Current Issues in the Presentation of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Fourth International Workshop

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Objective: This report summarizes data on traditional and nontraditional manifestations of primary hyperparathyroidism (PHPT) that have been published since the last International Workshop on PHPT.

Participants: This subgroup was constituted by the Steering Committee to address key questions related to the presentation of PHPT. Consensus was established at a closed meeting of the Expert Panel that followed.

Evidence: Data from the 5-year period between 2008 and 2013 were presented and discussed to determine whether they support changes in recommendations for surgery or nonsurgical follow-up.

Consensus Process: Questions were developed by the International Task Force on PHPT. A comprehensive literature search for relevant studies was undertaken. After extensive review and discussion, the subgroup came to agreement on what changes in the recommendations for surgery or nonsurgical follow-up of asymptomatic PHPT should be made to the Expert Panel.

Conclusions: 1) There are limited new data available on the natural history of asymptomatic PHPT. Although recognition of normocalcemic PHPT (normal serum calcium with elevated PTH concentrations; no secondary cause for hyperparathyroidism) is increasing, data on the clinical presentation and natural history of this phenotype are limited. 2) Although there are geographic differences in the predominant phenotypes of PHPT (symptomatic, asymptomatic, normocalcemic), they do not justify geography-specific management guidelines. 3) Recent data using newer, higher resolution imaging and analytic methods have revealed that in asymptomatic PHPT, both trabecular bone and cortical bone are affected. 4) Clinically silent nephrolithiasis and nephrocalcinosis can be detected by renal imaging and should be listed as a new criterion for surgery. 5) Current data do not support a cardiovascular evaluation or surgery for the purpose of improving cardiovascular markers, anatomical or functional abnormalities. 6) Some patients with mild PHPT have neuropsychological complaints and cognitive abnormalities, and some of these patients may benefit from surgical intervention. However, it is not possible at this time to predict which patients with neuropsychological complaints or cognitive issues will improve after successful parathyroid surgery. **(*J Clin Endocrinol Metab* 99: 3580–3594, 2014)**

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Abbreviations: aBMD, areal BMD; Apo, apolipoprotein; BMD, bone mineral density; BMI, body mass index; CFR, coronary flow reserve; CI, confidence interval; CRP, C-reactive protein; CT, computed tomography; DXA, dual-energy x-ray absorptiometry; FGF23, fibroblast growth factor 23; HRpQCT, high-resolution pQCT; IMT, intimal medial thickness; LSC, least significant change; NPHPT, normocalcemic PHPT; $1,25(OH)_2D$, 1,25-dihydroxyvitamin D; PHPT, primary hyperparathyroidism; pQCT, peripheral QCT; PTX, parathyroidectomy; QCT, quantitative CT; QOL, quality of life; RCT, randomized controlled trial; SF-36, Short Form-36; TBS, trabecular bone score.

The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism (PHPT) revisited issues in light of additional data that have become available since the time of the last Workshop 5 years ago (1). The issues were formulated as a series of questions:

1. Is there new information on the natural history of PHPT?
2. Are there data to support the need for geography-specific guidelines for disease management?
3. What are the new data regarding the effects of PHPT on its two classical target organs: the skeleton?
4. And the kidney?
5. Are there new insights on nonclassical manifestations of PHPT, namely those affecting the cardiovascular system?
6. And neuropsychiatric/cognitive function?
7. Do new data on changes in serum calcium levels, renal function, or bone involvement (bone mineral density [BMD] and fragility fractures) over time suggest new guidelines for surgery?

After a series of presentations and discussion among the Working Groups, the Expert Panel convened to recommend the best evidence-based guidelines for the management of asymptomatic PHPT.

Materials and 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 the English language and human subjects published between June 2008 and June 2013. Relevant articles were reviewed in detail. Consensus responses reflect discussion of the available data by panel members.

Table 1. Literature Searches of Articles Published Between June 2008 and June 2013

Search Terms	No. of Studies Found
PHPT + clinical presentation	22
PHPT + natural history	11
PHPT + epidemiology	120
PHPT + Europe	57
PHPT + Brazil	27
PHPT + Asia	25
PHPT + fracture	1
PHPT + BMD/bone density/QCT	30
PHPT + trabecular bone score	3
PHPT + bone biopsy/histomorphometry	4
Normocalcemic PHPT	21
PHPT + cognition	17
PHPT + depression	26
PHPT + psychiatric	12
PHPT + psychological	7
PHPT + cardiovascular	81
PHPT + mortality	67
PHPT + cerebrovascular	3
PHPT + kidney stone or urine calcium	23
PHPT + renal function	26

Update 1: Regarding the Presentation and Natural History of Asymptomatic PHPT

Asymptomatic PHPT has been the dominant clinical phenotype of PHPT in the United States and Western Europe for the past 40 years. Although overt symptoms are uncommon, PHPT patients still regularly demonstrate target organ involvement (see questions 3–6). Nephrolithiasis continues to be the most common overt complication of the disease, and skeletal involvement is detected by dual-energy x-ray absorptiometry (DXA), where lumbar spine BMD is relatively well preserved whereas the distal 1/3 radius is preferentially reduced (1–3). The proclivity of PTH to be more catabolic at the 1/3 radius, a cortical site, while much less so at the lumbar spine, a trabecular site, gave rise to the notion that the trabecular skeleton is spared in this disease when it presents in its common asymptomatic form. Recent data obtained by high-resolution and other imaging modalities as well as newer analytic methods have raised questions about the selectivity of PTH to erode bone in PHPT (see question 3). Nonspecific symptomatology, which is frequently present but not easily attributable to PHPT, has led some investigators to search for ways in which new metrics can address this point (see question 4).

Asymptomatic PHPT has a natural history that includes long-term, but not indefinite, stability and increases in BMD at all sites by DXA after successful parathyroidectomy (PTX) (2, 3). There have been very limited new data on the natural history of this most common variant of PHPT since the last conference.

Over the past 10 years, the most noteworthy change in the presentation of PHPT in the United Sates is the emergence of normocalcemic PHPT (NPHPT). Although NPHPT was first formally recognized at the time of the Third International Workshop on the Management of Asymptomatic PHPT in 2008 (1), the entity remains incompletely described, particularly regarding its epidemiology, natural history, and management. The diagnostic criteria and presentation of NPHPT are discussed in the accompanying article by Eastell et al (4). The epidemiology of NPHPT has been investigated in a number of populations (5–7), but the data are confounded by differing methods used to exclude secondary hyperparathyroidism among the various studies. Some patients with NPHPT have undergone parathyroid surgery, and their parathy-

roid gland pathology substantiates the existence of NPHPT (8, 9). There have been very limited new data adding to the literature on the presentation of this variant of PHPT, which will therefore only be mentioned in the ensuing sections in a very limited way. At this time, evidence-based guidelines for the management of NPHPT are lacking. The need for research on the effect of NPHPT on classical and nonclassical target organs of the hyperparathyroid process is clear.

Question 1: Does new information about the natural history of asymptomatic PHPT (both hypercalcemic and normocalcemic) help to determine when surgical therapy is appropriate in each variant of the disease?

Response: No. There is no new information on the natural history of PHPT that clarifies when surgical therapy is appropriate in either hypercalcemic or normocalcemic variants of the disease. Other information has become available to suggest newer guidelines, but they are not based upon the natural history of the disorder. Although many physicians are approaching management decisions in NPHPT in a manner similar to asymptomatic PHPT, evidence-based guidelines are lacking.

Update 2: Regional Geographic Differences in the Clinical Presentation of PHPT

With the recognition that prior Guidelines relied to a large extent on data collected in American cohorts, we sought to assess a wider geographic range in this regard.

United States

Recent data shed light on the epidemiology of PHPT in the United States. In a racially mixed population in Southern California (using the Kaiser-Permanente insurance database covering 3.5 million enrollees) (10), the incidence of PHPT varied from 34–120 per 100 000 person-years, with a mean of 66 per 100 000 person-years in women, and from 13 to 36 per 100 000 person-years in men. The incidence increased with advancing age, and was highest in blacks, followed by whites, with rates for Asians, Hispanics, and other races lower than for whites. The prevalence of PHPT tripled during the study period (1995–2010), increasing from 76 to 233 per 100 000 person-years in women, and from 30 to 85 per 100 000 person-years in men. Racial differences in prevalence were similar to those found in incidence.

Europe

There are no formal studies exploring the modalities used to characterize clinical presentation of PHPT in Europe. Within Europe, different modes of presentation may reflect prevailing practice patterns (routine serum calcium determination, for instance), socioeconomic conditions of the region, variable degree of awareness of the condition among physicians, and differing ability to detect the disease. In addition, many patients are now diagnosed with PHPT in tertiary care centers, as part of screening or investigation of the most common metabolic bone disease, osteoporosis. When these "asymptomatic" patients are thoroughly investigated, they may manifest both typical (ie, reduced BMD, kidney stones) and atypical (cardiovascular, gastrointestinal) complications of the disease.

A recent retrospective cross-sectional study evaluated the biochemical and skeletal manifestations of PHPT in two Caucasian populations (US and Italian) of men and women, matched for age and body mass index (BMI) (11). Although mean serum total and ionized calcium levels were significantly higher in Italian men compared to women, and in Italians compared to US patients, mean PTH levels did not differ by gender or national origin. Female US patients had higher BMI-adjusted hip BMD than did Italian women. Thus, it appears that despite similar levels of circulating PTH, Italian patients have more pronounced effects of the disease, with higher serum calcium and lower BMD.

Latin America

Although serum calcium measurements have become routine for over three decades in some Latin American institutions, most Latin American patients still present with symptomatic disease (12). In a case series of 124 patients from Recife, Brazil, 47% presented with no symptoms related to the disease, whereas 25% presented with osteitis fibrosa cystica, 25% with renal stone disease without overt bone involvement, and 2% with the typical neuropsychiatric syndrome (13). Bone density was extremely low in severely affected patients but showed remarkable recovery after surgical cure. Serum PTH and bone markers were considerably higher in these patients, who also had a high incidence of vitamin D deficiency. Histology revealed a single adenoma in 87% of patients, whereas 6.4% had multiple gland hyperplasia, and 3.8% had carcinoma. Similar patterns of clinical presentation were seen in São Paulo (14) and in an Argentinian case series (12).

The limited data from large epidemiological studies from this region suggest an evolution toward more asymptomatic disease. A study of 4207 patients age 18 and older attending public and private endocrine centers in Recife, Brazil (15), found a prevalence of 0.78% (95% confidence

interval [CI], 0.52–1.04), of which 81.8% were asymptomatic. The female:male ratio was 7.2:1, and 89.7% of these women were postmenopausal. Mean age was 61 ± 16 years, serum calcium level was 10.63 ± 1.33 mg/dL, and serum PTH was 182 ± 327 pg/mL. Osteitis fibrosa cystica was present in 6.1%, nephrolithiasis in 18.2%, and acute neuropsychiatric syndrome in 3%, with 51.5% having fatigue and 39.3% having muscle weakness. Almost half of the 70 patients with PHPT seen at one institution were normocalcemic. Normocalcemic and hypercalcemic patients did not differ in frequency of nephrolithiasis (18.2 vs 18.9%; $P = .937$) or history of fractures (15 vs 11%; $P = .726$) (16).

Asia

From 1958–1993, PHPT patients in Beijing, China, demonstrated a much higher serum calcium level (12.4 ± 1.1 vs 10.7 ± 10.7 mg/dL) and remarkably higher PTH concentration (21.4-fold vs 1.9-fold the upper limit of normal) than American patients with PHPT during this same time (17). Strikingly, 97% of the Beijing PHPT patients had skeletal disease (osteitis fibrosa cystica, osteoporosis, and pathological fractures), kidney stones, and other features of PHPT. More recent data provide evidence of changing clinical patterns of PHPT in China. Among 249 consecutive PHPT patients treated in a single clinical center in Shanghai from 2000 to 2010, 60% had classical symptoms (polydipsia, polyuria, urolithiasis, bone pain, fatigue), and 6% had parathyroid cancer (18). However, asymptomatic cases increased from less than 20% before 2006 to approximately 50% in 2007–2010. This change was driven by more routine serum calcium testing as well as incidental discovery of parathyroid nodules on thyroid ultrasonography. In Hong Kong, asymptomatic PHPT increased from 5% in 1973–1982 to 39% in 1983–1992 to 59% in 1993–2002 (19). In contrast to the evolving experience in China, other Asian countries (India, Iran, Saudi Arabia, Thailand) still report predominantly symptomatic disease with skeletal and renal manifestations, and asymptomatic PHPT is rare (0–2.2%) (20–23). Normocalcemic PHPT has not yet been formally described in Asian cohorts.

Question 2: Should regional geographic differences in the clinical presentation of PHPT lead to regional differences in surgical guidelines?

Response: Not yet. The presentation of PHPT is changing in many countries around the world. Where the most epidemiological data are available, the disease is changing from a high rate of symptomatic disease toward a large number of asymptomatic patients. In some countries where data are available, the normocalcemic variant is becoming more common. However, it is unclear that these data warrant regional differences in surgical guidelines.

Update 3: Classical Features—The Skeleton

The classical radiological features of osteitis fibrosa cystica (demineralized skeleton, salt-and-pepper appearance of the skull, radiological "loss" of the distal 1/3 of the clavicle, subperiosteal resorption of the phalanges, bone cysts, and brown tumors) are still seen in parts of the world where PHPT is most often symptomatic. In most places today, osteitis fibrosa cystica is rare, but skeletal involvement remains a hallmark of the disease. The cohorts described in the data presented below had mild PHPT, but most included some symptomatic subjects (ie, kidney stones).

BMD in asymptomatic PHPT

DXA is a standard of care for the evaluation of PHPT. DXA is used to determine the advisability of surgery in asymptomatic patients and to monitor patients over time, whether or not they have PTX. Typically, bone loss is greatest at the forearm (33% radius), a skeletal site that is almost totally comprised of cortical bone, and least at the lumbar spine, a skeletal site with a large component of trabecular bone (24). Occasionally, the postmenopausal osteoporotic pattern, in which bone loss is greatest at the spine, is seen (25). Based upon these observations by DXA, bolstered by bone biopsy data, it was concluded that PHPT has catabolic effects on cortical bone and relative sparing of trabecular bone. Despite the recommendation at the time of the last Workshop that patients with PHPT have BMD measured at three skeletal sites (lumbar spine, hip, and forearm) (1), a recent study suggests that the forearm is commonly not included in most preoperative DXA testing (26). Patients who do not have distal forearm measurements may have unrecognized but substantial cortical bone loss.

Successful PTX is associated with increases in BMD that are greatest and most rapid at the lumbar spine and hip, followed later by increases in the distal 1/3 radius (2, 3). Antiresorptive therapy with agents that include bisphosphonates and estrogen increase BMD in patients who do not have surgery (27, 28). A meta-analysis of randomized controlled trials and observational studies concluded that increases in BMD are similar with surgery and antiresorptive therapy (29). Cinacalcet reduces the elevated serum calcium to normal in most subjects but does not improve BMD (30).

Bone turnover markers in PHPT

These markers reflect the activity of bone cells: the osteoblast (bone formation markers: osteocalcin, procollagen I N-propeptide, bone isoform of alkaline phosphatase) and the osteoclast (bone resorption markers C- and N-telopeptide of type I collagen, deoxypyridinoline, tartrate-resistant acid phosphatase). Although they can be measured using automated immunoassay technology, technical and biological variability make reliable and reproducible measurements a challenge. Procollagen I N-propeptide and C-telopeptide of type I collagen measurements are recommended in countries where they are available (31).

As many as half of all patients with PHPT have bone turnover markers that are above the reference range (32). In the absence of intervention, markers tend to be stable, at least over several years. Parathyroidectomy results in a normalization of bone markers. Bone turnover markers have been shown to relate to postoperative changes in BMD, with higher preoperative markers associated with greater postoperative increases in BMD. Greater reductions in bone turnover markers after surgery are also associated with greater postoperative increases in BMD (33). Bone resorption markers decline within hours of surgery, whereas changes in bone formation markers decline more slowly (34). Newer markers of bone metabolism, not yet routinely available, include osteoprotegerin, a regulator of receptor activator of nuclear factor kappa-B ligand, circulating levels of which are normal and unchanged after surgery (35), whereas circulating levels of sclerostin, a regulator of the Wnt signaling pathway, are low in PHPT and increase shortly after surgery (36). The observations of sclerostin in PHPT are consistent with current concepts that PTH inhibits sclerostin.

Medical treatments for PHPT also result in changes in bone turnover markers. Both estrogen replacement hormone therapy and raloxifene reduce bone turnover markers (27, 37). Cinacalcet therapy does not lower bone turnover markers, despite lowering PTH levels somewhat. In some situations, bone turnover markers may even increase. In one trial, in which alendronate was compared to cinacalcet in PHPT, only alendronate reduced bone turnover markers (38).

Thus, bone turnover markers reflect the effects of PHPT on the skeleton. Levels before treatment can predict the treatment response, whether that treatment is surgical or medical (39). Because bone turnover markers still represent a clinical challenge in terms of reliable measurements, their role in the evaluation and management of PHPT is not established.

The bone biopsy in PHPT

Histomorphometric analysis of bone biopsies has helped to elucidate the effects of PHPT on bone structure, turnover, and material properties. Most insights from the bone biopsy, however, were obtained well over 5 years ago (33, 40–45). By dynamic parameters, bone turnover is increased in PHPT. Consistent with DXA data, microstructural abnormalities are predominantly seen in cortical bone (reduced cortical width and increased porosity), whereas the trabecular compartment is relatively well preserved. The cortical thinning has been attributed to increased osteoclastic erosion depth on the endocortical surface. Parathyroidectomy leads to reduced bone turnover, increased cancellous bone volume and decreased cortical porosity, all attributable to closure of the remodeling space (33, 44, 45).

More recently, but still over 5 years ago, the bone biopsy was used to study material properties of bone matrix. Quantitative backscattered electron imaging demonstrates that mineralization density is reduced in PHPT and that the heterogeneity of mineralization is increased, consistent with an increase in the proportion of newly formed bone undergoing primary mineralization. Similarly, collagen is less mature with a reduced collagen cross-link ratio. These effects on mineralization density and collagen cross-links are reversed by PTX (46, 47). Thus major effects on both the structural and material properties of bone are readily demonstrable in asymptomatic PHPT.

High-resolution imaging

DXA technology is readily available and is the "gold standard" in the evaluation of any metabolic bone disease. However, it is an areal quantity (g/cm^2), not a true bone density (g/cm^3). Quantitative computed tomography (QCT) measures true volumetric BMD (mg/cm^3), and can distinguish between cortical and trabecular bone. With peripheral QCT (pQCT), reductions in trabecular and cortical bone along with thinning of the cortex due to apparent trabeculation of cortical bone have been described (48, 49).

High-resolution pQCT (HRpQCT) permits noninvasive assessment of trabecular and cortical microarchitecture and volumetric BMD at the distal radius and tibia with a nominal isotropic voxel size of 82 μm. The resolution by HRpQCT is considerably greater than QCT. HRpQCT indices are associated with prevalent fracture independently of areal BMD (aBMD) as measured by DXA (50, 51). HRpQCT can also assess age-related bone loss and response to pharmacological treatment for osteoporosis (52, 53). Using microfinite element analysis, HRpQCT can be used to estimate bone strength (54). Analysis of cortical and trabecular compartments of two

nonvertebral sites, distal radius and tibia, provides data on sites directly relevant to nonvertebral fractures, in contrast with the iliac crest biopsy site, which may differ from sites at risk for fracture.

Recent HRpQCT data in PHPT are concordant with biopsy data at the cortical but not the trabecular compartment. In a case-control study (27 patients), Hansen et al (55) reported an alteration of the cortical (decreased cortical area, thickness, and volumetric BMD) and trabecular compartments (decreased trabecular volumetric BMD and trabecular number, along with increased trabecular separation) at the radius. Cortical and trabecular deficits were also reported at both the radius and tibia in a study on 43 PHPT patients, and another of 51 postmenopausal women with PHPT (56, 57). In the latter study, women with PHPT showed decreased volumetric BMD, thinner cortices, and more widely spaced and heterogeneously distributed trabeculae at both sites compared to controls. The radius was affected to a greater extent in the trabecular compartment than the tibia, with fewer and thinner trabeculae in PHPT. These abnormalities resulted in decreased whole-bone stiffness, as assessed by finite element modeling and individual trabecula analysis (58). Short-term studies have shown improvements as early as 1 year after PTX (56).

Thus, HRpQCT demonstrates microstructural abnormalities in both cortical and trabecular compartments at sites that are likely to represent sites relevant to fracture risk. The results are more compatible with fracture incidence data than the results obtained by DXA or by the bone biopsy (see Questions 3A–3C). Unfortunately, HRpQCT is available in only a few sites in the world and is unlikely to become widely used.

Trabecular bone score (TBS)

TBS is a novel gray-level textural analysis that can be applied to DXA images to estimate trabecular microarchitecture (59–62). TBS is associated with direct measures of bone microarchitecture and fracture risk and can differentiate between three-dimensional bone structures that exhibit the same aBMD but different trabecular microarchitecture. A high TBS value reflects a dense, homogeneous trabecular network associated with greater bone strength, whereas a low TBS value reflects a more porous, heterogeneous trabecular network and reduced bone strength. TBS analysis is readily available from the lumbar spine DXA image without further imaging and can enhance the ability of DXA to discriminate among those with and without fractures and to predict osteoporotic fractures, independent of aBMD.

In 22 postmenopausal women with PHPT (77% asymptomatic; fragility fracture, n = 4; nephrolithiasis, n = 1), lumbar spine T-score by DXA was normal (by World Health Organization criteria) in over half of all subjects, whereas only three (14%) were classified as osteoporotic and seven (32%) as osteopenic (63). In contrast, the mean TBS was low at 1.24 (normal, $\geq$1.35), concordant with HRpQCT results showing abnormal trabecular microstructure. Microarchitecture was "degraded" (TBS $\leq$ 1.20) in eight (36%) patients, partially degraded (1.20 $<$ TBS $<$ 1.35) in an additional eight (36%), and normal (TBS $\geq$ 1.35) in only six (27%) subjects.

TBS correlated significantly with all radius HRpQCT and biomechanical parameters (r = 0.44–0.51; $P < .05$) except total area, trabecular thickness, and trabecular stiffness (significance persisted after weight adjustment). TBS was significantly associated with tibia HRpQCT measures of volumetric density (r = 0.47–0.62), cortical thickness (r = 0.52), and whole bone stiffness (r = 0.52) ($P < .05$ for all). All indices of trabecular microarchitecture, except trabecular thickness, became significant after adjusting for body weight (r = 0.48–0.57).

Despite similar lumbar spine BMD between 73 postmenopausal women with PHPT and 74 age-matched controls, Romagnoli et al (64) found lower TBS in PHPT vs controls (1.19 $\pm$ 0.10 vs 1.24 $\pm$ 0.09; $P < .01$). TBS was also worse in PHPT subjects with (n = 29) than without (n = 44) a vertebral fracture (64). TBS was associated with vertebral fracture (area under the curve, 0.716; 95% CI, 0.590–0.841; $P = .002$), with scores $<$ 1.2 showing the best performance in identifying prevalent vertebral fracture. In another study, lumbar spine BMD and TBS were lower in a mixed group of 74 postmenopausal women and 18 men with PHPT than in sex-matched healthy controls (65). TBS was associated with vertebral fractures in PHPT patients and improved 2 years after successful parathyroid surgery (65).

Thus, in PHPT TBS may identify trabecular abnormalities not captured by lumbar spine aBMD. It has the major advantage of being readily available from images of DXA, a test routinely performed in PHPT. With significant correlations between TBS and volumetric and microstructural indices, as well as biomechanical measurements by HRpQCT, a method with greater resolving power that is not widely accessible, TBS could become a helpful clinical tool for skeletal assessment in PHPT. TBS data are also compatible with epidemiological evidence of increased fracture risk at vertebral and nonvertebral sites in PHPT.

Fracture risk in PHPT

Whether mild PHPT is associated with increased fracture risk is unclear. Most published fracture data represent a mixture of patients with mild or asymptomatic disease and the more severe form, well known to be associated

with increased fractures. Cohort studies report an increased risk of any fracture, and fracture risk seems to be reduced after cure (66–68).

Data on fractures at specific skeletal sites are less uniform. The risk of forearm fractures is increased, whereas PHPT does not seem to be common in patients with hip fracture (67–70). Variable results have been reported on the risk of vertebral fractures. Risk of vertebral fractures was not increased in several studies, but most studies do report an increased risk (67, 68, 71, 72). In a more recent study using vertebral fracture assessment by DXA, vertebral fractures were significantly more prevalent in the 150 PHPT women (24.6%) than in 300 matched healthy controls (4.0%), and more common in symptomatic (34.1%) compared with asymptomatic (21.1%) patients (72). Among asymptomatic patients, vertebral fractures were more prevalent in those who met the criteria for PTX (28.1%) compared with those who did not (11.1%). Compared with controls, the prevalence of vertebral fractures was significantly higher in patients with symptomatic and asymptomatic PHPT who met the criteria for surgery and only tended to be more prevalent in asymptomatic subjects who did not meet criteria for surgery ($P = .06$).

Thus, findings from densitometric and histomorphometric studies conflict with epidemiological data on distribution of fractures at different skeletal sites. Neither DXA nor the bone biopsy provides information that is compatible with data obtained either by HRpQCT or by TBS, in which trabecular abnormalities seem to be more concordant with the epidemiological data on fracture risk. Because the fracture data are most consistent with risk at vertebral and nonvertebral sites, one might question whether lumbar spine BMD measures bone strength and predicts fracture as well in PHPT as it does in postmenopausal women without PHPT. The results, on the whole, suggest caution in interpreting lumbar spine BMD in PHPT.

Metabolic factors may also affect fracture risk in PHPT. Changes in bone turnover, composition, and geometry probably influence bone strength differently in PHPT and postmenopausal osteoporosis. Moreover, low 25-hydroxyvitamin D levels in PHPT may influence effects of high PTH levels on bone, as has been documented in secondary hyperparathyroidism (73), where high PTH levels were associated with a lower BMD and an increased fracture risk if 25-hydroxyvitamin D levels were below 80 nmol/L, whereas high PTH levels were not associated with adverse skeletal outcomes in women who were vitamin D replete.

Available studies on fracture risk in PHPT are limited by their retrospective design, small sample size, selection of patients and controls, and variable definitions of vertebral fractures. Data on the effect of PTX on fracture risk are limited by their nonrandomized study design. Although antiresorptive drugs increased BMD in placebo-controlled trials, no data are available on whether these agents reduce fracture risk in PHPT.

Overall, data from mixed case populations suggest an increased risk of fractures in PHPT, although discrepant findings at different skeletal sites have been reported. The limited data available on patients with mild PHPT also suggest that risk of vertebral fracture is increased. Well-designed prospective clinical trials are needed to improve our knowledge on risk of fracture in asymptomatic PHPT and the correlation between BMD at different skeletal sites and risk of fracture.

Normocalcemic PHPT

Data are limited on the skeleton in NPHPT (74). There is significant selection bias in the cohorts described, many coming from bone disease clinics. In one, at the time of diagnosis, 57% of subjects had osteoporosis, and 11% had documented fragility fractures (8). After PTX, one study assessing NPHPT patients found a BMD gain of 4.1% at the femoral neck at 1 year ($P = .04$), without significant change at the spine or radius (75).

Questions 3A—3E: Skeletal features

3A. Do the new data on the skeletal manifestations of PHPT support a re-examination of skeletal criteria for surgery?

Response: Yes. New data obtained using HRpQCT and TBS suggest that assessment using time-honored methods of DXA and the transiliac bone biopsy may not accurately reflect the quality or strength of trabecular bone in PHPT, whereas cortical abnormalities by HRpQCT are consistent with DXA and transiliac crest bone biopsy data. These new observations raise questions about the accuracy of lumbar spine DXA in PHPT. To screen for vertebral fracture, an indication for surgery, we recommend vertebral imaging (by x-ray, CT, or TBS; see Table 2).

3B. Do the new data warrant a change in guidelines for monitoring with or without parathyroid surgery?

Response: No. New data continue to show improvement in BMD after surgery, and early data with HRpQCT

Table 2. Recommendations for Evaluation

Target Organ	Initial Evaluation
Bone	DXA (three sites; must include the forearm) Vertebral imaging by x-ray, CT, or TBS
Kidney	Creatinine clearance Renal imaging by ultrasound, x-ray, or CT
Cardiovascular	No specific evaluation
Neurocognitive	No specific evaluation

and TBS also confirm postoperative improvements in skeletal microstructure. Therefore, there does not appear to be any reason to change the guidelines for monitoring with or without parathyroid surgery.

3C. Should there be a change in the densitometric threshold for surgery?

Response: Not at this time. There are no studies that predict fracture risk in PHPT based upon DXA or other quantitative modalities. Thus, it is not clear that the T-score in PHPT reflects the same fracture risk as it does in individuals without PHPT. Furthermore, new data indicate that lumbar spine DXA gives information that is inconsistent with central vertebral fracture risk in PHPT. Abnormalities are noted both by HRpQCT and by TBS, even when the spine DXA is normal. DXA and TBS, when used together, give better concordance with microstructural parameters by HRpQCT. With greater availability of TBS, perhaps both should be used together to determine a densitometric threshold for surgery. It is premature to predict what algorithm should be used in that case, and no change is currently recommended regarding spine measurements.

The cortical skeleton does not appear to present the same dilemma because abnormalities by DXA at the 1/3 radius, and by bone biopsy, are concordant with abnormalities measured by HRpQCT. Although we do not have predictive fracture data using DXA at any site, it would seem reasonable to maintain the threshold set at T-score ≤ -2.5 at the distal 1/3 radius. At the hip, again without clear and convincing data, there is probably no reason to change the threshold of T-score ≤ 2.5.

3D. Should bone density at the lumbar spine, hip, and distal radius sites be viewed differently with regard to recommendations for surgery?

Response: Perhaps. It appears that the lumbar spine DXA value is overestimating bone strength in PHPT, whereas the distal 1/3 radius value is likely to be consistent with microarchitectural studies. This observation highlights the importance of the 1/3 radius measurement in *all* patients with PHPT.

3E. Is there a role for FRAX or other fracture risk assessment tools in assessing fracture risk in patients with PHPT, and should this be included in the recommendations for surgery?

Response: Not yet. No fracture risk assessment tool has yet been applied to cohorts with PHPT, so it is not clear whether FRAX would predict fractures in the same way in PHPT that it does in individuals without PHPT.

Update 4: Classical Features—The Kidney

The kidney occupies a unique position in PHPT because it helps to regulate the concentration of calcium and phosphate in serum and to determine whole body calcium and phosphate. In addition, the kidney continues to be the organ that is most likely to demonstrate clinically overt complications of PHPT (nephrolithiasis or nephrocalcinosis).

Renal tubular reabsorption of calcium is regulated by PTH acting in concert with a variety of factors, including the calcium-sensing receptor, filtered sodium load, and integrity of tubular calcium transporters (76). PTH receptor 1 is expressed in proximal, thick ascending and distal tubules. There is both transcellular and paracellular transport, the latter by the claudin family of ion channels. In PHPT, increased PTH secretion induces a "right shift" in the relationship between excreted and filtered calcium. Renal tubular reabsorption of phosphate, on the other hand, has a classical tubular maximum capacity above which the relationship between filtered and excreted phosphate is unity. PTH decreases tubular reabsorption of phosphate largely by decreasing tubular Na/Pi-cotransporter activity. Renal tubular 1-α hydroxylase activity is regulated by PTH; in PHPT, serum 1,25-dihydroxyvitamin D [1,25$(OH)_2$D] is increased, resulting in increased active absorption of dietary calcium. This results in the classical biochemical signature of PHPT: increased serum PTH accompanied by increased serum calcium, decreased serum phosphate, increased 1,25$(OH)_2$D, and absorptive hypercalciuria.

Serum fibroblast growth factor 23 (FGF23) is increased in PHPT, and levels decrease after PTX (77). More studies are required to establish the role of FGF23 in determining the biochemical profile of PHPT because FGF23 acts like PTH on the proximal tubular Na/Pi transporters to decrease phosphate reabsorption and acts on the FGF fibroblast growth factor receptor-Klotho complex to decrease 1,25$(OH)_2$D secretion. Chronic reduction in glomerular filtration rate, either from complications of PHPT itself or from comorbid diseases, induces abnormal mineral homeostasis that alters both the biochemical and the clinical manifestations of the disease (78). Because renal failure is accompanied by an early increase in serum FGF23, studies are needed to establish the early effects of chronic renal failure on disease progression in patients with PHPT. Some data suggest biochemical effects in PHPT when the glomerular filtration rate falls below 60 mL/min (78).

Calcium stone disease remains the most common clinical manifestation of PHPT, ranging between 15 and 20% in most series. About 3% of patients with stone disease have PHPT, and about 10% of patients with PHPT pres-

ent with recurrent calcium stone disease (79). The cause of stone formation is multifactorial, but hyperabsorption of calcium and phosphate, high absorption of oxalate from increased bioavailability, and increased urinary pH are important urinary risk factors that lead to oversaturation of urine with calcium oxalate and phosphate (76). However, because only a minority of PHPT patients ever develop stones, more definitive studies are required to determine the urinary and nonurinary risk factors responsible for stone formation. Of the nonurinary factors, genetic polymorphisms probably play an important role (80). In more severe forms of PHPT, mineralization in the kidney tissue itself occurs and is diagnosed radiographically as nephrocalcinosis. However, Randall's plaques, small deposits of calcium phosphate in the renal papillae are common, are not seen radiologically and are considered to be important in the pathogenesis of urinary calcium stone formation and perhaps nephrocalcinosis (81). New and sensitive techniques for visualizing calcium mineralization are needed to determine the incidence of Randall's plaques and their relationship to stone formation, nephrocalcinosis, and calcium deposits in nonrenal tissues in PHPT.

Question 4: Renal features. Are there new data on the renal manifestations of PHPT (stones, urinary calcium excretion, renal function)? Should the new data, if they exist, change recommendations for surgery based upon these renal manifestations?

Response: Yes. The diagnosis of renal calcification currently relies on renal imaging. However, current modalities underestimate the amount of calcification present. Improved methods are required, and using these methods, studies are required to establish: 1) the relationship to renal stone formation; 2) the relationship to biochemistry; 3) the relationship to calcifications elsewhere in the body, particularly the cardiovascular system; and 4) the response to PTX. First, we recommend renal imaging for subclinical stone disease or nephrocalcinosis (Table 2). Possible imaging techniques for this purpose include renal ultrasound, abdominal x-ray, and spiral CT scan of the kidneys (although the "gold standard" for nephrolithiasis, physicians may not want to subject their patients to the radiation associated with this technique in the absence of clinical symptoms). Positive imaging shall constitute an indication for surgery. Second, we recommend that risk factors for stone formation be assessed, including consideration of: 1) the calcium-phosphate and calcium-oxalate products; 2) the concentration of urinary inhibitors of stone formation; and 3) family history/genetic polymorphisms once testing is available. Finally, above average fluid intake should be stressed for all PHPT patients followed without surgery.

Update 5: Nonclassical Features—Cardiovascular

The presence, nature, and reversibility of cardiovascular manifestations of PHPT are unsettled issues. Both hypercalcemia and PHPT could have deleterious consequences in this regard. Although cardiovascular outcomes and mortality were clearly increased in classical disease, the effects of mild or asymptomatic disease on the cardiovascular system are less clear.

Mortality

New data are limited. Data from Scotland (PEARS study) found increased cardiovascular mortality in PHPT and reported further that serum PTH levels predict risk (82, 83). These data are limited because: the diagnosis of PHPT was made in the absence of PTH levels in some cases; vitamin D levels were not available, raising the possibility that PTH levels could have been a proxy for vitamin D deficiency and risk for cardiovascular mortality; and there was an extremely high overall mortality rate in this cohort (30%).

Heart

There are no data on cardiac outcomes. With regard to cardiac structure and function, a single center subgroup of the Scandinavian randomized controlled trial (RCT) of surgery vs observation (n = 49; mean calcium, 10.6 mg/dL) found that baseline left ventricular dimension correlated with PTH levels, but there was no echocardiographic difference in cardiac structure or function between groups after 2 years (84). A case-control study of 51 patients with mild PHPT (mean calcium, 10.5 mg/dL) found increased aortic valve calcification area that was associated with PTH levels, but no improvement in any cardiac index 2 years after PTX (85–87). Another case-control study of mild PHPT (mean calcium, 10.5 mg/dL) found no difference in cardiac structure or function between PHPT patients undergoing PTX who had no cardiovascular risks (12% of 410 consecutive patients) and controls. There were no changes after PTX (88). Several small studies assessed coronary calcifications but shed no definitive light (89). A study of coronary microvascular function in 100 PHPT patients with more severe hypercalcemia (mean calcium, 11.8 mg/dL; PTH, 188 pg/mL) found no differences in cardiac structure or diastolic function, but did find that coronary flow reserve (CFR) was lower than controls and inversely associated with PTH ($r = -0.3$; $P < .0004$) but not calcium (90). The normal coronary arteries found in

26 of the 27 patients with low CFR raises questions about this functional precursor of coronary disease. CFR improved 6 months after PTX, although these data were uncontrolled and could represent regression to the mean (91).

Large vessel disease

Studies prior to the last consensus conference demonstrated increased aortic stiffness that was associated with PTH levels, using augmentation index, an indirect measure that is influenced by BMI and blood pressure (92). Tordjman et al (93) reported no difference in arterial stiffness between normocalcemic and hypercalcemic PHPT. Recently, the carotid bed was investigated in 52 patients with mild PHPT (mean calcium, 10.5 mg/dL) (94). Intimal medial thickness (IMT) was elevated, and those with carotid plaque had an increase in plaque thickness, suggesting that PHPT may not initiate but could propagate abnormalities (similar to aortic valve calcification). This study, the first to directly measure large vessel compliance in PHPT, also found abnormal stiffness and distensibility, and that PTH levels, but not calcium concentration, predicted carotid stiffness ($P = .04$), strain ($P = .06$), and distensibility ($P = .07$). It is not known whether these carotid abnormalities predict the same cardiovascular outcomes in PHPT as in atherosclerosis. Neither IMT nor carotid stiffness improved 1 or 2 years after PTX (87).

Cardiovascular risk factors

Baseline and 2-year data from a randomized controlled trial of surgery (n = 54) vs observation (n = 62) in mild PHPT (calcium, 10.8 mg/dL) revealed that both surgery and observation were associated with increased total cholesterol and high-density lipoprotein and apolipoprotein (Apo)-A, and decreased blood pressure (95). BMI, glucose, insulin or insulin derivatives, homeostatic model of assessment for beta-cell function and insulin resistance did not change, whereas adiponectin increased in both groups by about 15%. Markers of endothelial function (von Willebrand factor, vascular cell adhesion molecule) did not change, nor did C-reactive protein (CRP) or osteoprotegerin. Case control data from a cohort with no cardiovascular risk factors found no difference in cholesterol, Apo-A1, Apo-B, Apo-B/Apo-A1 ratio/von Willebrand factor, CRP, homocysteine, IGF-1, or plasminogen activator inhibitor type 1 (96). Systolic blood pressure and triglycerides were higher within the normal range in cases than controls. After PTX, BMI, Apo-B (but not Apo-B1/Apo-A1 ratio, the more important risk predictor for cardiovascular disease), and CRP all increased, but interpretation is limited by the fact that there were no longitudinal data in control subjects.

Questions 5A and 5B: Nonclassical features—cardiovascular

5A: Should evaluation of PHPT include assessment for cardiovascular abnormalities? Response: No (Table 2).

5B: Should cardiovascular manifestations be considered in decisions regarding surgery? Response: No.

There are no prospective data on cardiovascular outcomes in asymptomatic PHPT. Studies published since the last consensus conference have assessed varying cardiovascular risks, as well as structural and functional abnormalities in different vascular beds. The carotid bed seems to be more affected than the heart, with elevated carotid IMT and increased plaque thickness, whereas cardiac structure was mostly normal. When present, carotid plaque was thicker and aortic valve calcification area greater, suggesting that the hyperparathyroid state may be associated with propagation of vascular calcification once established. Available data highlight a closer association of some cardiovascular indices (left ventricular mass, CFR, carotid stiffness, and aortic plaque area) with PTH, as opposed to calcium concentration in PHPT. Randomized controlled trial data found no benefit of surgery with regard to markers of the metabolic syndrome, including hypertension, cholesterol, inflammatory markers, adipokines, and other cardiovascular risk markers. They also found no benefit of surgery on cardiac structure or function. Observational studies in patients with and without cardiovascular risk factors also found no improvement in cardiac, carotid, or other surrogate markers of cardiovascular risk. Thus, at this time, there are no data that suggest that cardiovascular evaluation should be part of the workup of PHPT, or that surgery should be undertaken for the purpose of improving cardiovascular markers or anatomical abnormalities.

Update 6: Nonclassical Features—Neuropsychiatric and Cognitive

Classical PHPT had obvious neuropsychological sequelae. Many patients with asymptomatic PHPT report nonspecific complaints including weakness, fatigue, depression and anxiety, decreased memory and concentration, loss of initiative, irritability, and disturbed sleep. Most older studies suggest that symptoms improve after PTX, but many are limited by design flaws, including small sample sizes, inclusion of subjects with symptomatic PHPT, and lack of controls. Others have failed to use objective tests or performed testing at short intervals after surgery. Three RCTs of PTX vs observation upon quality of life (QOL) and psychological functioning in asymptomatic PHPT patients with mild hypercalcemia were re-

viewed at the time of the last Workshop in 2008 (97–99). Because specific findings across studies were inconsistent despite using the same tool (the Short Form-36 [SF-36] general health survey), psychiatric and cognitive symptoms were not added to the list of criteria for PTX (1). This summary focuses on controlled studies in the areas of depression/psychiatric disease, QOL, and cognitive function published since the last Workshop.

Psychiatric symptoms

A prospective case-control study assessing the prevalence of depression in PHPT and the benefit of PTX in 169 (symptomatic and asymptomatic) PHPT patients (mean calcium, 10.6 mg/dL), concluded that depression was present in PHPT, that it related to serum calcium levels, and that improvement was not due to a surgical placebo effect (100). However, the PHPT patients self-selecting for surgery had higher serum calcium and PTH and lower 25-hydroxy vitamin D levels, had more symptomatic disease, and had more depressive symptoms at baseline compared to those who did not have PTX. Thus, it is not clear whether treatment differences were due to surgery or other factors. An epidemiological cohort study in Scotland that included 1424 patients with asymptomatic PHPT (serum calcium $<$ 12 mg/dL; mean, 10.5 mg/dL) reported that those with PHPT who had more comorbidities at baseline had a 4.25-fold (95% CI, 2.33–7.77) increased risk of psychiatric disease (82). Another study used the Hospital Anxiety and Depression scale and the Mood Rating Scale to compare 24 patients with asymptomatic PHPT (mean calcium, 10.8 mg/dL) before and after PTX to 23 controls undergoing hemithyroidectomy (101). They found more baseline depression in PHPT and improvement in depression, but not anxiety, whereas the thyroid surgery group did not change. Thus, all three new studies suggest the presence of depression or psychiatric disease in PHPT, and in the two studies that assessed patients after PTX, there was improvement in depressive symptoms.

Quality of life

Ten years after PTX, QOL was assessed using the Parathyroid Assessment of Symptoms (PAS) scores (correlates with SF-36 scores) in 78 of 122 symptomatic and asymptomatic PHPT patients and 39 of 58 thyroidectomy patients. QOL was worse in PHPT at baseline, and PTX resulted in improvement that was sustained for 10 years (no change in controls) (102, 103). Conversely, persistently worse QOL (using the SF-36) was reported 5 years after PTX in a cross-sectional study of 51 PHPT patients vs 51 population-based age matched controls (104). The authors acknowledged that the reduced QOL in their participants was difficult to attribute solely to the history of PHPT. Opposite findings using the same SF-36 testing vehicle were reported in 24 PHPT patients (mean calcium, 11.2 mg/dL) preoperatively and 6 months postoperatively, with improvements in six of eight domains (105). Other data used nonvalidated questionnaires. In sum, these studies suggest impaired QOL, but improvement after PTX was inconsistent across studies.

Cognitive function

A cohort with mild symptomatic and asymptomatic PHPT (n = 39; mean calcium, 10.6 mg/dL) performed worse on validated tests of verbal memory and nonverbal abstraction/pattern recognition compared with 89 non-PHPT controls (106). Nonverbal abstraction and some aspects of verbal memory improved after PTX such that scores were no longer different from controls. Both baseline differences and postoperative improvement were independent of anxiety and depressive symptoms, which were more common in PHPT. However, the absence of a surgical control group raises the possibility of a placebo effect of surgery. A prospective case-control study of 35 PHPT patients (mean calcium, 11.1 mg/dL) undergoing PTX compared to 35 non-PHPT surgical controls found that PHPT patients had more depression, as well as impaired concentration, nonverbal learning, direct memory, verbal fluency, and visual constructive abilities (107). Controlling for depression, PTX was associated with an improvement in visual memory and visual-constructive abilities. Since 2008, only one randomized controlled study of PTX vs observation has been performed. This very small study (n = 18) focused on cognition in asymptomatic PHPT (calcium, 10.5 mg/dL) and also assessed sleep and brain function using functional magnetic resonance imaging (108). They report that daytime sleepiness decreased temporarily in those who underwent PTX vs observation (at 6 wk postoperatively), but differences were no longer significant at 6 months. Additionally, there were no between-group differences in changes in cognition. There were no changes in functional magnetic resonance imaging voxel counts, although the change in PTH level was associated with a change in voxel activity in the left precentral gyrus at 6 months. In an uncontrolled study (46 of 111 PHPT patients; calcium, 10.7 mg/dL), mean Z-scores on all tests of cognitive function were not impaired (as defined by a Z-score ≤ -1.5) (109). However, the percentage of participants whose performance was considered impaired ranged from 3.6% on the tests of attention and visual processing to 29% on tests of eye-hand coordination and motor speed, and 35% of participants met criteria for clinically significant impairment (defined as ≥ 3 Z-scores ≤ -1.5). Among 67 patients who returned for repeat testing 1 month after PTX, $\geq$10% of

participants had improvements in the areas of fine motor speed and information processing. Another uncontrolled study of 212 symptomatic and asymptomatic PHPT patients (mean calcium, 10.8 mg/dL) reported post-PTX improvement in depression, anxiety, verbal memory, and spatial working memory (110). Change in PTH was associated with reduced postoperative anxiety, and improved performance was associated with decreases in depression and anxiety. There was significant attrition in this study and no control group. In the aggregate, these studies suggest that various aspects of cognition, including verbal and visual memory, hand/eye coordination, and information processing, as well as pattern recognition may be affected by PHPT. However, the specific components of cognition affected by PHPT varied across studies, making definitive conclusions difficult. Furthermore, the improvements after PTX noted in observational studies were not confirmed by the only RCT of cognition, although the study was underpowered.

Question 6: Nonclassical features—neuropsychiatric and cognitive. Should neuropsychiatric and cognitive dysfunction be considered in decisions about surgery for PHPT?

Response: No. There is evidence to suggest that PHPT is associated with neuropsychological dysfunction including depression, reduced QOL, and changes in cognition among others. Cognitive dysfunction may in part be related to the presence of depression. Data regarding improvement in neuropsychological symptoms and cognitive function after PTX are inconsistent between studies. At this time, there is insufficient evidence of predictable improvement of specific symptoms in a given patient to recommend PTX on the basis of neurological or psychological symptoms, although some patients do experience symptomatic improvements after surgery. There are also insufficient data to recommend formal neuropsychiatric or neurocognitive testing in PHPT (Table 2).

Update 7: Considering the Long-Term Variability in These Parameters, What Represents a Clinically Important Change in Serum Calcium, Renal Function, and BMD in the Nonsurgical Management of PHPT?

Serum calcium

No recent evidence clarifies how much of a change in serum calcium is necessary to suggest a change in management. Most clinicians recommend surgery when the serum calcium is consistently >1.0 mg/dL above the upper limit of normal. The threshold could be present at the time of initial evaluation or during monitoring of the patient. The rationale for using a threshold is based upon an older literature that correlated the signs and symptoms of PHPT to the level of the serum calcium.

Bone mineral density

A clinically important change in BMD is based upon the guidelines of the International Society of Clinical Densitometry (ISCD). The importance of quality control is emphasized with regard to regular quality control assessment of the DXA instrument, certification of radiological technologists, and the interpreters of the results. The ISCD states that a significant change in a measurement is one that exceeds the least significant change (LSC) of the measurement site. The LSC can and should be calculated for each site (lumbar spine, hip, and distal forearm) and for each facility based upon a universally accepted method that is available on the ISCD web site. If a change in BMD exceeds the LSC for that site, it is considered to be significant at the 95% CI. If the BMD at any site is <-2.5 by T-score at the time of evaluation or falls significantly to a level <-2.5 at any site, this should lead to a recommendation for surgery.

Renal function

Some studies in PHPT suggest that there are no deleterious effects of renal failure until a GFR <60 mL/min occurs. Renal specialists have begun to point out that a reduction in creatinine clearance to <70 mL/min begins a pathophysiological process of clinical significance. At this time, however, it seems reasonable to maintain the threshold value of <60 mL/min.

Question 7: In patients with PHPT who are followed without surgery, what represents a clinically significant change in serum calcium, renal function, and BMD that would constitute an indication for surgery?

Indications are: 1) an increase in serum calcium to levels >1 mg/dL above the upper limit of normal; 2) if the reduction is > LSC of the measurement to a T-score that is <-2.5, then surgery is recommended; and if the patient demonstrates a progressive reduction in BMD that exceeds the LSC at any site and is between -2.0 and -2.5, the physician may opt to recommend surgery although guidelines have not been strictly met; and 3) a reduction in creatinine clearance to <60 mL/min.

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