REVIEW

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Evaluation and Management of Primary Hyperparathyroidism: Summary Statement and Guidelines from the Fifth International Workshop

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ABSTRACT

The last international guidelines on the evaluation and management of primary hyperparathyroidism (PHPT) were published in 2014. Research since that time has led to new insights into epidemiology, pathophysiology, diagnosis, measurements, genetics, outcomes, presentations, new imaging modalities, target and other organ systems, pregnancy, evaluation, and management. Advances in all these areas are demonstrated by the reference list in which the majority of listings were published after the last set of guidelines. It was thus, timely to convene an international group of over 50 experts to review these advances in our knowledge. Four Task Forces considered: 1. Epidemiology, Pathophysiology, and Genetics; 2. Classical and Nonclassical Features; 3. Surgical Aspects; and 4. Management. For Task Force 4 on the Management of PHPT, Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology addressed surgical management of asymptomatic PHPT and non-surgical medical management of PHPT. The findings of this systematic review that applied GRADE methods to randomized trials are published as part of this series. Task Force 4 also reviewed a much larger body of new knowledge from observations studies that did not specifically fit the criteria of GRADE methodology. The full reports of these 4 Task Forces immediately follow this summary statement. Distilling the essence of all deliberations of all Task Force reports and Methodological reviews, we offer, in this summary statement, evidence-based recommendations and guidelines for the evaluation and management of PHPT. Different from the conclusions of the last workshop, these deliberations have led to revisions of renal guidelines and more evidence for the other recommendations. The accompanying papers present an in-depth discussion of topics summarized in this report. © 2022 The Authors. *Journal of Bone and Mineral Research* published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research (ASBMR).

KEY WORDS: PTH/VIT D/FGF23; ENDOCRINE PATHWAYS; PARATHYROID-RELATED DISORDERS

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Summary of Recommendations

The following recommendations are intended to guide practice and are not intended to be used for the development of reimbursement policies. With the exception of reference 4, which was based, in part, upon Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) analysis, all others either did not address issues of diagnsois, progosis, or therapy and/or the available data were evaluated without using GRADE methods (1–3, 5–9). The GRADE approach was applied only to the systematic reviews but not to the process of moving from evidence to recommendations. The approach to GRADE methodology is summarized in Methods.

1. **How should primary hyperparathyroidism (PHPT) be diagnosed?**
   - 1.1. Hypercalcemic PHPT: an elevated serum calcium adjusted for albumin in the presence of an elevated or inappropriately normal intact parathyroid hormone (PTH) (utilizing either a second or third generation assay) on two occasions at least 2 weeks apart.
   - 1.2. What is the differential diagnosis of hypercalcemia and elevated levels of PTH?
     - 1.2.1. Familial hypocalciuric hypercalcemia (FHH) may be suspected in younger individuals with a urinary calcium /creatinine clearance ratio <0.01 and/or those with a family history of hypercalcemia.
     - 1.2.2. Thiazide diuretics and lithium (see text)
     - 1.2.3. Ectopic secretion of PTH (very rare)
   - 1.3. Normocalcemic PHPT: normal adjusted total calcium and normal ionized calcium levels along with elevated intact PTH (utilizing either a second or third generation assay) on at least two occasions over 3–6 months after all alternative causes for secondary hyperparathyroidism have been ruled out.

2. **What are the clinical phenotypes of PHPT?**
   - 2.1. Symptomatic PHPT: associated with overt skeletal and renal complications that may include osteitis fibrosa cystica and/or fractures, chronic kidney disease, nephrolithiasis and/or nephrocalcinosis
   - 2.2. Asymptomatic PHPT: no overt symptoms or signs; typically discovered by biochemical screening. Two forms of asymptomatic PHPT are defined after evaluation:
     - 2.2.1. with target organ involvement
     - 2.2.2. without target organ involvement
   - 2.3. Normocalcemic PHPT: Skeletal or renal complications may or may not exist in those whose presentation fits this definition.

3. **How should patients with PHPT be evaluated?**
   - 3.1. Biochemical: Measure adjusted total serum calcium (ionized if normocalcemic PHPT is a consideration), phosphorus, intact PTH, 25OHD, creatinine
   - 3.2. Skeletal: Three-site dual-energy X-ray absorptiometry (DXA) (lumbar spine, hip, distal 1/3 radius); imaging for vertebral fractures (vertebral fracture assessment [VFA] or vertebral X-rays); trabecular bone score (TBS) if available
   - 3.3. Renal: Estimated glomerular filtration rate (eGFR) or, preferably, creatinine clearance, 24-hour urinary calcium and for biochemical risk factors for stones; imaging for nephrolithiasis/nephrocalcinosis
   - 3.4. Nonclassical manifestations (neurocognitive, quality of life, cardiovascular): there are no data to support routine evaluation for these putative manifestations
   - 3.5. Genetic: genetic evaluation should be considered for patients <30 years old, those with multigland disease by history or imaging, and/or those with a family history of hypercalcemia and/or a syndromic disease

4. **What are the indications and role for surgical management of asymptomatic PHPT? (GRADEd Recommendation)**

In patients with asymptomatic PHPT, we recommend surgery to cure the disease (strong recommendation/high quality evidence).

5. **For which patients is parathyroidectomy an option?**
   - 5.1. Although parathyroidectomy is an option for all patients, with concurrence of the patient and the physician and if there are no contraindications, the panel recommends surgery in all those in whom one or more of the following is present (including those who are asymptomatic):
     - 5.1.1. Serum calcium >1 mg/dL (0.25 mmol/L) above the upper limit of normal or
     - 5.1.2. Skeletal involvement:
       - 5.1.2.1. A fracture by VFA or vertebral X-ray or
       - 5.1.2.2. Bone mineral density (BMD) by *T*-score ≤ -2.5 at any site or
     - 5.1.3. Renal involvement:
       - 5.1.3.1. eGFR or creatinine clearance <60 mL/min
       - 5.1.3.2. Nephrocalcinosis or nephrolithiasis by X-ray, ultrasound, or other imaging modality
       - 5.1.3.3. Hypercalciuria (eg, >250 mg/day in women; >300 mg/day in men) or.
     - 5.1.4. Age <50 years (no other indications are necessary; age <50 years is a sufficient indication)
   - 5.2. Surgery should be performed by an experienced parathyroid surgeon
   - 5.3. Surgery cannot be recommended to improve neurocognitive function, quality of life, and/or cardiovascular indices because the evidence is inconclusive.

6. **What is the role of preoperative imaging and intraoperative PTH measurements? Panel recommendations**
   - 6.1. Preoperative imaging is not recommended for diagnostic purposes.
   - 6.2. Preoperative imaging is recommended for those who are going to have parathyroid surgery in order to locate the abnormal parathyroid gland(s).
   - 6.3. Preoperative imaging modalities include high resolution neck ultrasound, technetium-99 m-sestamibi subtraction scintigraphy, and contrast-enhanced four-dimensional (4D) computed tomography (CT).
   - 6.4. With successful preoperative imaging, selective parathyroidectomy, combined or not with intraoperative PTH monitoring, achieves high cure rates in the hands of experienced surgeons.
   - 6.5. Advantages of the selective approach include: shorter operative time, less tissue scarring, less risk to

surrounding structures, and reduced hospital costs. No head-to-head comparisons are available.

7. **What is the role of nonsurgical, medical management of PHPT?**

Patients with PHPT who do not meet guidelines for parathyroidectomy (see 5 above) can be followed without pharmacological intervention. For those who choose not to have surgery, but who meet specific guidelines (e.g., calcium or bone mineral density), medical options are available as recommended by the Panel.

- 7.1. Cinacalcet to reduce the serum calcium concentration into the normal range.
- 7.2. Calcium intake/supplementation should follow the Institute of Medicine nutritional guidelines: 800 mg/day for women <50 and men <70 years old; 1000 mg/day for women >50 and men >70 years old.
- 7.3. Vitamin D supplementation: the panel recommends levels of 25OHD >30 ng/mL and < the upper limit of normal for the laboratory reference range (eg, <50 ng/mL).
- 7.4. Alendronate or denosumab can be used to increase bone density if there are no contraindications.
- 7.5. Estrogen has been shown to increase BMD. Its effect on the reduction of serum calcium is inconsistent.
- 7.6. Raloxifene cannot be recommended because the data are insufficient to reach any conclusions.

8. **How should normocalcemic PHPT be managed? Panel recommendations**
   - 8.1. Because of limited data, we cannot recommend guidelines for surgery in normocalcemic PHPT at this time.

9. **What monitoring plan is recommended in patients who do not undergo PTX? Panel recommendations**
   - 9.1. Serum calcium and 25OHD concentrations: annually. PTH levels can also be measured, as clinically indicated.
   - 9.2. Skeletal:
     - 9.2.1. Three-site DXA every 1 or 2 years unless the BMD is normal (see text)
     - 9.2.2. Vertebral X-ray, VFA, or TBS if clinically indicated
   - 9.3. Renal:
     - 9.3.1. Creatinine clearance (preferred over eGFR), annually
     - 9.3.2. Abdominal imaging (X-ray, CT, or ultrasound) if clinically indicated
     - 9.3.3. 24-Hour urine for calcium, if clinically indicated.

10. **When should surgery be recommended in those who are being monitored? Panel recommendations**
    - 10.1. Serum calcium becomes consistently >1 mg/dL (0.25 mmol/L) above the upper limit of normal.
    - 10.2. A low trauma fracture.
    - 10.3. A kidney stone.
    - 10.4. A significant reduction in BMD to a *T*-score ≤ -2.5 at any site.
    - 10.5. A significant reduction in creatinine clearance.

11. **In patients who meet surgical guidelines but do not have surgery what non-surgical approaches are reasonable? Panel recommendations.**
    - 11.1. Calcium intake should be consistent with nutritional guidelines
    - 11.2. Vitamin D should be maintained >30 ng/mL. Cautious supplementation with parental forms of vitamin D (eg, cholecalciferol) is advised, as clinically indicated.
    - 11.3. When indicated to reduce the serum calcium, cinacalcet is effective
    - 11.4. When indicated to increase BMD, bisphosphonates or denosumab can be used
    - 11.5. When indicated to lower the serum calcium and to increase BMD bisphosphonates or denosumab in combination with cinacalcet can be considered.

12. **How should PHPT be managed during pregnancy? Panel recommendations**
    - 12.1. Mild cases should be managed by maintaining good hydration and monitoring calcium levels
    - 12.2. Bisphosphonates and denosumab should not be used
    - 12.3. Data are very limited on use of cinacalcet
    - 12.4. Consider surgery in the second trimester for patients with serum calcium >11.0 mg/dL and for whom surgery is not contraindicated
    - 12.5. Preoperative imaging should be limited to ultrasound
    - 12.6. If surgery is deferred, the neonate should be closely monitored for hypocalcemia
    - 12.7. If surgery is deferred, PTX should be done after delivery, and before a subsequent pregnancy.

Introduction

The last international guidelines on the evaluation and management of primary hyperparathyroidism (PHPT) were published in 2014.[1] Since that time, advances in our understanding of the disease in its many clinical, pathophysiological, and therapeutic aspects have led to new insights into this common endocrine disorder. The new information is documented by the references a majority of which have been published since 2013. These new insights encompass epidemiology, outcomes, genetics, physiology, pathophysiology, presentations, new imaging modalities, target and other organ systems diagnosis, measurements, pregnancy, evaluation, and management. To incorporate these advances into guidelines for its evaluation and management, an international group was convened. It consisted of over 50 experts whose knowledge of this disease is broad, deep, and current. In addition, some aspects of this comprehensive review lent themselves to systematic reviews using Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) methodology.[2] Altogether, the efforts of the workshop led to seven manuscripts, along with an editorial, that constitute this series. Four papers provide an evidence-based review of the Epidemiology, Pathophysiology, and Genetics of PHPT[3]; Classical and Nonclassical Manifestations[4]; Surgical Aspects[5]; and Management[6]; as well as one document following GRADE methodology for surgical and medical management of PHPT.[7] A paper describing the methodology of the evidence-based reviews is also included in this series.[8]

The summary statement maintains or revises the guidelines, based upon the expanded database of evidence currently available. In this report, we present a distillation of this information as a summary statement of conclusions and guidelines for the

evaluation and management of PHPT. Despite the progress of the past several years, we recognize the need for more research to augment our current knowledge base. Thus, this summary statement also provides a blueprint for future research in this disease.

Methods

Co-chairs of the four Task Forces worked entirely virtually over an 18-month period, because of the coronavirus disease 2019 (COVID-19) pandemic. Meetings were held in virtual platforms regularly with specific tasks designated to individuals or subsets of Task Force Members. A comprehensive review of the literature was undertaken by each of the Task Forces using search engines that are described individually in the papers. They included PubMed, Medline, Embase, and Cochrane.

The search included systematic reviews, meta-analyses, and a targeted search for original publications, references to this field extended to 1940 for historical reference but more recently, since 1970 for all other aspects of PHPT.

For questions specifically related to surgical and medical management of PHPT, GRADE methodology was employed.[8] GRADEd recommendations followed a structured process that included framing questions in patient/intervention/comparator/outcome format; conduct of a systematic evidence search and associated summary; specification of values and preferences; and classifying and presenting recommendations as strong or weak with the corresponding quality of evidence. A strong recommendation was made when the desirable effects were much greater then undesirable effects or vice versa. The word "recommend" is applied to systematic reviews that reach this conclusion. A weak recommendation was made if there was low certainty of evidence or a close balance between desirable and undesirable effects. The word, "suggest" is applied to systematic reviews that reach this conclusion.

Recognizing that this rigorous approach to evidence-based review may necessarily omit worthy observations, due to the screening criteria for selection, the evidence from the GRADE methodology was amplified in order to incorporate other noteworthy observations. When recommendations based upon narrative reviews are made, the terms "the Panel recommends" or "the Panel proposes" or "Panel Recommendations (ungraded)" clearly distinguish these ungraded recommendations from the recommendations based upon the systematic reviews.

The Steering Committee (JPB, AAK, MLB, BC, MM, and JTP) organized the Task Forces with two co-chairs designated for each of the workshops (RVT and SM for Epidemiology, Pathophysiology, and Genetics; GEHF and CM for Classical and Nonclassical manifestations; NP and AS-S for Surgical Aspects; JPB and SJS for Evaluation and Management). In collaboration with these Task Force co-chairs, Task Force members were appointed. Participants were chosen from a roster of experts in PHPT as evidenced by their international standing, publication record, and by their ongoing contributions to our understanding of this disease. We were mindful of the need for international representation as well as a balance of gender, diversity, and age. We had to necessarily limit the number of participants, nine to 12 per task force, in order to ensure optimal efficiency of this project. They are acknowledged in this report. The methodological reviews were led by one of the co-authors (GG).

After drafts of each paper were prepared, a meeting was held of PHPT Task Force members and also those involved in the companion effort on the evaluation and management of hypoparathyroidism.[9–13] Task Forces members constituting the hypoparathyroidism initiative were comprised of a similarly large group of experts. A virtual meeting was held next, attended by representatives from all societies, organizations, and patient advocacy groups that expressed interest in our work with a view toward endorsing the guidelines. Recommendations from both meetings, each attended by about 100 individuals, were considered in revising and finalizing the papers that form the basis for this summary statement[3–8] and their integration into this summary statement. The document was circulated to all organizations during a 6-week to 8-week comment period. The organizations that have endorsed these guidelines are listed at the end of the reference section.

The abbreviations follow standard guidelines of the *Journal of Bone and Mineral Research* (*JBMR*).

Measurement of phosphate

Chemistry laboratories measure phosphate as elemental phosphorus. Although both phosphate and phosphorus are often used interchangeably, in this paper we use phosphorus when the term is used to describe the measurement of elemental phosphorus contained in the serum phosphate.[14]

Results

Epidemiology

The reported incidence and prevalence of PHPT in the United States and Europe increased with the advent of automated chemistry panels that routinely measure serum calcium concentration.[15–19] Recent estimates of age-adjusted prevalence in the United States are 233 and 85 per 100,000 women and men, respectively.[16] The cohort of individuals whose PHPT was identified in this way, namely by biochemical screening without any known antecedent clinical features of PHPT, constitute individuals with asymptomatic PHPT. When parathyroid hormone (PTH) became a routine measurement in individuals with osteoporosis but without hypercalcemia, recognition of the normocalcemic variant became evident.[20] In countries where screening is not routine, PHPT tends to present less commonly and as a more symptomatic disease.[21–27] In countries where screening becomes more routine, the incidence rises along with a presentation that is more likely to be asymptomatic.[28–31] Thus, the change in clinical profile toward the asymptomatic and even the normocalcemic variants of PHPT can be accounted for by evolving clinical paradigms of population screening as well as healthcare system practices.

Severe, classical PHPT is associated with increased mortality. Acute PHPT, a condition associated with the presentation of life-threatening hypercalcemia, led to an estimated mortality of about 60% in reports prior to 1970.[32] However, this presentation appears to be associated with a 10-fold lower risk (6%) of death in subsequent reports.[32] The impact of less severe forms of PHPT, such as asymptomatic PHPT, on survival is uncertain. Some reports, even when the serum calcium is only mildly elevated, have noted an increase in mortality, primarily from cardiovascular disease or cancer.[33–39] Other studies have not confirmed this point.[40,41] A number of variables, none of which has been clearly linked to mortality, include hypercalcemia per se,[40,42,43] disease severity or gland size,[34,41] PTH levels,[39,41–

[43] and age.[38,40–43] Causality between PHPT and mortality remains uncertain.

Physiology and pathophysiology

Clonally dysregulated overgrowth of parathyroid tissue with excessive secretion of PTH, along with reduced expression of the cell surface calcium sensing receptor (CaSR), are major pathophysiological features of PHPT.[44,45] They perturb normal conditions in which PTH maintains a constant extracellular ionized calcium level with very little variability within the normal range.[46] The parathyroid glands sense the concentration of extracellular calcium via the CaSR. Although it also recognizes other divalent cations, Ca++ is the most sensitive.[47] Activation of the CaSR inhibits PTH secretion, PTH gene expression, and parathyroid cell proliferation.[48–51] PTH secretion is also regulated by $1,25(OH)_2D$ via its receptor.[52] The CaSR may also play a role in the activation of $1,25(OH)_2D$ in the parathyroid cell.[53] The kidney CaSR promotes calcium excretion from the cortical thick ascending limb of the Loop of Henle.

PTH defends against hypocalcemia by stimulating renal reabsorption of calcium, suppressing renal reabsorption of phosphate, increasing bone resorption, and stimulating intestinal calcium absorption by increasing the production of $1,25(OH)_2D$ in the proximal renal tubule.[46,52,54,55] The gut microbiota may influence the ability of PTH to stimulate bone metabolism.[56]

An abnormality in any of these physiologic processes contributes to the pathophysiology of PHPT. In particular, the set point for calcium-induced inhibition of PTH secretion is higher than normal, the rate of bone resorption is accelerated, renal tubular reabsorption of calcium is facilitated, and intestinal calcium absorption is increased.[47,55] Reduced renal phosphate reabsorption can lead to hypophosphatemia.[54]

Sporadic PHPT is most often caused by a single benign parathyroid adenoma (85%), less often by multiple parathyroid gland involvement (hyperplasia and less frequently synchronous or asynchronous adenomas [15%]), and very rarely by parathyroid carcinoma (<1%).[57,58] Atypical parathyroid adenomas, in which the histology can have features of malignancy in the absence of unequivocal evidence of invasive growth, or hyperplasia, are included in this breakdown.[59] Multigland disease is more likely to have a genetic or hereditary basis. Multigland disease is also a feature of lithium-associated PHPT.[60] Parathyroid cancer is a very rare cause of PTH-associated hypercalcemia.[58] Its clinical characteristics are typically those related to the phenotype of symptomatic PHPT with marked hypercalcemia and target organ involvement.

Clinical consequences of dysregulated parathyroid function

Dysregulated PTH function, due to clonally abnormal, overactive parathyroid tissue leads to hypercalcemia, the classic biochemical feature of PHPT.[4,44,45] In many patients, the hypercalcemic state, typically within 1 mg/dL of the upper limit of normal, remains stable for years.[57] However, rapidly increasing serum calcium levels can also occur.[60,61] Volume depletion (eg, dehydration), immobilization, or intercurrent illness are all important predisposing factors. As we now appreciate, on the other hand, PHPT can present without hypercalcemia.[4] Although biochemically more benign, as will be described subsequently, normocalcemic PHPT is also associated with significant issues related to the target organs of PTH.[20]

The clinical consequences of these abnormal pathophysiological aspects of PHPT lead to a number of potential outcomes. An increase in bone resorption leads to bone loss at cortically enriched skeletal sites such as the distal radius and hip regions.[62] Overall fracture risk is accounted for by these overt actions at cortical sites but also by more subtle abnormalities at trabecular bone.[63–66] Overstimulation of renal 1-alpha-hydroyxlase leads to increased production of $1,25(OH)_2D$, which accounts, in part, for hypercalciuria when calcium absorption from the gastrointestinal (GI) tract is facilitated. The increased renal flux of calcium places these patients at risk for nephrolithiasis and nephrocalcinosis.[67–70] Off-target involvement regarding cardiovascular disease, hypertension, and metabolic derangements are covered later, as well as putative neurocognitive abnormalities.

Genetics of PHPT

Studies of syndromic and nonsyndromic forms of familial PHPT have helped to identify genetic abnormalities involved in parathyroid tumorigenesis. More than 10% of patients with PHPT will have a mutation in one of 10 genes that have been implicated.[3,71] The genetics of PHPT are delineated in an accompanying report.[3] Testing for mutations in these genes, which is routinely available, can facilitate the diagnosis of a syndromic or nonsyndromic form of PHPT, and thereby help in the clinical management and treatment of PHPT patients and their relatives. Although confirmation of the clinical diagnosis of PHPT does not require genetic testing, and should not be a criterion for diagnosis, nevertheless, elucidation of genetic abnormalities can help in the following ways:

1. If the diagnosis is the hyperparathyroidism jaw tumor (HPT-JT) syndrome, early parathyroidectomy (bilateral exploration) is indicated because of the increased risk of parathyroid carcinoma.
2. If the diagnosis is multiple endocrine neoplasia type 1 (MEN1) or MEN2, a bilateral neck exploration is needed. Selective parathyroidectomy is contraindicated because of the presence of multiglandular disease in these patients.
3. In patients whose genetic testing reveals hypocalciuric hypercalcemia (FHH), surgery is contraindicated in most cases.
4. Genetic testing helps to identify family members who may or may not be at risk. Genetic counseling and evaluation, thus, should be considered for patients <30 years with PHPT, those with multigland disease by history or imaging, those with a family history of hypercalcemia or syndromic diseases such as MEN1, MEN2A, MEN4, or HPT-JT syndrome,[3,71] and in patients with atypical parathyroid adenoma and parathyroid carcinoma.[58,59]

In nonfamilial forms of PHPT, common single-nucleotide polymorphisms (SNPs) within the CaSR cytoplasmic domain may influence the clinical severity of PHPT.[72,73] Reduced parathyroid CaSR expression commonly occurs in PHPT and may arise from epigenetic alterations of the CASR promoter region.[44,45] Formation of heteromers comprising the CaSR and gamma-aminobutyric acid B1 receptor ($GABA_{B1}R$) may contribute to PTH hypersecretion in PHPT.[74]

Genetic factors may contribute to the development of renal calculi in PHPT. Patients harboring the AGQ haplotype of the CaSR have been found to be at a greater risk of developing renal calculi, whereas those with the SRQ haplotype having a lower risk.[75] However, more confirmatory data are required to secure

these observations. It is premature to be recommending evaluation of these haplotypes of the calcium-sensing receptor to identify the risk for renal calculi in patients with PHPT. In addition, these genetic forms of PHPT may have their own unique features of skeletal involvement.[76]

Diagnosis of primary PHPT

In PHPT, PTH secretion is inappropriately high for the serum calcium concentration, but at times the PTH level may be within the laboratory reference range. Conversely, as noted below, in normocalcemic PHPT, the PTH level is consistently elevated above the normal reference range. The serum calcium should be considered with regard to the serum albumin with adjustments to be made if this major calcium binding protein is below 4 g/dL. Because calcium bound to albumin constitutes approximately 50% of the total circulating calcium concentration, low albumin levels can lead to a lower total calcium level and one that does not reflect accurately the ionized calcium, which represents the other major circulating form of calcium.[77] An upward correction factor of 0.8 is generally used for every g/dL reduction in the serum albumin below 4 g/dL.[78–80] Adjustment by this same factor for albumin levels above 4 g/dL is not as clear. If an accurate ionized calcium analyzer is available, such uncertainties due to variability in albumin can be eliminated.[81] An ionized calcium determination is even more relevant when the total serum calcium is normal, but the PTH level is elevated.[82] Serum phosphorus may be low or low-normal due to the phosphaturic effect of excess PTH.

Differential diagnosis

When concurrent measurements of serum total calcium and intact PTH levels are both clearly above normal, it is highly likely that the patient has PHPT. The definition of PHPT presumes that the patient does not have end-stage kidney disease in which these same biochemical abnormalities can signal the existence of tertiary hyperparathyroidism. When the PTH is technically normal, it is also clearly evident that PHPT is the diagnosis in hypercalcemic patients, for reasons already elucidated. It is extremely rare for the hypercalcemia associated with malignant tumors to be associated with the ectopic secretion of PTH. More often, hypercalcemia in this setting is due to the secretion of PTH-related protein (PTHrP). Because assays for PTHrP and PTH do not cross-react, the hypercalcemia associated with malignancy is rarely confused with PHPT. Biotin supplements may interfere with the accuracy of some PTH assays, leading to a falsely low determination. Thus, discontinuation of biotin for at least 48 hours prior to PTH measurement has been suggested.[83] Another aspect of the differential diagnosis is FHH. The urinary calcium /creatinine clearance ratio may be helpful as a distinguishing point. A clearance ratio of <0.01 favors a diagnosis of FFH (it is present in 70%–80% of subjects with FHH). Up to 20% of patients with PHPT can have a calcium-creatinine clearance (Ca/Cr Cl) ratio <0.01 and up to 10% of patients with FHH can have Ca/Cr Cl ratio >0.02, a range that is more commonly seen in PHPT. About 40% of patients with either disease can have values between 0.01 and 0.02.[84–87]

Another point to bear in mind is that urinary calcium measurements are not likely to be accurate if patients are on lithium or thiazide diuretics. Vitamin D deficiency or chronic kidney disease can also be associated with reduced urinary calcium excretion. FHH becomes an important point to consider in patients whose hypercalcemia is lifelong, if they are under 30 years old, or have a family history of hypercalcemia.[3] As noted above, genetic testing is indicated when FHH is a consideration. Another differential point related to lithium or thiazides is that either medication can be associated with hypercalcemia and PTH level above normal. More often than not, the history of these medications leads to a diagnosis of PHPT. If the medication is withdrawn, and the serum calcium is retested several months later, hypercalcemia is likely still to be present. Lithium-associated PHPT may also feature thyroid dysfunction and impaired renal function.[88]

Previously, the distinction between secondary hyperparathyroid states, such as Stage 3–5 chronic kidney disease, vitamin D deficiency, calcium malabsorption, bisphosphonate or denosumab use, and PHPT was clear because the serum calcium in secondary hyperparathyroidism states is usually normal or low. However, with recognition of normocalcemic PHPT, these other entities must be considered and ruled out if a diagnosis of normocalcemic PHPT is to be made. If the serum calcium concentration is low, as can be seen in secondary hyperparathyroid states, normocalcemic PHPT is ruled out. It is when the serum calcium is normal that these secondary causes need consideration vis-à-vis the diagnosis of normocalcemic PHPT. Also, to be considered in the differential diagnosis of hypercalcemia and high PTH levels is tertiary hyperparathyroidism, a clinical state due to evolution of long-standing secondary hyperparathyroidism, such as malabsorption syndromes (eg, active celiac disease, extensive bowel resection, gastric bypass surgery) or uncontrolled renal insufficiency, into a hypercalcemic state. Tertiary hyperparathyroidism is readily identified by the clinical context in which the hypercalcemia presents.

Noteworthy among causes of hypercalcemia is hypercalcemia of malignancy due to osteolytic metastases or by tumors producing excess PTHrP, or $1,25(OH)_2D$.[6] Granulomatous diseases, such as sarcoidosis and tuberculosis, can produce hypercalcemia by production of $1,25(OH)_2D$[89,90] These hypercalcemic states are all characterized by suppressed parathyroid hormone levels. Thus, the differential diagnosis of hypercalcemia hinges importantly on the measurement of PTH. Only when the PTH is suppressed does a search for causes on this list become relevant.

Clinical presentations of PHPT

Symptomatic hypercalcemic PHPT

Prior to the development, in the 1970s, of standardized blood chemistry panels that included serum calcium, PHPT typically came to clinical attention when patients presented with a constellation of skeletal and renal complications that included bone pain due to osteitis fibrosa cystica and fractures, chronic kidney disease due to nephrocalcinosis, and renal colic associated with nephrolithiasis.[91] Neuromuscular manifestations with proximal myopathy were also common. Other complications include pancreatitis, parathyrotoxic crisis, and, rarely, spontaneous neck hematoma due to a ruptured parathyroid adenoma.[92] This "classical" form of PHPT is now uncommon in developed countries, but still is relatively common in regions of the world where laboratory screening tests including calcium levels are not measured as part of standard medical practice.[93]

Asymptomatic hypercalcemic PHPT

Where biochemical screening is commonly performed, most patients with PHPT come to clinical attention when hypercalcemia is found unexpectedly in the context of an investigation of an unrelated problem or simply upon routine testing. If the PTH level is also

found to be high, or even in the normal range, the most likely diagnosis is asymptomatic hypercalcemic PHPT. It is important to distinguish this terminology from involvement of target organs that may become apparent after patients are evaluated. For example, discovery of low bone density by dual-energy X-ray absorptiometry (DXA) or a kidney stone by ultrasound, does not redefine these patients as symptomatic but rather the terminology is modified to indicate that they have target organ involvement. It is thus, useful, to consider this form of PHPT in two ways: those with or those without evidence for target organ involvement after a standard evaluation. They are both "asymptomatic" because they did not come to attention because of clinically evident target organ involvement. This refinement of the terminology preserves the term, symptomatic PHPT, which is reserved for those individuals who are truly symptomatic as noted.[4]

Normocalcemic PHPT

PTH levels may be measured in the evaluation of medical conditions such as osteoporosis, low bone mass, or nephrolithiasis. Normocalcemic PHPT (NPHPT) is characterized by persistently normal albumin-adjusted total and ionized serum calcium levels, accompanied by elevated levels of PTH on at least two consecutive measurements, over a 3-month to 6-month period. Estimated recent prevalence figures place it at 0.18% among those referred for measurement of bone mineral density (BMD).[94] Given that these patients are often discovered in the context of an evaluation for kidney stones or low bone density, selection bias may render these estimates inaccurate. Other diseases and drugs that cause high levels of PTH, namely secondary hyperparathyroidism, should be excluded. The 24-hour urinary calcium is normal.[5] Patients with NPHPT may have evidence of skeletal or renal involvement (eg, osteoporosis, nephrolithiasis). The natural history of NPHPT is unclear in part because studies have not always used consistent diagnostic criteria nor a regular follow up at defined time points to determine possible progression to hypercalcemia.[94–99] A caveat to describing this entity, thus includes the possibility that some studies may have included those with classic hypercalcemic PHPT. Some studies have shown progression, over time, to hypercalcemia in a proportion of patients, whereas others have not. Clinical features of NPHPT can be similar to the ones described in PHPT (skeletal, renal complications, and nonclassical manifestations).

Evaluation of classical manifestations

Biochemical

After the diagnosis has been established, additional serum and urine testing is recommended. The 25OHD should be measured to identify patients whose PHPT may be accompanied by deleterious effects of a further stimulus to PTH secretion when the 25OHD is low (eg, a secondary hyperparathyroidism becomes superimposed upon PHPT). An estimate of renal function by estimated glomerular filtration rate (eGFR) or creatinine clearance, along with a 24-hour urinary calcium determination, should be a standard part of the evaluation. Although a fasting urine sample can be obtained for an estimate of urinary calcium excretion, experts measure a full 24-hour urine collection in view of circadian variability.[100] High sodium diets can increase urinary calcium excretion.[101] It is not essential to measure the serum phosphorus in every patient, although typically the serum phosphorus concentration will be in the lower range of normal. However, it can be helpful. It is rarely necessary to measure urinary phosphorus excretion. The value of measuring bone formation (eg, bone-specific alkaline phosphatase, procollagen type 1 N propeptide [P1NP], osteocalcin) or bone resorption (eg, type I collagen cross-linked C-telopeptide [CTX-1], amino-terminal cross-linking telopeptide of type 1 collagen [NTX]) markers as an index of skeletal activity of the disease or to predict changes in BMD after parathyroidectomy (PTX) is uncertain.[102–104] They are not recommended in the standard evaluation of PHPT.

Skeletal

Fracture risk is increased in patients with PHPT at vertebral and nonvertebral sites.[4,72,105–110] Using either X-rays or vertebral fracture assessment (VFA), by DXA, asymptomatic fractures can be detected in patients who do not have a history of fracture.[106] Because DXA became a widely available clinical tool, in the 1980s, it has become an essential method to determine skeletal involvement in PHPT.[62] Consistent with the known effects of PTH, low BMD by DXA is especially prevalent at sites with high proportions of cortical bone, such as the one-third distal radius.[62,64] The lumbar spine, primarily comprised of trabecular bone, is generally better preserved by DXA in PHPT. BMD values intermediate between that of the one-third distal radius and the lumbar spine, when compared to age-matched norms, have been reported at the femoral neck, which comprises both trabecular and cortical bone.[62] Whether the same DXA pattern exists in NPHPT has not been established. Although the description of a preferential reduction in cortical bone is a classical densitometric feature of PHPT, many other patterns can be seen. In particular, an opposite pattern with preferential reduction in lumbar spine bone density may be observed in some postmenopausal women.[111] Occasionally, a *T*-score ≤ -2.5 is observed at the one-third radius only. In studies of the natural history of PHPT, BMD may be stable for several years, but may ultimately decline at the hip and radius when observation exceeds 10 years.[112]

Because both osteoporosis and PHPT are predominantly seen in postmenopausal women, in addition to DXA, other risk factors that are part of Fracture Risk Assessment Tool (FRAX®)[113]—mostly age—may be important in PHPT. A risk assessment tool such as FRAX would help to estimate absolute fracture risk, but at this point, disease-specific data in PHPT are not available. It is likely that the factors identified by FRAX are as important in PHPT as they are in subjects without PHPT, but this remains to be demonstrated. Results are awaited from ongoing studies.

The vexing discordance between the selective pattern of cortical bone loss seen by DXA and fracture locations that extend more globally, to include both cortical and trabecular sites, has been clarified by other imaging modalities. Using these noninvasive imaging approaches, it is evident that trabecular bone is also affected in PHPT, correcting earlier views that PHPT spares the trabecular compartment. Using high-resolution peripheral quantitative computed tomography (HRpQCT), for example, microstructural trabecular and cortical abnormalities in PHPT have been demonstrated and help to account more completely than DXA for the increase in vertebral and nonvertebral fracture risk.[66,114] By HRpQCT, women with PHPT demonstrate decreased trabecular and cortical volumetric densities, thinner cortices, and more widely spaced trabeculae at both radial and tibial sites.[66,115] These HRpQCT studies appear to be more representative of skeletal features in PHPT than DXA or the transiliac bone biopsy.[116] However, because HRpQCT is not widely available, it is not recommended as a standard component of the skeletal evaluation of PHPT.

Trabecular bone score (TBS), a semiquantitative, noninvasive index of trabecular microarchitecture, has also shown abnormalities in PHPT.[117,118] The presence of vertebral fractures was associated with TBS values <1.2.[118,119] Other studies have not shown that TBS is associated or correlated with fractures.[120,121] Because of its uncertain value, to date, in PHPT, TBS is not recommended because it may not add to the other imaging modalities like vertebral X-rays or VFA. On the other hand, it does not add to radiation exposure and could be helpful as an adjunctive test.

Renal

Evaluation of renal function

The threshold creatinine clearance value below which deleterious effects of PHPT on renal function occur is unclear. It is also unclear whether reduced renal function in those who present with PHPT is due to the disease itself or to independent factors. A widely regarded threshold value is 60 mL/min. It originates primarily from observations after PTX. Those with creatinine clearance values <60 mL/min stabilized their renal function after successful PTX, whereas those who did not undergo surgery showed continued declines.[122,123] Nephrolithiasis or nephrocalcinosis and repeated urinary infections and urological procedures can contribute to reduced renal function.[124]

Reduced eGFR can also be associated with greater reductions in BMD, particularly at cortical sites.[125] Thus, even mild reductions in eGFR can be associated with adverse renal and skeletal effects in PHPT. We still, however, are left with uncertainty about the precise eGFR threshold below which deleterious effects on renal and skeletal function are seen. Moreover, the eGFR threshold below which further elevations of PTH levels occur, if at all, has also not been established.[123]

It is also important to consider how renal function is assessed. Although an estimate of eGFR is readily available by formulas used for standard printouts from commercial laboratories,[126] they are useful only for screening purposes. An actual measurement of creatinine clearance is more accurate and, over time, repeated calculations of creatinine clearance give a more accurate depiction of any change that may occur. There is controversy over the methodology to measure creatinine clearance as well as what constitutes a significant decline over time. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines provide some guidance by noting that annual declines of 3 mL/min from repeated determinations over 1–2 years are significant.[126] Declines in renal function to <60 mL/min are associated with an increase in fracture risk,[127–130] but these observations are not specifically related to those with PHPT.

Evaluation for kidney stones

Hypercalciuria is a risk factor for renal calculi,[68] but by itself does not fully explain the increased risk for nephrolithiasis in all patients with PHPT, raising the possibility that other risk factors may play a role,[70,131] such as hyperuricosuria, hypomagnesuria, hyperoxaluria, hypocitraturia, or cystinuria.[132,133] Nevertheless, the 24-hour urine calcium is higher in patients with PHPT and nephrolithiasis when compared with patients with PHPT and no nephrolithiasis.[134,135] Marked hypercalciuria is seen in approximately one-third of patients with PHPT and kidney stones.[136,137] Based primarily upon these observations, but without any data that describe the performance characteristics of this value (eg, sensitivity/specificity), The 4h International Workshop on Asymptomatic PHPT recommended a threshold of >400 mg/day.[1] The value did not stipulate any adjustment for differences in urinary creatinine, sex, race, salt intake, or body weight. It is virtually impossible to make specific recommendations that would consider all these variables. On balance, though, threshold values for hypercalciuria are reasonably expressed as >250 mg/day for women and >300 mg/day for men. Although hypercalciuria, by itself, might be considered to reasonably account for stone risk in PHPT, there may be other important factors to consider. This is even more relevant to those with kidney stones who do not have marked hypercalciuria. Thus, a more extensive biochemical evaluation for stone risk factors in all patients with kidney stones is reasonable. This more extensive evaluation also recognizes that PHPT is not necessarily etiologic in those with kidney stones. Stones could be due to factors, besides PHPT.[138]

Because clinically silent renal calculi are reported in up to 22% of patients with asymptomatic PHPT,[139] renal imaging is recommended in patients with PHPT.[1] Imaging modalities include spiral computed tomography (CT), ultrasound, or conventional X-ray of the abdomen.

A summary of panel recommendations for evaluation

Biochemical:

1. Measure adjusted total serum calcium (ionized if NPHPT is a consideration), phosphorus, intact PTH, 25OHD, creatinine

Skeletal:

2. Three-site DXA (lumbar spine, hip, distal 1/3 radius); imaging for vertebral fractures (VFA or vertebral X-rays). As an adjunctive test, the TBS can be helpful if available.

Renal:

3. eGFR or, preferably, creatinine clearance, full 24-hour urinary calcium. Imaging for nephrolithiasis/nephrocalcinosis. In those with hypercalciuria, a stone risk profile is recommended. In those with stones (an indication for surgery) a stone risk profile is recommended whether or not the patient has hypercalciuria.

Evaluation of nonclassical manifestations

Neurocognitive and quality of life

One of the most frequent but nonclassical manifestations of PHPT relates to neurocognitive or neuropsychiatric function. Although there is no doubt that symptomatic PHPT with severe hypercalcemia can be associated with altered mental status,[140] it is uncertain if more subtle manifestations of neurocognitive function relate specifically to PHPT when the serum calcium is not markedly elevated. The 4th International Workshop guidelines concluded that there was no clear evidence to suggest that asymptomatic PHPT is associated with neurocognitive dysfunction and that there did not exist clear evidence to recommend formal neurocognitive or neuropsychiatric testing in PHPT.[1] The psychiatric and surgical literature continues to emphasize the association of otherwise asymptomatic PHPT with depression and decreased quality of life.[141,142] In fact, it has been recommended by the American Association of Endocrine Surgeons that neuropsychiatric symptoms be assessed in all patients with PHPT and that they should be considered as a relative indication for PTX.[143,144] The conflicting literature on this subject has been

clarified recently by a recent prospective, randomized controlled prospective 10-year clinical trial in which a putative association between neurocognitive function and PHPT could not be substantiated. This study included those who underwent successful parathyroid surgery.[145] If there are mechanisms underlying neurocognitive manifestations, the methodologies are not well defined, and randomized, controlled trial (RCT) data do not demonstrate clear or consistent reversibility after PTX.

A summary of panel recommendations

1. Neurocognitive or neuropsychiatric testing should not be routinely conducted in PHPT.
2. Neurocognitive or neuropsychiatric manifestations, if present, should not be used, by themselves, to recommend parathyroid surgery.
3. More research is needed including further development of a disease-specific quality of life tool.

Cardiovascular/metabolic

Although small studies have reported hypertension, left ventricular hypertrophy, arterial stiffness, and impaired diastolic filling in patients with PHPT,[146,147] these observations do not have a clear pathophysiologic basis nor are they clearly changed after successful PTX.[146–148] Similarly, metabolic indices such as the Homeostatic Model of Assessment-Insulin Resistance (HOMA-IR) are not consistently associated or improved following PTX.[149–151]

A summary of panel recommendations

1. Cardiovascular or metabolic evaluations in PHPT are not recommended.
2. Cardiovascular or metabolic abnormalities, if present, are not clearly related to PHPT.
3. Cardiovascular or metabolic abnormalities, if present, should not be used as criteria for decision making vis-à-vis PTX.

Gastrointestinal manifestations

Classic gastrointestinal manifestations in symptomatic PHPT include abdominal pain, constipation, nausea, vomiting, peptic ulcer disease, cholelithiasis, and pancreatitis. The bulk of evidence in the more common forms of PHPT, namely asymptomatic and NPHPT, do not provide evidence that GI manifestations are linked. The only exception to this are patients with MEN 1 and the Zollinger-Ellison syndrome in which gastrointestinal symptomatology is common and pathophysiologically linked.[3]

A summary of panel recommendations

1. There is no indication for a gastrointestinal evaluation in PHPT
2. If gastrointestinal manifestations are present, they are not clearly linked to PHPT, unless the patient has the symptomatic form of the disease, or MEN with Zollinger Ellison syndrome.

Surgical Aspects of PHPT

The key decision to be made in PHPT is whether the patient should undergo curative PTX. The reasons for recommending parathyroid surgery are straightforward in those with symptomatic disease. Unless there are extenuating medical issues, parathyroid surgery is indicated. In those with asymptomatic PHPT, however, criteria have been developed based upon the presence of target organ involvement and evidence for improvement after successful surgery. To reconsider this topic, as comprehensively as possible, two approaches were employed: a systematic review utilizing GRADE methodology[7] and a narrative review that incorporated noteworthy information that could not be included in the systematic review.[6] In addition, a task force designated to consider specific aspects of parathyroid surgery helped to identify advances in technical aspects and outcomes of parathyroid surgery.[5]

Systematic review

The systematic review included trials in which patients with asymptomatic PHPT were randomized to surgery with or without medical therapy or management without surgery with or without medical management.[103,141,145,151–159] For patients with asymptomatic PHPT, PTX achieved a biochemical cure in 97.8% (high quality evidence for cure rate). This percentage is consistent with the majority of outcomes that have been published from major medical centers with expertise in this disease.[160,161]

Although BMD clearly increased after PTX, uncertainty regarding whether the association of changes in bone density with changes in fracture risk in post-menopausal osteoporosis apply equally in PHPT led us to rate down certainty in evidence twice for indirectness. Thus, we remain very uncertain about the extent to which surgery will reduce fracture in patients with PHPT.

Table 1 summarizes the results of this systematic review. The review did not draw any conclusions as to whether PTX improves quality of life, reduce the incidence of kidney stones, or improves renal function.

A summary of recommendations on the surgical management of PHPT

What is the role of surgical management of PHPT? GRADed Panel Recommendations:

1. In the hands of experienced surgeons, surgery should be used to achieve a biochemical cure, if there are no contraindications (high quality evidence)
2. Ungraded Panel Recommendations

    2a. Surgery is recommended if patients meet any one of the guidelines for surgery and there are no contraindications (see guidelines below).
    2b. Surgery cannot be recommended to improve neurocognitive function, quality of life and/or cardiovascular indices because the evidence is inconclusive.

Narrative review

The narrative review permitted a more expansive, albeit heterogeneous, view of the published literature related to the merits and consequences of PTX. Although not as rigorous as the systematic review, this narrative review was nevertheless valuable as it incorporated a larger body of worthy data. As noted in the

Table 1. Trials Included in Systematic Review of Parathyroid Surgery[7]

Categories of subjects	[Calcium] (mg/dL)	[PTH] (pg/mL)	Urinary Ca (mg/day)	Conclusions of all systematic reviews (both rows)	References
No surgical criteria	10.3 ± 0.46	105 ± 38	239 ± 104	Surgery results in biochemical cure; patients are not cured if they do not undergo surgery.	Ambrogini and colleagues[153]; Morris and colleagues[158], Perrier and colleagues[145]; Rao and colleagues[152]
Asymptomatic with or without surgical criteria	10.9 ± 0.38	92 ± 31	264 ± 121	Surgery increases BMD See text and systematic review[7] for more details	Almqvist and colleagues[155,156]; Ejlsmark-Svensson and colleagues[157]; Lundstam and colleagues[103]; Pretorius and colleagues[145]; Persson and colleagues[151]; Ambrogini and colleagues[153]; Bollerslev and colleagues[220]; Lundstam and colleagues[159].

Task Force report,[6] the narrative review is consistent with the results of the systematic review. Specific aspects of PTX are presented in another article in this series.[5]

PTX is a safe, well-tolerated, and successful operation in the hands of experienced surgeons. Although the definition of an experienced parathyroid surgeon can be debated, the surgeon who performs at least 50 parathyroidectomies per year is considered by most endocrine surgeons to be experienced.[162] Recent advances in parathyroid imaging and in surgical approaches have been impressive. Outcomes include durable improvement in biochemical manifestations and, in many cases, improvements in classic end-organ features. Previous retrospective, observational, single-institution studies have been supported by more recent contributions that have included randomized clinical trials and population-based approaches.

The benign single-gland adenoma, the most common abnormality, can be cured by identification and resection of the single offending gland. More challenging is multigland disease, including double adenoma and four-gland hyperplasia. It requires a different operative approach. Although bilateral neck explorations have historically been associated with 95% success rates,[160] the advent of advanced imaging modalities (eg, high-resolution neck ultrasound, technetium-99m-sestamibi subtraction scintigraphy, and/or contrast enhanced four-dimensional [4D] CT) have facilitated the operative approach. Some studies have shown that in normocalcemic disease, the value of preoperative localization studies is not as clear as it is in hypercalcemic disease.[95,96,163] This may be due to a greater incidence of multiglandular disease and smaller adenoma size found in some but not all studies.[96,163–165] For all forms of PHPT, preoperative imaging approaches are reserved for those in whom the decision for surgery has been made. Parathyroid imaging is not used for diagnostic purposes.

When selective PTX is offered to appropriate patients combined or not with the results of intraoperative PTH monitoring (IOPTH) using a structured protocol, these minimally invasive approach achieves success rates of 95%–97%. The potential benefits of this selective approach include shorter operative time, less tissue scarring, less risk to surrounding structures, and decreased hospital costs.[161] Head-to-head comparisons between the selective procedure and the bilateral neck exploration are now available.[166]

For both bilateral and selective approaches, PTX incisions are usually small and can be performed under general or local anesthesia. Recovery is usually straightforward, often with only mild throat discomfort and a few days of postoperative fatigue. Most patients can be discharged on the day of operation. Narcotic use for pain control is rarely needed.

Surgical complications after PTX are exceedingly rare. Most large single-institution series with experienced surgeons show very low rates of complications, including a 1% incidence of permanent injury to the recurrent laryngeal nerve, 2%–5% risk of persistent or recurrent disease and 0.5% risk of a neck hematoma.[161] Although also rare, post-PTX hypoparathyroidism occurs in well under 10% of patients who undergo multiple gland resections.[5] Nevertheless, among patients with hypoparathyroidism, anterior neck surgery—mostly total thyroidectomy—is the most common cause.[5,9,167,168] PTX is safe even in elderly patients or in those identified with physiologic frailty.[169]

After PTX, bone density increases.[152–154,170] Factors leading to significant BMD increases are severe disease, young age, and good renal function.[154] Gains in BMD in NPHPT patients have also been observed in most, but not all, studies.[96,98,99,171,172]

Although the systematic review did not provide clear evidence for a reduction in the incidence of nephrolithiasis, observational data suggest that it does appear to be reduced after PTX, with kidney stone events falling to that of controls 10 years after surgery.[173]

Successful PTX does appear to mitigate expected declines in renal function. Salutary effects on putative non-classical manifestations of PHPT, such as quality of life, are uncertain, as noted previously.

Certainly, all symptomatic patients should be considered for PTX. Among those who are classified as asymptomatic, the recommended evaluation will identify those with a biochemical calcium threshold above which complications of the disease become more likely (eg, calcium >1 mg/dL [0.25 mmol/L]) above the upper limit of normal. Any aspect of skeletal involvement as determined by DXA (*T*-score ≤ −2.5) or a morphometric vertebral fracture by X-ray of VFA would constitute a surgical indication. It is acknowledged that the *T*-score in the osteoporotic range at any site could be due to factors besides PHPT. For example, the patient may have had a low *T*-score prior to the development of PHPT or concomitant factors such as estrogen deficiency could contribute to reduced bone density. Nevertheless, the evidence that PHPT can reduce bone density identifies it as a factor that can be definitively managed. Additionally, the literature reviewed elsewhere in detail documents verifiable improvements in BMD after successfully PTX notwithstanding the presence of other factors that might also have been contributing to reduced bone mass. Thus, the argument to use bone density as a criterion for surgery is compelling.

Any aspect of renal involvement as determined by a creatinine clearance of <60 mL/min, evidence by imaging for nephrolithiasis or nephrocalcinosis, or hypercalciuria (>250 mg/day [women] or >300 mg/day [men]) would constitute an indication for surgery.

Table 2. Guidelines for Surgery in Asymptomatic Primary Hyperparathyroidism: A Comparison of Current Recommendations with Previous Ones

Parameter	1990	2002	2008	2013	2022
Serum Calcium (>upper limit of normal)	1–1.6 mg/dL (0.25–0.4 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)	1.0 mg/dL (0.25 mmol/L)
Skeletal	BMD by DXA: *Z*-score < −2.0 (site unspecified)	BMD by DXA: *T*-score < −2.5 at any site	BMD by DXA: *T*-score < −2.5 at any site Previous fragility fracture	a. BMD by DXA: *T*-score < −2.5 at lumbar spine, total hip, femoral neck or distal 1/3 radius b. Vertebral fracture by X-ray, CT, MRI, or VFA	a. BMD by DXA: *T*-score < −2.5 at lumbar spine, total hip, femoral neck or distal 1/3 radius* b.Vertebral fracture by X-ray, CT, MRI or VFA
Renal	a. eGFR reduced by >30% from expected. b. 24-Hour urine for calcium >400 mg/day (>10 mmol/day)	a. eGFR reduced by >30% from expected b. 24-Hour urine for calcium >400 mg/day (>10 mmol/day)	a. eGFR <60 cc/min b. 24-Hour urine for calcium not recommended	a. eGFR <60 cc/min b. 24-hour urine for calcium >400 mg/day (>10 mmol/day) and increased stone risk by biochemical stone risk analysis c. Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT	a. eGFR <60 cc/min** b. Complete 24-hour urine for calcium >250 mg/day in women (>6.25 mmol/day) or > 300 mg/day in men (>7.5 mmol/day) c. Presence of nephrolithiasis or nephrocalcinosis by X-ray, ultrasound, or CT
Age	<50 years	<50 years	<50 years	<50 years	<50 years

This table does not include the clearcut indication for surgery in anyone who has symptomatic PHPT (marked hypercalcemia, kidney stones, fractures). Surgery is also indicated in patients for whom medical surveillance is neither desired nor possible and also in patients opting for surgery, in the absence of meeting any guidelines, as long as there are no medical contraindications. Patients need meet only one of these criteria to be advised to have parathyroid surgery. They do not have to meet more than one.

*Consistent with the position established by ISCD the use of *Z*-scores instead of *T*-scores is recommended in evaluating BMD in premenopausal women and men younger than 50 years.[174] These individuals meet criteria for surgery by virtue of age.

**Special consideration might be justified in those whose eGFR is >60 cc/min but in whom there is only one kidney. In those situations, parathyroidectomy could be considered to be special indication for surgery.

We also regard those under 50 years as more likely to experience negative consequences upon conservative follow up.

In patients who do not meet these criteria, and for whom there are no medical contraindications, PTX can be considered if patients opt for it in concurrence with their physician.

A summary of panel recommendations for surgical management of PHPT

1. Symptomatic PHPT: all symptomatic patients should be offered parathyroid surgery unless medically contraindicated.
2. Asymptomatic PHPT
   - A. Serum calcium >1 mg/dL (0.25 mmol/L) above the upper limit of normal
   - B. Skeletal involvement:
     - a. A fracture by VFA or vertebral X-ray or
     - b. BMD by *T*-score ≤ −2.5 at any site or
   - C. Renal involvement:
     - a. eGFR or creatinine clearance <60 mL/min or
     - b. Nephrocalcinosis or nephrolithiasis by X-ray, ultrasound, or other imaging modality or
     - c. Urinary calcium excretion: hypercalciuria (eg, >250 mg/day in women; >300 mg/day in men).
   - D. Age <50 years (no other indications are necessary; age <50 years is a sufficient indication)
   - E. If no aforementioned guidelines are met, PTX is still an option with concurrence of the patient and physician and if there are no contraindications

Although the current guidelines are similar to the previous guidelines, there are changes in renal indications, and they are based upon a stronger set of data (Table 2).

Current, limited data in NPHPT did not permit the Panel to come to any conclusions regarding surgery for this form of the disease. We acknowledge, however, that many clinicians may find the indications for surgery in the hypercalcemic form of the disease to provide helpful guidance.

Monitoring

In those patients who do not meet guidelines for PTX and are not to undergo PTX, recommendations for monitoring include annual measurements of calcium and 25OHD, and an annual estimate of renal function (creatinine clearance or eGFR). PTH measurements are also reasonable, if clinically indicated.

Three-site DXA should be obtained every 1 or 2 years, as clinically indicated. If the three-site DXA measurement is normal, less frequent DXA measurements are reasonable. As recommended by the International Society of Clinical Densitometry, in order to be confident of a change over time, the same DXA facility should be utilized. Knowing the precision of the instrument, a significant reduction is defined as a change that exceeds the least significant change of the measurement. If the precision of the lumbar spine measurement is 1%, for example, the change would have to exceed 2.77% in order to be 95% confident that the change over time is a significant one.[174] If the significant change leads to a *T*-score ≤ −2.5, the nongraded panel advice is to recommend PTX.

With this recommended approach to monitoring, patients may become candidate for parathyroid surgery over time. They may meet the guidelines for surgery with regard to the serum calcium concentration, skeletal or renal involvement as described above.

Panel recommendations for surgery among those with hypercalcemia who are being monitored (ungraded)

1. Serum calcium becomes consistently >1 mg/dL (0.25 mmol/L) above the upper limit of normal or
2. A nontraumatic fracture or
3. A kidney stone or
4. A significant reduction in BMD (> the least significant change of the measurement and to a *T*-score ≤ −2.5) or
5. A significant reduction in creatinine clearance (averaging >3 mL/min over a 1-year to 2-year period) to <60 cc/min if associated with other changes that indicate progression.

Medical/Management of PHPT

Surgery is not always performed in patients who meet guidelines for PTX. The decision against surgery could be based upon extenuating medical contraindications, persistent disease after a failed surgical exploration by an experienced surgeon, or choice. Nevertheless, these patients may have levels of serum calcium that need specific attention (eg, >11 mg/dL) or whose BMD is low and thus at risk for fracture. To reconsider this topic, since the last international workshop, as comprehensively as possible, two approaches were employed: a systematic review utilizing GRADE methodology[8] and a narrative review that incorporated noteworthy information that could not be included in the systematic review.[6]

Systematic review

The systematic review of 11 publications included 423 eligible patients (Table 3). Randomized trials compared nonsurgical management with medical therapy versus nonsurgical management without medical therapy.[8] Medications included the use of several different agents with the number of trials reviewed noted in parentheses: alendronate (3), denosumab (1), cinacalcet (2), vitamin D (2), and estrogen or estrogen analogue therapy (3). With the caveat that we cannot be sure that the association of BMD and fracture in PHPT is identical to that in postmenopausal osteoporosis, we examined gains in BMD as a surrogate for expected reductions in fracture incidence,[7,175] and found the following:

1. Alendronate increases bone mineral density
2. Denosumab increases bone mineral density.
3. Vitamin D increases bone mineral density
4. Estrogen increases bone mineral density
5. Cinacalcet reduces serum calcium and PTH levels.

Table 3. Trials Included in Systematic Review of Medical therapy[8]

Intervention	[Calcium] (mg/dL)	[PTH] (pg/mL)	Urinary Ca (mg/day)	Conclusions of systematic reviews (effect on bone density*)	Conclusions of systematic reviews (effect on serum calcium)	References
Alendronate	11.0 ± 0.5	170 ± 95	204 ± 109	Increases bone mineral density**	No effect	Chow and colleagues[193]; Khan and colleagues[190]; Rossini and colleagues[194]
Estrogen (raloxifene data are sparse)	10.6 ± 0.16	149 ± 32	240 ± 41	Increases bone mineral density***	Reduced***	Grey and colleagues[197]; Rubin and colleagues[198]
Cinacalcet	11.2 ± 0.45	138 ± 46	290.0 ± 120	No effect	Reduced**	Khan and colleagues[202]; Peacock and colleagues[201]
Denosumab	10.9 ± 0.1	115 ± 16	NR	Increases bone mineral density	No effect	Leere and colleagues[205]
Vitamin D	11.0 ± 0.3	83 ± 15	376 (320–432)	Increases bone mineral** density***	No effect	Lind and colleagues[184]; Roglighed and colleagues[182,183]

NR = not reported.

Using GRADE methodology to reflect quality of available data: *There are no data documenting a direct effect on fracture incidence, associated with an increase in bone mineral density. **Medication "probably" effects outcome: moderate quality evidence. ***Medication "may" effect outcome: low quality evidence.

Narrative review

The narrative review permitted a more expansive view of the published literature related to the medical options in PHPT. Although not as rigorous as the systematic review, this narrative review was nevertheless valuable as it incorporated a larger body of worthy data.

Nutritional aspects

Calcium supplementation

The advice among many clinicians is to eliminate supplemental calcium and to restrict dietary sources of calcium in PHPT. This recommendation is not advisable because PTH levels could rise further even though the serum calcium might not change measurably when calcium intake is restricted.[57,176] The Institute of Medicine guidelines for calcium intake in the general population is appropriate for the subjects with PHPT.[177] For the adult population this amounts to approximately 1000–1200 mg of calcium, from all sources.

Vitamin D supplementation

In a meta-analysis of 10 studies including 340 patients with PHPT with varying baseline serum 25OHD levels, across a dosage range of 800 IU daily to 50,000 IU twice weekly, vitamin D was not associated with worsening hypercalcemia.[178] The concomitant serum PTH level fell on average by 33% ($p = 0.003$).[178] These observations underscore the pathophysiological processes associated with excess PTH secretion in PHPT. Vitamin D insufficiency could stimulate further PTH synthesis and secretion, and lead to a further increase in PTH. It is not clear, however, what is meant by "insufficient," which is a very controversial topic.[177–181] The safe use of vitamin D supplementation is also relevant to this discussion.[182–184] The meta-analyses by Song and colleagues[185] and by Loh and colleagues[186] found that over a range of 25OHD concentrations, serum calcium and urine calcium excretion remain stable. Thus, despite uncertainties in what value is optimal,[187] it seems prudent, based upon the evidence, to recommend levels of 25OHD levels >30 ng/mL in PHPT.

Specific pharmacological intervention

Bisphosphonates

In numerous studies, bisphosphonates, primarily alendronate, have been shown to improve BMD and to reduce bone turnover in PHPT, but without any consistent reductions in the serum calcium concentration.[188–192]

Because the BMD-fracture risk relationship is not well-defined in PHPT, we cannot conclude, with confidence, that fracture risk at vertebral or nonvertebral sites is lowered to the same degree in PHPT with increases in BMD as in postmenopausal osteoporosis. The results were similar among men and older individuals[193,194] In NPHPT, alendronate also appears to improve BMD.[195]

Estrogens and selective estrogen receptor modulators

BMD increased relative to placebo by 7.3% in the lumbar spine.[196] The effect of conjugated estrogen on the reduction of serum calcium is inconsistent.[196,197] A very short-term report with raloxifene demonstrated a significant reduction in the serum calcium concentration, by 13%.[198]

Denosumab

Retrospective studies with this receptor activator of nuclear factor κB ligand (RANKL) inhibitor, for 1–2 years, showed improvements in BMD.[199] Although changes in BMD favored surgery over denosumab, improvement in TBS favored denosumab over surgery. Serum calcium did not change but serum PTH increased by 28% ($p < 0.05$).[199] With denosumab inhibiting a classic bone catabolic pathway for PTH, namely RANKL, the increase in PTH would not be expected to have an adverse skeletal effect. In another retrospective study on 50 elderly women, denosumab was associated with a greater increase in BMD over 2 years in comparison to osteoporotic patients without PHPT.[200]

Cinacalcet

In contrast to antiresorptive agents that collectively appear to increase BMD in PHPT but do not reduce the serum calcium, the calcimimetic cinacalcet would be expected to reduce the serum calcium without necessarily improving BMD. These expectations have been confirmed in several prospective studies in which cinacalcet significantly reduced the serum calcium in most patients over a 1–5-year period.[201–203] Although the mean PTH level falls, due to the mechanism of action of the drug, it nevertheless does not fall to the same extent as does the serum calcium concentration. Cinacalcet does not affect BMD.[202]

In NPHPT, at doses sufficient to reduce PTH concentrations, cinacalcet reduced the number and diameter of kidney stones.[204]

Cinacalcet and denosumab

The differing actions of antiresorptive therapy, to increase bone density but not to reduce the serum calcium, and cinacalcet, to reduce the serum calcium but not to improve BMD, has led to an attempt to use both agents in combination. In a short 50-week randomized, placebo-controlled clinical trial, serum calcium was normalized in 64% of patients, along with an increase in lumbar spine and femoral neck BMD.[205]

It should be emphasized that pharmacological approaches to the management of PHPT should be reserved in those for whom surgery is not an option but for whom there is need to manage either the hypercalcemia, the reduced BMD or both.

Summary of panel recommendations for nutritional and pharmacological management of PHPT in those not to undergo parathyroid surgery (GRADEd)

1. In patients with PHPT who do not undergo PTX, pharmacological management should be used only for specific indications.
   a. In patients with low BMD who do not undergo PTX, we suggest bisphosphonates (eg, alendronate) or denosumab (weak recommendation based on very low-quality evidence)
   b. In patients with PHPT and serum calcium levels >11.0 mg/dL (>0.25 mmol/L) above the upper limit of normal who do not undergo PTX, we suggest cinacalcet (weak recommendation based on low quality of evidence)
2. In patients with PHPT and vitamin D insufficiency (25OH vitamin D <30 ng/mL (75 nmol/L) or deficiency (<12 ng/mL; <30 nmol/L), we suggest vitamin D supplementation (weak recommendation based on very low-quality evidence)

Comment: Although there is controversy over the goal for vitamin D sufficiency, most experts aim for a 25-hydroxyvitamin D level >30 ng/mL (>75 nmol/L) in individuals with metabolic bone disease.

Summary of panel's recommendations for management of PHPT in those not to undergo parathyroid surgery whether or not a pharmacological intervention is implemented (unGRADEd)

1. Nutritional guidelines for calcium should follow the Institute of Medicine. 800 mg/day for women <50 years and men <70 years; 1000 mg/day for women >50 years and men >70 years.
2. Annual measurement of the serum calcium and 25-hydroxyvitamin D concentration.
3. BMD every 1 or 2 years, If BMD is normal, a longer interval might be reasonable. If clinically indicated. Vertebral imaging by X-ray or VFA is reasonable. If available, TBS might be a useful adjunctive test.
4. Renal function yearly by creatinine clearance or eGFR. If clinically indicated, renal imaging (X-ray, ultrasound, or CT) or 24-hour for calcium) is reasonable.

PHPT in Pregnancy

PHPT in pregnancy is a rare event,[206,207] but the actual incidence of PHPT in pregnancy is not known. In part, this is because many of its nonspecific symptoms such as fatigue, constipation, and nausea may be a manifestation of the pregnancy.[206] It is also not known what percentage of pregnant women with PHPT had the disorder prior to the onset of their pregnancy. The disease in pregnancy is usually mild with albumin-adjusted serum calcium values within 1 mg/dL of the upper limit of normal.[206] PHPT in pregnancy was not found to be associated with deleterious obstetric outcomes in a study performed in a large managed care organization in Israel,[206] whereas, on the other hand, a 3.5-fold increased rate of fetal loss was reported in another study from the United States.[208] The varying outcomes observed in these two studies could be related to screening methodology[206] and to the serum calcium level.[209] Some features of pregnancy such as hyperemesis gravidarum, and preeclampsia can coexist with features that are classical features of PHPT such as nephrolithiasis.[210]

During normal pregnancy, unadjusted serum total calcium levels fall because of an increase in extracellular volume and reduced serum albumin levels. Ionized serum calcium values do not change. There is also a reduction in PTH to low-normal levels during the first trimester and then a steady rise into the mid-normal range by term.[210] Mild cases of PHPT can usually be managed without surgical or pharmacological intervention. The drugs potentially available in PHPT, namely calcitonin, bisphosphonates, denosumab, and cinacalcet have had limited experience and carry with them cautionary labelling for pregnancy.[208,211–214]

Indications for surgery include symptoms and signs of PHPT and are similar to other patients as noted in other sections of this report. The opportune timing of PTX under general anesthesia is during the first half of the second trimester.[209] Preoperative imaging should be limited to ultrasound scanning. Other scanning methods carry with them unacceptable risks due to radiation or contrast agents that cross the placenta.[215–217] In those who do not undergo PTX during pregnancy, patient education and maintaining good hydration are important measures.[218] PTX is recommended by most experts after delivery. In particular, if another pregnancy is desired, PTX before the next pregnancy, is an even stronger recommendation.

After delivery, neonatal hypocalcemia can emerge due to intrauterine suppression of the fetal parathyroid glands.[219] Close monitoring of the neonate with frequent testing of serum calcium levels is appropriate at the time of, and at regular intervals after, delivery.

Panel recommendations for management of PHPT during pregnancy (unGRADEd)

1. Mild cases should be managed with hydration and monitoring of calcium levels
2. Bisphosphonates and denosumab should not be used
3. Data are very limited on use of cinacalcet
4. Consider surgery in the second trimester for patients with serum calcium >1 mg/dL (>0.25 mmol/L) above the upper limits of normal and for whom surgery is not contraindicated
5. Preoperative imaging should be limited to ultrasound
6. If surgery is deferred, the neonate should be closely monitored for hypocalcemia
7. If surgery is deferred, PTX should be done after delivery, and before a subsequent pregnancy

Research Agenda

In this evidence-based review of PHPT, many issues are covered for which we need more information. These items are listed in Table 4. We need more information on the epidemiology and clinical presentations of the various forms of PHPT. This research should include attention to global factors that may be responsible for demographics and how the disease presents in different parts of the world. The natural history of asymptomatic PHPT with and without end organ damage, of NPHPT, and of nonclassical disease manifestations, need to be elucidated. Renal aspects of PHPT need attention with regard to risk of nephrolithiasis, factors associated with worsening renal function, and how to document significant worsening renal function. Predictive models for worsening target organ function (eg, development of nephrolithiasis or fractures) are needed to enable the development of clinical care pathways and guidelines. The pathophysiology of PHPT, although elucidated more clearly over the past decade, needs more attention as to how the hypercalcemic and normocalcemic variants can be accounted for. Further understanding of the role of the CaSR's signaling pathways in abnormal parathyroid tissue and at classical and nonclassical target organs is needed. A new frontier has emerged exploring the microbiome and how it may influence clinical manifestations of PHPT. The genetics of PHPT are more completely understood, but specific genes implicated in the pathophysiology, pathology, and varying presentations of PHPT remain to be elucidated. We need more guidance on when genetic testing is clinically indicated and what modalities to use. Adjustments to be made in the measured serum calcium when the serum albumin is above average are not clear. Although it is agreed that 25OHD is the

Table 4. Research Agenda

1. Epidemiology and clinical presentations
   a. Global presentations and factors to account for differences
   b. Global differences in incidence and prevalence of the symptomatic, asymptomatic (with and without target organ involvement) and NPHPT variants of the disease.
   c. Long-term consequences/natural history of hypercalcemic and normocalcemic forms of PHPT followed with or without PTX.
   d. Definition of normocalcemic PHPT
   e. A global registry
2. Pathophysiology
   a. Differences among the hypercalcemic and normocalcemic variants
   b. Accounting for differences in predominant presentations of each form *vis a vis* single or multi-glandular disease
   c. Potential role of diet and the microbiome on clinical manifestations of PHPT.
   d. Potential role of CaSR signaling pathways in abnormal parathyroid tissue
3. Genetics
   a. CaSR mutations as they relate to PHPT vs FHH: similar or different?
   b. Potential role of GNA11 or AP2S1 on pathogenesis
   c. Role of genetic testing in altering management outcomes in younger patients, those with a family history of PHPT, multi-glandular parathyroid disease, parathyroid carcinoma.
   d. Utility of genetic testing modalities (single gene tests, gene panels, exome sequencing or whole genome sequencing)
   e. Identification of heretofore unidentified, causative genes for hypercalcemic and normocalcemic forms of PHPT.
4. Serum calcium
   a. How/whether to adjust downward for a serum albumin of >4 g/dL
   b. Is there a threshold at which PTX is indicated?
5. Vitamin D
   a. What level of serum 25OHD best prevents further increases in PTH due to vitamin D insufficiency
   b. What is the best way to replete vitamin D in PHPT?
6. Renal
   a. Stone Risk in PHPT. What are the risk factors as measured by urinary analyte measurements?
   b. Can a predictive model be developed to document risk?
   c. Threshold values of renal function for recommending surgery in PHPT
   d. Factors associated with worsening renal function
   e. Relationship between reduced creatinine clearance and PTH, calcium, phosphorus, and $1,25(OH)_2D$
   f. Medical and surgical therapeutics vis a vis ameliorating or reversing renal involvement (e.g., stones, nephrocalcinosis, reduced renal function)
7. Skeletal
   a. TBS and other measures of bone quality in PHPT such as HRpQCT and their predictive value
   b. FRAX tool as a risk factor in PHPT and its predictive value
   c. Factors associated with reduced bone density and/or fractures
   d. Fracture risk before and after PTX
8. Nonclassical, putative manifestations of PHPT
   a. Neurocognitive
      i. Further development of a disease-specific tool
      ii. Functional/imaging studies of the CNS
      iii. RCTs to delineate potential involvement and its reversibility
   b. Cardiovascular and metabolic aspects of PHPT and PTX
      i. Are these attributable manifestations?
      ii. Are there consequences over time with or without PTX?
      iii. Predictive factors of risk
      iv. Reversibility of indices, if present, by surgical or pharmacological intervention
9. Surgical Aspects
   a. Better description of increased risks of complications when combined thyroid and parathyroid procedures are undertaken
   b. Risk factors for parathyromatosis and local recurrence
   c. Timing of initiating of medical therapy for osteoporosis after successful parathyroidectomy
   d. Review of complications including but not limited to recurrent laryngeal nerve injury in the era of magnified optics and increased electrothermy
   e. Improved surgical and interventional approaches to parathyroid carcinoma
   f. The role of genetics in decision-making for PTX and the kind of procedure.

best index of body vitamin D stores, more information is needed on levels as they relate to threshold values below which PTH levels rise further. How best to replete patients with vitamin D in PHPT needs further investigation. Renal aspects of PHPT need attention with regard to risk for nephrolithiasis, factors associated with worsening renal function, and how to document significant worsening of renal function. Also not well understood is how surgical intervention or pharmacological approaches to

PHPT can influence the natural history of renal function in PHPT. Our understanding of skeletal features in PHPT could be enhanced by appreciating more completely aspects of bone quality by TBS or other measures such as HRpQCT. The FRAX tool could conceivably have value in fracture risk assessment. We need more disease-specific information on factors associated with worsening bone density and/or fracture risk. How surgical or pharmacological intervention influences fracture risk is another area in need of more research. A very large scope of research should relate to the nonclassical manifestations of PHPT with particular attention to neurocognitive, cardiovascular, and metabolic aspects of the disease. Finally, advances in surgery need to be complimented by further understanding of risks, timing of medical intervention after surgery, and postsurgical improvements in classic and nonclassical aspects of PHPT. Some of these questions are best addressed by collaborative international clinical trials.

Summary and Conclusions

The recommendations and guidelines provided in this report on the evaluation and management of PHPT represent a comprehensive evidence-based review utilizing both GRADE and more inclusive methodologies. Also new since the last set of guidelines is a large number of recent publications that have provided new insights in worldwide epidemiology, genetics, outcomes, physiology, pathophysiology, clinical presentations, new imaging modalities, target and other organ systems diagnosis, measurements, pregnancy, and management. Specifically different from the conclusions of the last workshop, these deliberations have led to revisions of renal guidelines and more evidence for the other recommendations. The international guidelines are, thus, based upon a more solid evidence-based set of both systematic and narrative reviews. This evidentiary base is summarized in this report and provided in greater detail in the reports to follow. The recommendations and guidelines are provided both in the text and in the tables. Guidelines for parathyroid surgery should be helpful for those who present with symptomatic, asymptomatic or NPHPT. In those who do not meet any guideline, but for whom there are no medical contraindications, surgery is an appropriate option. Conversely, there are patients who meet surgical guideline(s) but in whom surgery will not be performed. In these situations, medical approaches are reasonable to consider when the serum calcium is >1 mg/dL above the upper limits of normal or if BMD *T*-score is ≤ -2.5. In those who are not going to undergo PTX, a set of guidelines for monitoring is provided. This review also highlights areas for which more research is needed.

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After completion but prior to submission, we became aware of a publication by Bollerslev et al on the European Expert Consensus on specific aspects of parathyroid disorders (European J Endocrinol, 12-3-2021).

The societies that have endorsed these guidelines are listed here: American Society for Bone and Mineral Research (ASBMR); International Society of Endocrinology (ISE); International Association of Endocrine Surgeons (IAES); HypoPARAthyroidism Association, Inc.; AMEND; Parathyroid UK; FIRMO Foundation; Brazilian Society of Endocrinology and Metabolism; Endocrine Chapter of the Academy of Medicine, Singapore; Italian Society of Endocrinology (SIE); Italian Society of Orthopedics, Medicine, and Rare Skeletal Diseases (ORTOMED); Australia New Zealand Bone and Mineral Society (ANZBMS); Russian Association of Endocrinologists; Armenian Osteoporosis Association; Society for Endocrinology and Metabolism of Turkey; Saudi Osteoporosis Society; Qatar Osteoporosis Association; Hungarian Society for Endocrinology and Metabolism; Iranian Endocrinology and Metabolism Research Institute; Romanian Society of Endocrinology; Chilean Society of Endocrinology and Diabetes (SOCHED); Japan Endocrine Society; Japanese Society for Bone and Mineral Research; Brazilian Society of Bone and Bone Metabolism (ABRASSO); Argentine Association of Osteology and Mineral Metabolism (AAOMM); Mexican Society of Nutrition and Endocrinology; Afghanistan Endocrine Society; Endocrinology and Diabetes Association of Mauritius; Philippine Society of Endocrinology, Diabetes, and Metabolism (PSEDM); Korean Endocrine Society; Mexican Society of Pediatric Endocrinology; American Association of Clinical Endocrinology (AACE); Argentine Association of Osteoporosis (SAO); Argentine Society of Endocrinology (SAEM); Argentine Federation of Endocrine Societies (FASEN); Costa Rica Society of Endocrinology (ASCEND); Canadian Society of Endocrinology and Metabolism (CSEM); Bangladesh Endocrine Society; Endocrine Society of India; Georgian Association of Skeletal Metabolism Diseases; German Society of Endocrinology; Hellenic Society of Endocrine Surgeons; Hong Kong Society of Endocrinology, Metabolism, and Reproduction (HKSEMR); HypoPara Support & Advocacy; Indonesian Society of Endocrinology; Japan Association of Endocrine Surgery; Jordanian Osteoporosis Society; Kuwait Osteoporosis Society; Lebanese Society of Endocrinology, Diabetes, and Lipids; Peruvian Diabetes Association; Russian Association of Endocrine Surgeons; Russian Association of Osteoporosis; South

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Conflicts of Interest

JPB: Consultant for Amgen, Radius, Ascendis, Calcilytix, Takeda, Amolyt, Rani Therapeutics, MBX, Novo-Nordisk, Ipsen, Ultragenyx; Speaker for Amgen and Radius; Research, Abiogen. AAK: Speaker for Amgen, Shire/Takeda, Ultragenyx, Alexion, Chugai; grants from Alexion, Amgen, Amolyt, Ascendis, Chugai, Radius, Takeda, Ultragenyx; consultant for Alexion, Amgen, Amolyt, Ascendis, Chugai, Radius, Takeda, Ultragenyx. SM: Speaker for Abiogen, Amgen, Bruno Farmaceutici, Diasorin, Eli Lilly, Shire, Sandoz, Takeda; Advisory Board: Abiogen, Kyowa Kirin, Pfizer, UCB. MM: Consultant for Takeda, Amolyt, and Chugai; Grants from Takeda and Chugai. JTP: Consultant for Radius Pharma. BLC: Consultant for Takeda/Shire, Amolyt Pharma, Calcilytix; grants from Takeda/Shire, Ascendis. MLB: Honoraria from Amgen, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, UCB; grants and/or speaker: Abiogen, Alexion, Amgen, Bruno Farmaceutici, Echolight, Eli Lilly, Kyowa Kirin, SPA, Theramex, UCB; consultant: Alexion, Amolyt, Bruno Farmaceutici, Calcilytix, Kyowa Kirin, UCB. All other authors have nothing to disclose.

Ethical Statement

These papers are retrospective reviews and did not require ethics committee approval.

Peer Review

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Data Availability Statement

The data that support the findings in this study are openly available in PubMed, MEDLINE, EMBASE, and the Cochrane databases.

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