RD, Poindexter JR, Padalino PK, Pak CY 2007 Biochemical characterization of primary hyperparathyroidism with and without kidney stones. *Urol Res* 35:123–128
  86. Peacock M, Robertson WG 1989 Urinary calcium stone disease. In: DeGroot LJ, Besser GB, Cahill Jr GF, Marshall JC, Nelson DH, Odell WD, Potts Jr JT,

- Rubenstein AH, Steinberger E, eds. *Endocrinology*. 2nd ed. Philadelphia: WB Saunders Company; 1111–1132
87. Peacock M 2002 Primary hyperparathyroidism and the kidney: biochemical and clinical spectrum. *J Bone Miner Res* 17(Suppl 2): N87–N94
  88. Bulusu L, Hodgkinson A, Nordin BEC, Peacock M 1970 Urinary excretion of calcium and creatinine in relation to age and body weight in normal subjects and patients with renal calculi. *Clin Sci* 38:601–612
  89. Albright F, Aub JC, Bauer W 1934 Hyperparathyroidism: a common and polymorphic condition as illustrated by seventeen proved cases from one clinic. *JAMA* 102:1276–1287
  90. Miller PD, Bilezikian JP 2002 Bone densitometry in asymptomatic primary hyperparathyroidism. *J Bone Miner Res* 17:N98–N102
  91. Silverberg SJ, Bilezikian JP 1996 Evaluation and management of primary hyperparathyroidism. *J Clin Endocrinol Metab* 81:2036–2040
  92. WHO Study Group on Assessment of Fracture Risk and its Application to Screening for Postmenopausal Osteoporosis 1994 Assessment of fracture risk and its application to screening for postmenopausal osteoporosis. Tech Rep Ser 843. Geneva: World Health Organization
  93. Silverberg SJ, Locker FG, Bilezikian JP 1996 Vertebral osteopenia: a new indication for surgery in primary hyperparathyroidism. *J Clin Endocrinol Metab* 81:4007–4012
  94. Khosla S, Melton III LJ 2002 Fracture risk in primary hyperparathyroidism. *J Bone Miner Res* 17:N103–N107
  95. Abugassa S, Nordenstrom J, Eriksson S, Mollerstrom G, Alverdy A 1990 Skeletal remineralization after surgery for primary and secondary hyperparathyroidism. *Surgery* 107:128–133
  96. Valdemarsson S, Lindergard B, Tibblin S, Bergenfelz A 1998 Increased biochemical markers of bone formation and resorption in primary hyperparathyroidism with special reference to patients with mild disease. *J Intern Med* 243:115–122
  97. Eriksen EF 2002 Primary hyperparathyroidism: lessons from bone histomorphometry. *J Bone Miner Res* 17:N95–N97
  98. Dempster DW, Muller R, Zhou H, Kohler T, Shane E, Parisien M, Silverberg SJ, Bilezikian JP 2007 Preserved three-dimensional cancellous bone structure in mild primary hyperparathyroidism. *Bone* 41:19–24
  99. Roschger P, Dempster DW, Zhou H, Paschalis EP, Silverberg SJ, Shane E, Bilezikian JP, Klaushofer K 2007 New observations on bone quality in mild primary hyperparathyroidism as determined by quantitative backscattered electron imaging. *J Bone Miner Res* 22:717–723
  100. Tamura Y, Araki A, Chiba Y, Mori S, Hosoi T, Horiuchi T 2007 Remarkable increase in lumbar spine bone mineral density and amelioration in biochemical markers of bone turnover after parathyroidectomy in elderly patients with primary hyperparathyroidism: a 5-year follow-up study. *J Bone Miner Metab* 25:226–231
  101. Chen Q, Kaji H, Iu MF, Nomura R, Sowa H, Yamauchi M, Tsukamoto T, Sugimoto T, Chihara K 2003 Effects of an excess and a deficiency of endogenous parathyroid hormone on volumetric bone mineral density and bone geometry determined by peripheral quantitative computed tomography in female subjects. *J Clin Endocrinol Metab* 88:4655–4658
  102. Charopoulos I, Tournis S, Trovas G, Raptou P, Kaldrymides P, Skarandavos G, Katsalira K, Lyrakis GP 2006 Effect of primary hyperparathyroidism on volumetric bone mineral density and bone geometry assessed by peripheral quantitative computed tomography in postmenopausal women. *J Clin Endocrinol Metab* 91:1748–1753
  103. Bonnick SL, Johnston Jr CC, Kleerekoper M, Lindsay R, Miller P, Sherwood L, Siris E 2001 Importance of precision in bone density measurements. *J Clin Densitom* 4:105–110
  104. Baim S, Binkley N, Bilezikian JP, Kendler DL, Hans DB, Lewiecki EM, Silverman S 2008 Official positions of the International Society for Clinical Densitometry and Executive Summary of the 2007 Position Development Conference. *J Clin Densitom* 11:75–91
  105. Shepherd JA, Lu Y, Wilson K, Fuerst T, Genant H, Hangartner TN, Wilson C, Hans D, Leib ES 2006 Cross-calibration and minimum precision standards for dual-energy x-ray absorptiometry: the 2005 ISCD official positions. *J Clin Densitom* 9:31–36