REVIEW

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Classical and Nonclassical Manifestations of Primary Hyperparathyroidism

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ABSTRACT

This narrative review summarizes data on classical and nonclassical manifestations of primary hyperparathyroidism (PHPT). It is based on a rigorous literature search, inclusive of a Medline search for systematic reviews from 1940 to December 2020, coupled with a targeted search for original publications, covering four databases, from January 2013–December 2020, and relevant articles from authors' libraries. We present the most recent information, identify knowledge gaps, and suggest a research agenda. The shift in the presentation of PHPT from a predominantly symptomatic to an asymptomatic disease, with its varied manifestations, has presented several challenges. Subclinical nephrolithiasis and vertebral fractures are common in patients with asymptomatic disease. The natural history of asymptomatic PHPT with no end organ damage at diagnosis is unclear. Some observational and cross-sectional studies continue to show associations between PHPT and cardiovascular and neuropsychological abnormalities, among the different disease phenotypes. Their causal relationship is uncertain. Limited new data are available on the natural history of skeletal, renal, cardiovascular, neuropsychological, and neuromuscular manifestations and quality of life. Normocalcemic PHPT (NPHPT) is often diagnosed without the fulfillment of rigorous criteria. Randomized clinical trials have not demonstrated a consistent long-term benefit of parathyroidectomy (PTX) versus observation on nonclassical manifestations. We propose further refining the definition of asymptomatic disease, into two phenotypes: one without and one with evidence of target organ involvement, upon the standard evaluation detailed in our recommendations. Each of these phenotypes can present with or without non-classical manifestations. We propose multiple albumin-adjusted serum calcium determinations (albumin-adjusted and ionized) and exclusion of all secondary causes of high parathyroid hormone (PTH) when establishing the diagnosis of NPHPT. Refining the definition of asymptomatic disease into the phenotypes proposed will afford insights into their natural history and response to interventions. This would also pave the

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Additional Supporting Information may be found in the online version of this article.
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Recommendations

Members of this Task Force reached consensus on the following non-graded recommendations. These stem from a systematic literature search that focused on the various clinical manifestations of primary hyperparathyroidism (PHPT), followed by several virtual meetings to discuss and finalize findings presented in this review. Both recommendations (see below points 1 and 2) address classification of the various subtypes of PHPT patients initially present with. This would enable better characterization of their natural history, assessment of response to intervention, and ultimately formulation of evidence-based clinical practice guidelines.

1. We propose to refine the definition of asymptomatic PHPT based on its initial presentation into two categories:
   a. with no evidence of target organ involvement
   b. with evidence of target organ involvement

   Target organ involvement evaluation should include:

- Skeletal: inquire about fracture history, order BMD (spine, hip, forearm), and imaging of the spine to rule out asymptomatic fractures
- Renal: obtain estimated glomerular filtration rate (eGFR) or, preferably creatinine clearance, kidney imaging studies (ultrasound or spiral computed tomography [CT]), and 24-hour calcium excretion

2. When considering the diagnosis of normocalcemic PHPT, we recommend obtaining multiple serum calcium levels (albumin-adjusted and ionized) along with serum parathyroid hormone (PTH) levels, at least a week apart over a 3-month to 6-month period. Measurements should be in reliable laboratories, and this diagnosis can only be entertained after excluding all secondary causes of high PTH levels (detailed in the text).

Introduction

Primary hyperparathyroidism (PHPT) is the most common cause of hypercalcemia in an outpatient population. Automated serum calcium measurements led to a shift in disease presentation from symptomatic disease to a predominantly asymptomatic one, in most parts of the world. The Fourth International Workshop on the Management of Asymptomatic PHPT focused on relevant new clinical information and diagnostic procedures and provided an update in the guidelines for management.[1,2] This narrative review revisits the clinical manifestations of PHPT, summarizes novel information since that workshop, identifies knowledge gaps, and suggests a research agenda. It is based on a rigorous literature search, inclusive of a Medline search for systematic reviews and meta-analyses from 1940–December 2020, coupled with a targeted search for original publications, covering four databases (PubMed, Medline, Embase, and Cochrane), from January 2013–December 2020, using relevant key words and medical subject heading (MESH) terms to clinical manifestations of PHPT (Table 1, and Appendix S1), and relevant articles from authors' libraries.

Clinical manifestations of primary hyperparathyroidism

In the last 50 years, the phenotype of PHPT has dramatically changed with an evolution from a symptomatic to a largely asymptomatic disease in many countries worldwide,[3-19] as detailed in the article entitled "Epidemiology, Pathophysiology, and Genetics of Primary Hyperparathyroidism" in this issue.[20] Symptoms and organ involvement in PHPT depend on disease severity and chronicity, as will be described. Asymptomatic PHPT is the most common presentation and usually occurs in the setting of mild hypercalcemia (albumin-adjusted serum calcium less than 1 mg/dL above upper limit of normal). Given the typical upper limit of normal among laboratories varies but is most commonly 10.4 mg/dL (2.60 mmol/L), this means that most patients with asymptomatic PHPT have levels below 11.4 mg/dL (ie, 2.85 mmol/L, depending on the laboratory). The classical symptomatic manifestations of PHPT are usually, but not always, described in patients whose albumin-adjusted serum calcium is above this threshold. The terminology "moderate hypercalcemia" is often used to describe an albumin-adjusted serum calcium range that is higher, namely 11. 4 to 14 mg/dL (2.85 to 3.5 mmol/L). The terminology "severe hypercalcemia" is often used to describe an albumin-adjusted serum calcium that is >14 mg/dL (>3.5 mmol/L). Parathyroid carcinoma presents most often in the setting of severe hypercalcemia and should be considered in the differential diagnosis of patients who present with such high albumin-adjusted serum calcium levels. The classical symptoms of PHPT include overt bone disease (bone pain, fractures, cysts, brown tumors), nephrolithiasis/nephrocalcinosis, and proximal myopathy. The nonclassical manifestations of PHPT refer most to cardiovascular (CV), neurobehavioral, and neurocognitive features. These nonclassical features are derived mostly from association studies, and may occur over the spectrum of serum calcium elevations including mild cases.[2,21] The most common presentation in countries where routine calcium testing is performed is that of asymptomatic disease, with mild hypercalcemia.[2] Osteoporosis, silent nephrolithiasis, nephrocalcinosis, or asymptomatic vertebral fractures may be detected upon further investigations. The classification of these individuals as asymptomatic does not change even if these features are detected upon further investigation because they were not the reason for presenting to clinical attention.

Disease causality has been clearly established only for biochemical abnormalities, and for skeletal and renal manifestations. These are summarized in Fig. 1 and detailed further in the following sections. Hypercalcemia mediates many effects of PHPT on several organ systems.[22,23] It can cause polyuria, polydipsia (nephrogenic diabetes insipidus), dehydration, acute kidney injury, and indirectly, is a risk factor for kidney stones. It can also cause nausea, vomiting, constipation, headache, and altered mental status. Some manifestations are exclusively due to the direct effects of PTH on the skeleton and kidneys,[24] as detailed in the preceding article.

Asymptomatic PHPT, familial hypocalciuric hypercalcemia (FHH) (see Renal manifestations, and the preceding article), and

Table 1. Overview of Literature Search by Data Base, Overall, and By Subject

Topic	Medline	Cochrane	Embase	PubMed	Total
General search[a]	73				
Cardiovascular	137	7	408	7	559
Gastrointestinal	213	27	492	42	774
Mortality	273	20	547	21	861
Neuromuscular	268	22	513	62	865
Normocalcemic	120	5	157	133	415
Renal	400	23	671	87	1181
Skeletal	456	33	588	91	1168

MA = meta-analysis; SR = systematic review.

[a]The general literature search only included SRs and MAs captured through Medline, from 1940 to December 2020. Organ system specific search was conducted for original citations, using four databases, for the period 2013–2020. The number of citations are expressed in individual cells, after removing duplicates. For further details see Appendix S1.

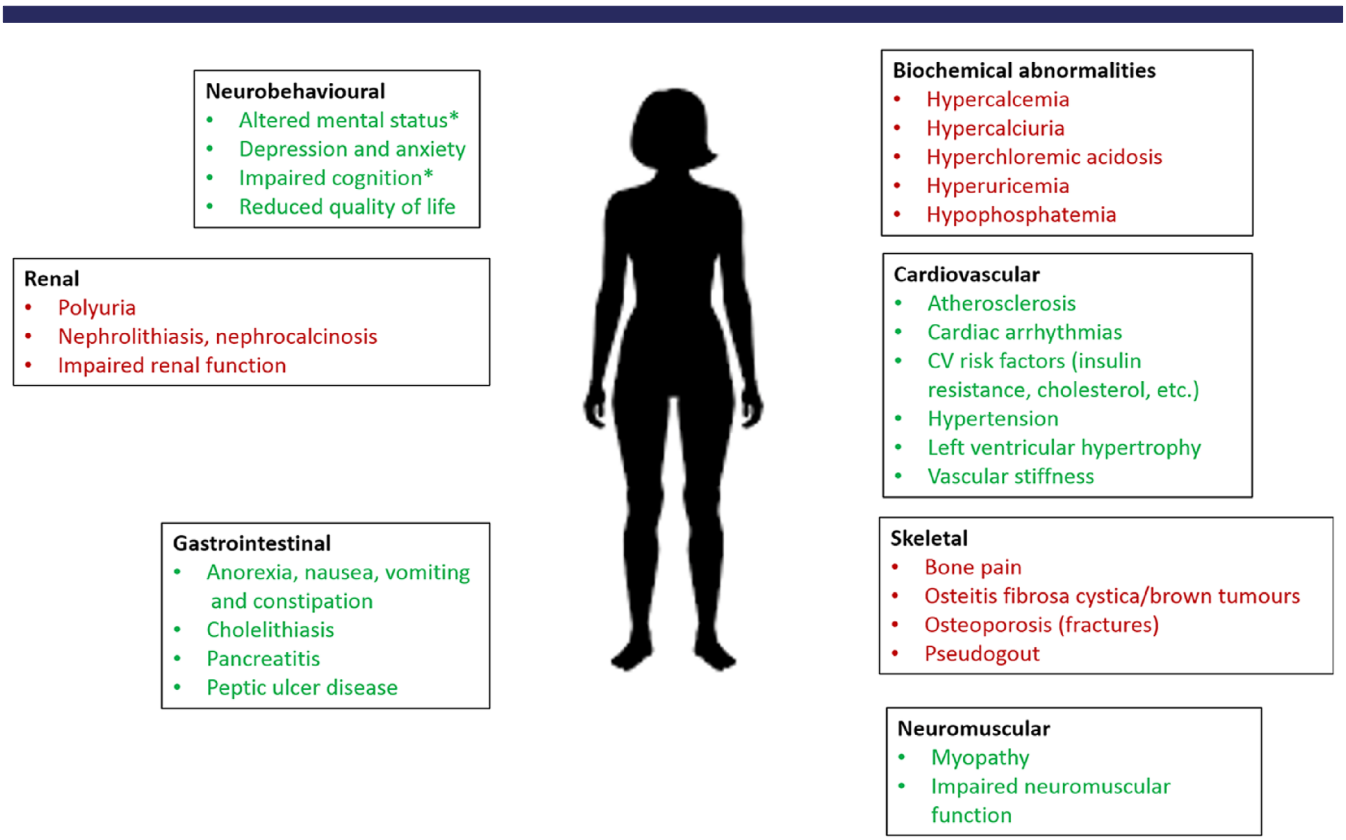

Fig. 1. Symptoms and organ involvement in patients with PHPT. Symptoms and complications depend on disease severity, as detailed in individual sections of the review. Color code: causal in red and association in green. Causality is implied from evidence by reversal with surgery or from mechanistic studies. *Moderate to severe hypercalcemia may cause changes in mental status or cognitive function that are often reversible with correction of the hypercalcemia.

normocalcemic PHPT (following section), can overlap clinically and biochemically.[25,26] This applies to serum levels of calcium, PTH, and calcium/creatinine clearance ratio [Ca/Cr] Cl ratio, provided subjects are vitamin D replete. Although the diagnosis of FHH becomes likely for values ≤0.01 and of PHPT for values ≥0.02, both conditions may occur when the ratio falls between 0.01 and 0.02[25,26] (see Renal Manifestations below for additional details). There are other distinguishing features as noted earlier (see preceding article). Elderly patients may be more likely to present with end organ damage, due to concomitant age-related decline in function.[27] Acute parathyroid crisis is a rare condition, in which patients present with symptoms from severe hypercalcemia (usually >14 mg/dL). It can be superimposed upon individuals who were known already to have mild hypercalcemia. The condition responds readily to hydration and intravenous bisphosphonates.[28]

The definition for what constitutes more or less severe PHPT, or its asymptomatic variant, may differ between studies. When referring to a particular study in the following sections, we usually adhere to the term as used in that particular study.

Normocalcemic primary hyperparathyroidism

Normocalcemic hyperparathyroidism (NPHPT) is characterized by persistently normal albumin-adjusted total and ionized serum calcium levels, on at least two consecutive measurements at least a week apart over a 3-month to 6-month period, confirmed by elevated levels of PTH. There are several indications for measuring PTH in a patient with normal kidney function and, when the serum adjusted calcium is normal: (i) in osteoporosis, as part of a laboratory workup for secondary causes for osteoporosis.[29] In this setting a high PTH is helpful in the interpretation of low 25(OH)D or hypercalciuria, or a selective reduction in distal 1/3 radius bone mineral density; (ii) in patients with kidney stones as these may be associated with normocalcemic hyperparathyroidism and a PTH level can be helpful in the interpretation of high urinary calcium excretion.[30] Other diseases and drugs that cause high levels of PTH should be excluded (serum vitamin D 25[OH]D <75 nmol/L or 30 ng/mL, chronic kidney disease [eGFR <60 mL/min/1.73 m^2], renal calcium loss [idiopathic hypercalciuria, and loop diuretics], and diseases of the gastrointestinal tract known to affect calcium absorption [inflammatory bowel disease, celiac disease, bariatric surgery], medications [denosumab, bisphosphonates, anticonvulsants, lithium, phosphorus]).[31,32]

This group of patients is challenging to identify and characterize. The prevalence of the disease in referral centers and the general population varies between 0.1% and 8.9%.[33] Studies that appear to overestimate the prevalence may not have adequately excluded all causes of secondary hyperparathyroidism. There have been attempts to better define NPHPT using nomograms[34,35] that include albumin-adjusted calcium and PTH,[34] and the use of albumin-adjusted calcium to phosphate ratios.[36] A better approach might be to obtain more robust estimate of the reference interval for albumin-adjusted serum calcium[37] and an understanding that PTH reference range increases with age, independently of vitamin D status or renal function.[38] Also, in day-to-day clinical practice, albumin-adjusted serum calcium can vary over time, with the least significant change, namely real change that is not due to variability of the assay, estimated to be around 0.25 mmol/L (or 1.0 mg/dL) in one study[39] (Fig. 2). The variability in total albumin-adjusted serum calcium can be reduced by obtaining samples at the same time and in the same position. Variability was described to be lower for ionized calcium, when performed under standardized conditions.[40]

The pathophysiology of NPHPT may be due to an increase in the calcium set point for PTH release. Disorders and factors to consider include: (i) mild PHPT (eg, due to adenoma) or FHH, (ii) genetic factors (eg, calcium-sensing receptor polymorphisms),[41] or (iii) increasing age.[42] Some studies have shown progression to hypercalcemia[43-45] or intermittent hypercalcemia, at follow-up,[44,46] whereas others have not[47,48] The natural history of the disorder is unclear in part because studies have not always used consistent definitions for NPHPT, nor has regular follow-up been consistent at defined time points. Clinical features of NPHPT can be similar to those described in PHPT (skeletal and renal complications). Studies from referral centers have shown that the frequency of skeletal complications, osteoporosis, and fractures, is similar to PHPT in some,[49-51] but not all studies.[45,52] Importantly, only one study[52] fulfilled the definition of NHPT. The data on kidney stones and nephrolithiasis are also inconclusive. One small cross-sectional study showed that the prevalence of kidney stones was higher in the NPHPT group than in controls, but this was based on medical record review.[53] When referencing studies using ultrasound, the prevalence of nephrolithiasis in another cross-sectional study was reported to be as high as 20%.[30] There are studies on glucose metabolism, hypertension, and quality of life in NPHPT but most of them are quite old, usually the sample size is small and without suitable controls, and the results are inconsistent.

Selection and ascertainment bias, and inability to fulfill the rigorous criteria for the diagnosis of NPHPT, are major limitations to the findings described herein. Clearly, more studies that investigate complications of NPHPT are needed.

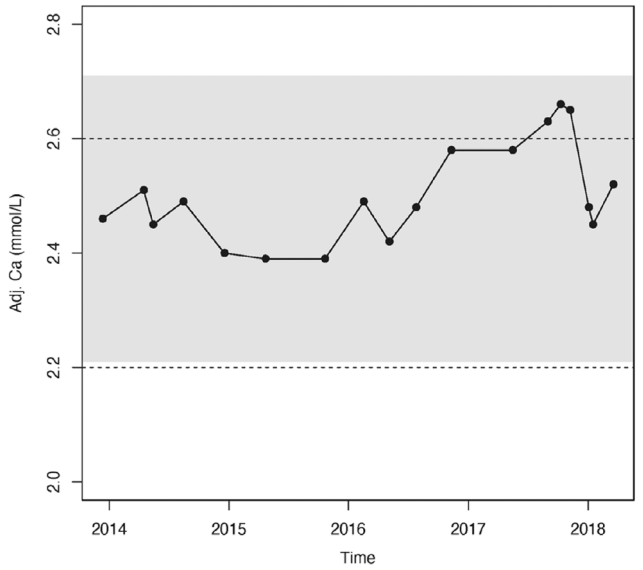

Fig. 2. Concept of least significant change in a patient with normocalcemic hyperparathyroidism having intermittent hypercalcemia. The dashed lines represent the reference interval for adjusted serum calcium. The least significant change is represented by the gray area and is symmetrical around the first data point. It is defined as 2.77 times the estimate of standard deviation based on multiple measurements for adjusted serum calcium made in 11 patients with normocalcemic hyperparathyroidism. It is estimated at 0.25 mmol/L. Figure adapted from Schini and colleagues.[37]

Skeletal manifestations

Involvement of the skeleton is a hallmark of PHPT, even in its mild forms. Bone remodeling is increased, as demonstrated by elevated bone turnover markers,[54] and by increased eroded, osteoid, and mineralizing surfaces by bone histomorphometry. At the level of cortical bone, increased porosity and thinning due to "trabecularization" of endocortical surface are present.[55,56] Conversely, cancellous bone volume and trabecular connectivity are preserved.[56] Sclerostin is reduced, and DKK1 is increased, compared to healthy controls.[57] In severe forms of PHPT, bone pain and classical radiological features of osteitis fibrosa cystica (OFC), including brown tumors, can still be found[58] (Fig. 3*A*,*B*). Chondrocalcinosis, pseudogout, synovitis, and sacroiliitis have also been described.[59,60]

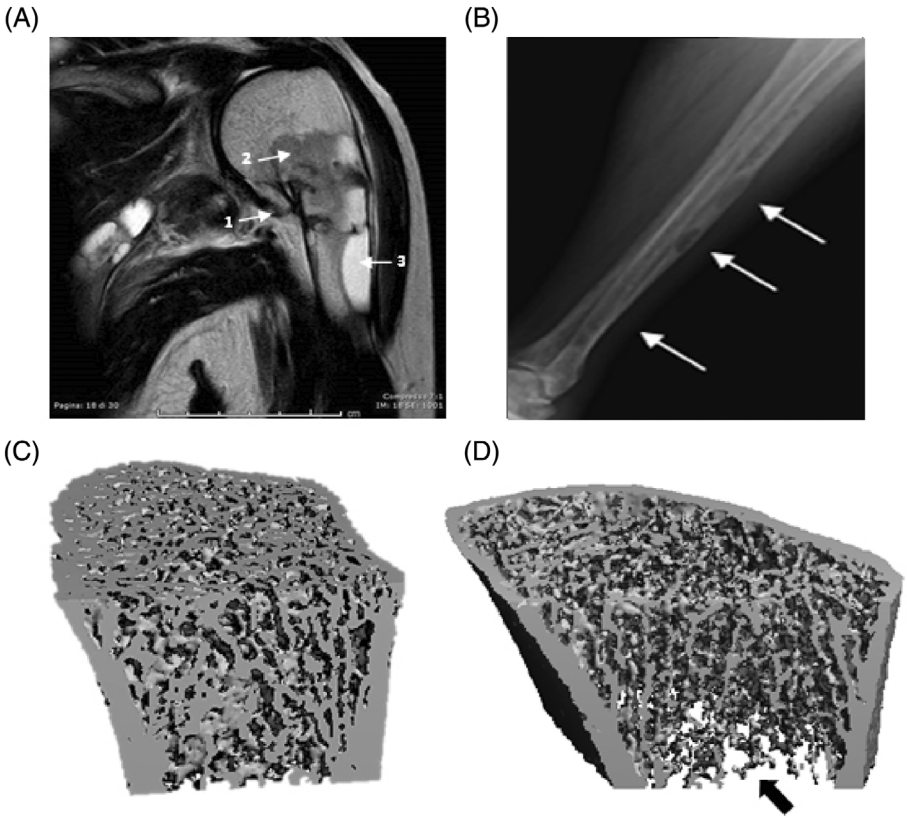

Fig. 3. Skeletal imaging in patients with PHPT. (*A*) Nuclear magnetic imaging of the left humerus, showing a medial fracture (arrow 1) and a brown tumor with solid (arrow 2) and liquid (T2-weighted image, arrow 3) components. (*B*) Radiograph of the left leg, showing cortical thinning and multiple lytic lesions (arrows) in tibia and fibula. (*C*,*D*) Representative HRpQCT images of the 1/3 distal radius of PHPT (*D*) and control (*C*) subjects. In PHPT (*D*), total vBMD is reduced (340.3 versus 771.4 mg HA/cm^3), cortical thickness is reduced (0.56 versus 0.7 mm), with a decrease in trabecular density (101 versus 179.2 mg HA/cm^3), number (1.64 versus 1.72 1/mm), and increase in trabecular separation (0.557 versus 0.494 mm) (arrow). Figure modified from Stein and colleagues.[83] HA = hydroxyapatite.

Bone densitometry

Bone mineral density (BMD) by dual-energy X-ray absorptiometry (DXA) is reduced, even in mild forms,[2,61,62] mostly at the cortical site (1/3 distal radius),[2,62-64] and least at the trabecular site (lumbar spine [LS]).[63] An opposite pattern may be observed, particularly in postmenopausal women.[2,65] Occasionally a *T*-score ≤ -2.5 is observed at the radius only. Thus, three-site DXA (LS, hip, and 1/3 radius) is always recommended.[2,66] The prevalence of osteoporosis currently ranges from ~50% to 65%,[61,62] particularly among postmenopausal women, older patients, and those with lower body mass index (BMI).[61,65,67,68] In mild PHPT, the frequency of osteoporosis may be comparable between patients with or without complications, such as nephrolithiasis and fractures.[62,64]

In a cohort of 36 patients with mild PHPT followed without parathyroidectomy (PTX), BMD remained stable at the LS for up 15 years. Conversely, at the femoral neck and, to a greater extent at the distal radius, BMD started to decline even before the 10-year time point, with a further deterioration in the six patients followed for up to 15 years.[63] Shorter trials have confirmed stability in BMD at the LS, decline at the hip, and inconsistent findings at the 1/3 distal radius.[69-73] Long-term studies with large cohorts are needed to better understand the natural course of bone involvement in patients with mild PHPT.

Trabecular bone score, QCT, and microindentation

In contrast to standard DXA and histomorphometric studies, trabecular bone score (TBS) and high-resolution peripheral quantitative computed tomography (HRpQCT) analyses show that there is deterioration in both cortical and trabecular bone in mild PHPT, providing additional insight into pathophysiology, and supporting fracture data, described in the Fractures section of this review. Several studies evaluated TBS in PHPT.[74-82] TBS was significantly lower in patients than in controls,[75,76,82] or it was degraded despite a well-preserved LS BMD by DXA.[74,76,78,81]

By HRpQCT, patients with mild PHPT have decreased volumetric BMDs (vBMD; total, cortical, and trabecular), cortical thickness, and trabecular number, and more widely spaced and heterogeneously distributed trabeculae, compared to controls[83-86] (Fig. 3*C*,*D*). These findings help to confirm that in PHPT, the trabecular skeleton is also affected. Increased cortical porosity,[87] and reduced bone stiffness and failure load by HRpQCT were also observed.[83,84] Vitamin D status seems to have no effect on vBMD, microarchitecture, or bone stiffness by HRpQCT,[88] or on LS (L_1–L_2) trabecular or integral vBMD and bone strength by central quantitative computed tomography (cQCT).[81] Peripheral QCT (pQCT) of the distal radius or tibia shows reduced trabecular and cortical vBMD, decreased cortical thickness, and increased endosteal circumference in patients with PHPT compared to controls.[2]

Microindentation studies reveal decreased bone material strength index, mainly in patients with fragility fractures,[89,90] suggesting a negative effect of high PTH on bone quality.

Fractures

Fracture risk is increased in patients with overt PHPT. In 1975, Dauphine and colleagues[91] first suggested that vertebral fracture (VFx) could be a manifestation of mild-to-moderate PHPT. In cohorts including patients with PHPT of different severity, increased fracture risk has been confirmed at the forearm and vertebrae, with controversial data at the hip.[92-94] A recent systematic review and meta-analysis of studies with a healthy control group confirm these data, with a twofold increase in risk of all fractures (odds ratio [OR] 2.01; 95% confidence interval [CI], 1.61–2.50). Analysis of fracture risk at specific skeletal sites showed increased risk at the forearm and spine but not at the hip. The risk of VFx was increased even when the analysis was restricted to patients with mild hypercalcemia (<11.6 mg/dL) or postmenopausal women.[95] Several cross-sectional studies, with retrospective ($n = 7$) and prospective ($n = 4$) data collection, evaluated the prevalence of morphometric VFx in patients with PHPT (Table 2).[62,72,96-105] The cohorts enrolled between 98 and 588 patients, mostly postmenopausal women, age 59–73 years. Disease severity was either heterogeneously defined or not reported. Mean serum calcium levels were below 11.5 mg/dL in most studies and mean PTH levels were 1.5-fold to twofold the upper normal limit of the assay. All except for one used spine X-ray to detect fractures, used the Genant classification,[104] but included variable vertebral levels, and were mostly evaluated by a single unblinded radiologist. Mild vertebral fractures (height loss <25%) can lead to misclassification due to positioning or to parallax effect and were only excluded in one study. The VFx rates ranged between 1.7% and 44%, with no clear relationship with disease severity. Interestingly, in a study of 150 postmenopausal women with PHPT, VFx rate was significantly increased in patients with clinically significant disease (either symptomatic or asymptomatic with surgical criteria) compared to age-matched controls.[102] Interestingly, fracture rate was not increased in the subgroup with asymptomatic disease and no criteria for surgery.[102] In another study of 55 patients with mild PHPT (49 women), 9.1% presented with a new morphometric VFx during a 5-year follow up.[73] Morphometric VFx may occur in the absence of a known diagnosis of osteoporosis.[62,102] Low TBS was associated with prevalent VFx in unadjusted models,[74] and in models controlling for age, BMI, and LS BMD.[76] TBS was also lower in patients with major osteoporotic fractures than in nonfractured subjects,[77,78] even after adjusting for age, BMI, gender, and years since menopause.[78] Conversely, in a study of 153 patients, of whom 7.6% had prevalent VFx and 13.2% nonvertebral fractures, TBS was not able to predict fractures in logistic regression analysis including age, years since menopause, LS BMD, femoral neck BMD, and TBS as covariates.[80]

Renal manifestations

The kidneys play a central role in the biochemical and clinical expression of PHPT.[2,106] Hypercalcemia and hypophosphatemia are due to the actions of PTH on the kidney tubule. PTH acting via the parathyroid receptor 1 (PTHR1) and calcium acting via the calcium-sensing receptor (CaSR) have major regulatory roles in the kidney resulting in increased calcium reabsorption.[107,108] PTH also indirectly determines dietary calcium and phosphate delivery into the circulation by regulating $1,25(OH)_2$ vitamin D via actions on renal CYP27B1 and CYP24A1 activity.[24,106]

The biochemical diagnosis of PHPT is usually definitive. However, the disease causing the most diagnostic challenge in its differential diagnosis is FHH, a genetically heterogeneous disease due to inactivating mutations of CaSR (see article entitled "Epidemiology, Pathophysiology and Genetics of Primary Hyperparathyroidism," in this issue).[20] It is characterized by high penetrance, manifests as benign hypercalcemia in early childhood, and is usually evident by the age of 30 years. FHH has several overlapping biochemical abnormalities with mild PHPT. Both conditions shift the Ca-PTH setpoint to the right. It has been suggested that FHH can be considered as an "atypical" form of PHPT.[109] However, FHH decreases renal calcium excretion more than PHPT would for the same filtered load of calcium resulting in relative hypocalciuria. Nevertheless, kidney stones have been rarely reported in FHH.[110] Importantly, there is considerable overlap in renal variables.[111,112] The diagnosis of FHH is most often made when the Ca/Cr Cl ratio is <0.01, and that of PHPT is more likely if it is >0.02. However, up to 10% of patients with FHH can have Ca/Cr Cl ratios >0.02 and up to 20% of patients with PHPT can have ratios <0.01. Around 40% of patients with either disease have values between 0.01 and 0.02.[27,28,110-112] PTX is contraindicated in FHH, because of the absence of end-organ damage and the fact that it does not cure hypercalcemia.

The most common clinical expression of PHPT is calcium nephrolithiasis, consisting of calcium oxalate or calcium phosphate calculi, with a prevalence ranging from 5% to 55%.[113-119] Such a wide range may be explained by differences in the technologies used for kidney imaging, as well as severity of PHPT. Although hypercalciuria is widely used as the single risk predictor of kidney stones, by itself it is a poor predictor of nephrolithiasis, independently of the cutoff used to define hypercalciuria.[120] Other risk factors include hypomagnesuria, urinary Ca/Mg ratio and genetic factors (CaSR polymorphisms).[121-123] The last consensus workshop on PHPT emphasized the importance of considering a probability risk of nephrolithiasis that combines several urinary parameters,[1] as well as prerenal and genetic factors[122] when investigating the pathogenesis of nephrolithiasis.

In asymptomatic PHPT, the need to exclude silent nephrolithiasis/nephrocalcinosis was emphasized in the last consensus. Recent studies confirm that a significant number of PHPT and NHPTH (11%–35%) patients, on detailed imaging, have silent kidney stones in situ and are, therefore, candidates for PTX.[119,120,123-126] Nephrocalcinosis is a radiological diagnosis of diverse etiologies.[127] It is becoming increasingly clear that sub-radiographic calcium phosphate deposits in the kidneys are not uncommon, and that nephrolithiasis and nephrocalcinosis probably represent a spectrum of the same disease process.[128,129]

In a recent case-control study of 792 patients with mild PHPT, identified from Aarhus laboratory database between 2005 and 2015, 617 patients had a CT scan, 12% had nephrolithiasis, 12% had nephrocalcinosis, and 1% had both.[117] Chronic renal damage is also not uncommon in PHPT,[130] and needs to be considered and assessed before and after PTX.[131,132] Clinical studies reported a reduction in GFR (<60 mL/min) in 12% to 20.6% of PHPT patients[132,133] Furthermore, chronic renal impairment alters mineral metabolism, because it increases serum PTH and phosphate, and lowers calcium and $1,25(OH)_2$ vitamin

Table 2. Rate of Prevalent Vertebral Fractures in Cohorts of Patients with PHPT

Source	Patients *n* Age (years) Sex (%) Race (%)	Controls *n* Age (years) Sex (%)	Disease Severity[a]	Calcium mg/dL PTH pg/mL[b] (range)	Fracture evaluation[c]	Vertebral fracture *n* (%)	Notes
Dauphine and colleagues[91]	224 Mean 62 years Range 50–85 years 67% F	479 59 ± 7 years 55% F	NA	11.2 (10.3–13.4) 139 µLEq/mL (53–520)	Spine X-ray	PHPT: 14 (6.3%)*** Controls: 1 (0.2%)	
Kochersberger and colleagues[100]	191 median 61 years 79% F 17% white	192 median 61 years Controls (±5 years) 74% F 70% white	Surgical Registry, excluding those referred for bone disease	NA NA	Chest X-ray	PHPT: 38 (20%)* asymptomatic 17% symptomatic 23% ($p = .69$) Controls: 25 (13%)	Associated with age ($p = .004$), but not with sex and race, increased alkaline, and hypercalcemia
Wilson and colleagues[103]	174 mean 62 years 8.5% F 54.6% white 45.4 black	200 historical controls	Mild, asymptomatic	<12.0 Mean 11.1 NA	Spine X-ray T_5–L_3 2 blinded observers	PHPT: 3 (1.7%) Controls: none	10 with wrist fractures
Kaji and colleagues[99]	116 mean 60 years F 86% postMP	716 mean 61 years 100% F bone health check 87% postMP	NA	11.8 (9.3–16.1) 207 ± 238 (38–1400)	X-ray T_4–L_4	PHPT: 14 (12.1%)** Controls: 158 (22%)	Patients sustained VFx at lower BMD (particularly 1/3 radius) compared to controls
Eller-Vainicher and colleagues[98]	266 59 years 86% F 71% PostMP	NA	NA	11.1 ± 0.0 (10.0–17.2) 169 ± 131	X-ray T_4–L_4 2 blinded observers	100 (37.7%) PostMP (40.2%), preMP (20%), males (43.2%)	
Ejlsmark Svensson and colleagues[97]	588 Mean 64 years 77% F	NA	NA 29% osteoporosis	10.8 (10.6–11.2) 10.9 pmol/L (8.5–14.4)	X-ray T_8–L_3 2 observers	122 (20.7%); No difference between M and F 35 (29%) only mild; 52 (42%) at least one moderate;	VFx rate unrelated to hypercalcemia or PTH levels Predictor of VFx in multivariate analysis: age [OR = 1.03 (1.01–

(Continues)

Table 2. Continued

Source	Patients *n* Age (years) Sex (%) Race (%)	Controls *n* Age (years) Sex (%)	Disease Severity[a]	Calcium mg/dL PTH pg/mL[b] (range)	Fracture evaluation[c]	Vertebral fracture *n* (%)	Notes
						35 (29%) at least one severe	1.06), $p < 0.01$] and total hip BMD [OR = 0.85 (0.01–0.56), $p = 0.01$]
Liu and colleagues[101]d	117 73 years 94% PM 28% Hispanic 62% Non-Hispanic	NA	NA	10.5 (9.0–11.7) Median 74 (19–265)	VFA (Grade 1 excluded), confirmed by X-ray, CT or MRI	15 (13%) all in F VFA done as indicated by ISCD	VFx not identified by VFA were mild
Prospective Cohorts of Patients With PHPT							
De Geronimo and colleagues[96]	98 mean 61 years postMP	89 mean 61 years postMP matched for age, YSM, and BMI	25 mild with no surgical criteria 73 Non-mild	Mild: 10.7 ± 0.4 Mild 83 ± 37 Non-mild: 11.1 ± 1.0 Non-mild 168 ± 211	X-ray T_8–L_3 versus adjacent vertebra	PHPT: Mild 11 (44%)*** Non-mild 35 (48%)*** Controls: 8 (9%)	Non-mild: 21 OP, 22 nephrolithiasis, 2 pancreatitis 13 patients versus 17 controls with history of nonvertebral Fx (NS)
Vignali and colleagues[102]	150, 61 years All postMP	300 61 years PostMP matched 2:1 for age (±2 years) and YSA (±5 years)	109 asymptomatic 41 (27%) symptomatic	10.5 ± 0.7 166 ± 118	VFA blinded	PHPT: 37/150 (25%)***; OR 95% CI: 7.9 (4.0–15.6) Excluding cases with mild VF: 20/150 (13.3%)***; OR 95% CI: 5.6 (2.4–13.1) Symptomatic 14/41 (34%)***;	13 (8.7%) PHPT patients and 15 (5%) controls had a history of low-trauma clinical fractures No difference in VFx rate between symptomatic (34%) versus asymptomatic (21%)

(Continues)

Table 2. Continued

Source	Patients *n* Age (years) Sex (%) Race (%)	Controls *n* Age (years) Sex (%)	Disease Severity[a]	Calcium mg/dL PTH pg/mL[b] (range)	Fracture evaluation[c]	Vertebral fracture *n* (%)	Notes
						Asymptomatic 23/109 (21%)***; Asymptomatic with surgical criteria 18/64 (28%)*** without surgical criteria 5/45 (11%) (NS) Control: 12/300 (4%) Excluding cases with mild VF 8/300 (3%)	In multivariate analyses age ($p = 0.015$) and lumbar spine BMD ($p = 0.01$) were associated with VFx
Cipriani and colleagues[62]	140 63 years 91% F 86% postMP	NA	76 asymptomatic 64 symptomatic	11.2 ± 0.9 110 ± 95	X-ray T_8–L_3	49 (35%) Asymptomatic 27 (35%) Symptomatic 22 (34%)	39% of patients with VFx had osteoporosis at lumbar spine
Lundstam and colleagues[72]	106 62 years 87% F	NA	Mild, asymptomatic	10.6 ± 0.5 10.5 pmol/L	X-ray T4-L5	9 (8.5%) at baseline (all in F)	Follow up of 55 patients showed incidence of 9.1% new VFx over 5 years

The text in bold highlights data in patients with mild/asymptomatic PHPT.

μLEq = microliter equivalent; BMD = bone mineral density; CT = computed tomography, F = female; Fx = fracture; M = male; MRI = magnetic resonance imaging; NA = not available; NS = not significant; postMP = postmenopausal; OP = _____; TBS = trabecular bone score by dual x-ray densitometry; VFA = vertebral fracture assessment by dual x-ray densitometry; VFx = vertebral fractures; YSM = year since menopause.

[a]Definition of disease severity: Wilson and colleagues[103]: no symptoms of hyperparathyroidism; no current kidney stones, serum Ca < 12 mg/mL, no osteitis fibrosa cystica, forearm BMD *Z* score > −2; De Geronimo and colleagues[96]: mild: without; non-mild: with surgical criteria according to the 2002 Guidelines; Vignali and colleagues[102]: absence of symptoms of hypercalcemia, nephrolithiasis, osteitis fibrosa cystica, and low trauma fractures; Cipriani and colleagues[62]: absence of symptoms of hypercalcemia, history of fragility fractures (vertebra, hip, distal radius, humerus, and pelvis), history of nephrolithiasis or nephrocalcinosis (one episode of renal colic and/or positive kidney imaging); Lundstam and colleagues[73]: untreated, asymptomatic, albumin-adjusted serum calcium <11.4 mg/dL, age 50–80 years, and no kidney stones, drugs interfering with calcium metabolism, psychiatric disorders and creatinine >1.47 mg/dL.

[b]Unless otherwise specified.

[c]Fracture evaluation: according to Genant and colleagues.[104]

[d]Recruited among patients screened for VFA according to the 2013 NOF screening criteria by Chou and colleagues.[105]

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$ for PHPT patients versus controls.

D. Subclinical renal damage may be detected in patients with eGFR <60 mL/min using specific and sensitive biomarkers, namely serum levels of cystatin-C and urinary kidney injury molecule-1 (KIM-1).[134,135]

Neuromuscular and neurobehavioral manifestations

Neuromuscular complications

Neuromuscular manifestations in PHPT comprise a spectrum of symptoms and conditions, namely muscle weakness, fatigue, cramps, paresthesias, and proximal muscle atrophy, particularly in the lower limbs; some of them may be seen in non-PTH mediated hypercalcemic states. Indeed, there is not sufficient data to demonstrate a direct association between such conditions and PHPT. Nevertheless, their prevalence in PHPT patients has been shown to range between 4.8% and 63%.[19,59,136-141] Differences in the population studied, not only from genetic and geographical points of view, but also in severity of PHPT and in clinical settings (eg, endocrinology versus rheumatology) may explain such a wide range.[59,142,143]

Impairment of neuromuscular function may be seen in asymptomatic PHPT. In a Danish cohort, a reduction in knee extension and flexion muscle strength, as well as postural stability was observed in 58 asymptomatic patients with PHPT compared to matched controls.[144] Perturbation of electroneurographic parameters consistent with subclinical peripheral sensory-motor polyneuropathy in otherwise asymptomatic PHPT patients has been demonstrated.[145] These data suggest that abnormalities in nerve and neuromuscular conduction may be caused by chronic hypercalcemia, with negative effects on muscle function and on synaptic plasticity.[145,146] More recently, a similar prevalence of neuromuscular symptoms, assessed by a self-administered questionnaire, was noted in hypercalcemic (15%–33%) versus normocalcemic (25%–47%) PHPT.[147] Abnormal muscle strength and performance of the upper and lower limbs in both hypercalcemic and normocalcemic PHPT was also reported.[148]

Notwithstanding possible limitations made by ascertainment and selection biases and lack of adequate control groups, these observations suggest that high serum PTH, by acting on its specific receptor, may exert its effects on neuronal membrane or skeletal muscle to cause muscle loss.[148,149] Recent results derived from PHPT patients and mice model provide further evidence that high PTH level may be responsible for increased white adipose browning and lower lean mass and body weight.[150] Finally, hypophosphatemia and hypovitaminosis D need to be considered, at least as contributing factors, in the pathophysiology of neuromuscular manifestations of PHPT.[143]

Neuropsychiatric symptoms, cognition, and quality of life

Neuropsychiatric and cognitive symptoms in PHPT include depression, anxiety, irritability, suicidal ideation, altered mental status, sensory obtundation, psychosis, delirium, hallucinations, personality changes, sleep disturbance, loss of initiative and concentration, impaired cognition, and dementia.[146] Most of them are described only in severe PHPT; their prevalence ranges from 3% to 50%.[7,19,136-138,151-153] In patients not complaining of these features, specific questionnaires have yielded a high prevalence (18%–61%) of neuropsychiatric issues and cognitive impairment in some studies.[140,152,153-160] Depression, anxiety, suicidal ideation, impaired memory, and disturbances in attention and executive function were most frequently reported. Interestingly, Liu and colleagues[161] recently reported no difference in depression and cognitive indices between mild hypercalcemic and normocalcemic PHPT patients and patients with goiter. The heterogeneity of these results may be ascribed to varied range of PHPT severity and phenotypes (symptomatic; asymptomatic with or without indication for surgery; normocalcemic) between studies, and possibly to selection and ascertainment biases.

Quality of life (QoL) was assessed by several tools in recent studies. The country-specific Short Form Health Surveys (SF-36), the disease specific questionnaire for PHPT (PHPQoL-16), and the 15-D instrument were used.[160,162-164] Collectively, the data showed a reduction in several domains of the QoL in patients with different PHPT phenotypes. These domains include functional and physical capacity, mental function, depression, vitality, social and emotional function, general health state, discomfort, and pain.[162,164] Mild PHPT was associated with worst QoL, particularly in patients with longstanding disease.[162] Similar results were described in 114 patients with both hypercalcemic and normocalcemic PHPT.[147] Likewise, reduced QoL with impairment in mental health was observed in hypercalcemic participants and reduced general health perception in normocalcemic PHPT.[148]

Randomized clinical trials (RCTs) comparing PTX versus observation in mild PHPT showed no clear evidence for causal relationship between PHPT and neuropsychiatric symptoms.[69-71,165] Reversibility of such complications was not uniformly observed after surgery in a period of 1–10 years. Interestingly, none of the RCTs reported a clear worsening of neuropsychiatric symptoms in the observation group over time.[69-71,165] Pretorius and colleagues[165] recently showed an improvement in some psychiatric symptoms in the nonsurgical group over 10 years.

With regard to QoL, improvement was reported in all the RCTs in the surgery group, but was limited in three of them. A positive effect of surgery on different domains of the QoL was not uniformly observed in the RCTs.[69-71,165]

CV manifestations

Cardiac risk factors and hypertension

Data regarding associations between PHPT and the metabolic syndrome are conflicting. The prevalence of type 2 diabetes has been reported to be increased in patients with PHPT in a few, but not all, studies. Most RCTs and observational studies have, however, tended to investigate markers of insulin resistance rather than incidence or prevalence of diabetes.[166-168] A meta-analysis indicated greater insulin resistance, but not BMI, in PHPT patients versus controls.[169] Only hypercalcemic, not normocalcemic, PHPT patients had higher fasting glucose. Two RCTs addressed whether cardiac risk factors (CRFs) improve post-PTX. The Scandinavian Investigation of PHPT (SIPH) trial ($n = 119$) found no benefit of PTX on glucose/insulin, fat mass, or cholesterol 5-years postrandomization in asymptomatic PHPT.[170] In contrast, a Danish RCT ($n = 79$) showed PTX reduced cholesterol 3 months post-PTX in mild PHPT, but did not investigate insulin resistance.[171] Associations between PHPT and hypertension continue to be reported. An International Classification of Diseases, Ninth Revision (ICD9) diagnosis of PHPT in 37,922 inpatients increased risk for hypertension by 30%, but the mechanism remains elusive.[172] Blood pressure (BP) increased across PTH tertiles in another study.[173] Aldosterone-renin-ratio was related to BP and dependent on PTH level in a study of 136 patients with mild PHPT.[174]

Table 3. Summary of Studies on Cardiovascular Manifestations of PHPT 2013–2020

CV manifestation	? Mechanism	Association observational studies	Improvement observational studies	Improvement RCTs	Details
Hypertension	PTH or renin-aldosterone ratio	✓[172]	✓[175]	X[196]	Conflicting data; SIPH RCT trial negative
Impaired glucose insulin resistance		✓[169]		X[170]	Conflicting data; SIPH RCT trial negative
Fat mass/BMI		X[169]		X[170]	SIPH RCT trial negative
Cholesterol				X,[170] ✓[171]	Conflicting; SIPH RCT trial negative at 5 years; Danish RCT positive at 3 months post-PTX
Coronary calcification Aortic calcification Femoral calcification	? Calcium effect	✓,[183] X,[184] X[187] ✓[185] X[173]	X[187]		Limited, conflicting data
Vascular stiffness Flow mediated dilation	PTH associated with stiffness? Calcium	✓[178,185] X,[179] ✓[180]	X,[179] ✓[180]	X[171]	Conflicting data; Danish RCT negative but subgroup with highest calcium improved
Left ventricular mass	PTH → cardiac myocyte hypertrophy?	✓[190]	✓[192]	X[192,196]	Meta-analysis shows LVM improvement, but tends to be in observational studies with higher PTH
Short QT, VPBs	Calcium shortens QT	✓[195]		✓[195]	Small study size
CV events	? PTH	X[188]	✓[189]	X[73]	Limited data; SIPH trial no reduction CV events, limited events

Check stands for positive association or reversibility post-parathyroidectomy, X stands for lack of positive findings.

BMI = body mass index; CV = cardiovascular; LVM = left ventricular mass; PTH = parathyroid hormone; SIPH trial = Scandinavian Investigation of PHPT, ClinicalTrials.gov: NCT00522028; VPBs = ventricular premature beats.

Observational studies often indicate BP improves post-PTX.[175] A retrospective analysis ($n = 2380$) showed self-selection to PTX reduced BP and anti-hypertensive use versus observation.[176] RCTs in mild PHPT, however, show no benefit of surgery versus observation on control of blood pressure.[171,177]

Vascular changes and CV events

Aortic pulse wave velocity (PWV), augmentation index and retinal vessel narrowing were worse in PHPT ($n = 30$) versus controls, but only retinal findings were independent of hypertension and correlated with PTH.[178] Other studies showed opposing results regarding normalcy of flow-mediated dilatation and improvement post-PTX.[179-181] The Danish RCT found no benefit of PTX on vascular function overall, but in the subgroup with the highest calcium, PWV improved post-PTX.[171] A newly published meta-analysis that included nine nonrandomized studies and one RCT found that patients with mild PHPT ($n = 433$) had significantly higher aortic PWV compared with controls; PTX significantly reduced PWV.[182]

Data on atherosclerosis are conflicting. Higher coronary calcification scores (CAC) were present in a cohort with mild or classical PHPT ($n = 130$) versus controls, but presence of CAC was related to CRFs, not PTH or serum calcium.[183] No association was found between NPHPT ($n = 29$) and CAC.[184] Moderately severe PHPT ($n = 140$) was associated with aortic calcification and related to PHPT duration and PTH level.[185] In contrast, a case-control study ($n = 204$) indicated no association of symptomatic and asymptomatic PHPT with carotid or femoral plaque, or intima-media thickness (IMT).[173] Changes in atherosclerosis post-PTX are also inconsistent.[186,187] Prospective studies have reported inconsistent improvement in CV events post-PTX. A 21-year population-based study found no differences in myocardial infarction, stroke, or death in men with PHPT or NPHPT versus controls.[188] In contrast, a retrospective study indicated atherosclerotic CV events were reduced in those self-selecting to PTX.[189] The SIPH RCT showed no difference in CV events 5-years postrandomization to PTX or observation.[73]

Cardiac structure, function, and arrhythmias

There are conflicting data regarding effects of PHPT on cardiac function.[190,191] Left ventricular mass (LVM) was higher in PHPT versus controls in one study, similar to some prior studies.[190] A meta-analysis reported LVM regression post-PTX ($n = 457$)[192] in short, observational studies, not RCTs. Higher preoperative PTH levels were associated with a greater regression.[192] A second meta-analysis (with fewer studies) found PTX did not improve LVM or cardiac function.[193] Few studies assessed arrhythmia. In symptomatic and asymptomatic PHPT, PTX reduced ventricular premature beats (VPBs) during exercise testing and restored normal exercise-induced QT-interval adaptations.[194] An RCT ($n = 26$) showed PHPT was associated with a higher prevalence of premature beats and shorter QT-interval. PTX improved these indices versus observation.[195]

Table 4. Effects of Parathyroidectomy on Metabolic and Cardiovascular Endpoints in Randomized Controlled Trials 2013–2020

Study	Study duration	Serum calcium; symptomatic/asymptomatic	*n*	Cholesterol	Blood pressure	Glucose/IR	Fat mass	PWV	CV events	Arrhythmia/conduction/VPBs
Eijsmark-Svensson and colleagues[171] (2019)	3 months	Ionized ca 1.41 mmol/L; symptomatic and asymptomatic	79	Benefit	No benefit	NR	NR	No Benefit	NR	NR
SIPH Trial: Godang and colleagues[170] (2018) Lundstam and colleagues[73] (2015)	5 years	Albumin adjusted calcium 2.63 mmol/L or 10.5 mg/dL; asymptomatic	119	No benefit	No benefit	No benefit	No benefit	NR	No benefit	NR
Pepe and colleagues[195] (2018)	6 months	Ionized calcium 1.4 mmol/L or 10.9 mg/dL; symptomatic and asymptomatic	26 patients/26 control	NR	NR	NR	NR	NR	NR	Benefit

CV = cardiovascular; IR = insulin resistance; NR = not reported; PWC = pulse wave velocity; SIPH = Scandinavian Investigation of PHPT; VPBs = ventricular premature beats.

Despite the abundance of observational studies establishing an increased prevalence of abnormalities in surrogate markers of CV outcomes in patients with PHPT (Table 3),[73,169-173,175,178-180,183-185,187-190,192,195,196] little evidence exists on causality as could be inferred from reversibility post-PTX (Table 4).[74,170,171,195]

Gastrointestinal manifestations

Gastrointestinal (GI) manifestations, including abdominal pain, constipation, nausea, vomiting, peptic ulcer disease, cholelithiasis, and pancreatitis have been described in patients with symptomatic PHPT.[137,151,197-200] In a systematic review of the clinical presentation of PHPT in developing countries, where 80% of patients were described as symptomatic, 10% of subjects presented GI manifestations.[78] This frequency can be much higher in severe forms of PHPT.[137,199] Several studies have suggested a greater risk of acute and/or chronic pancreatitis in symptomatic PHPT, with higher serum calcium levels and male sex being identified as risk factors for this complication.[151,199,201-203] In contrast, in a community-based cohort of 684 patients with mild PHPT (mean age of 55.1 years; 74% female; mean serum calcium of 10.8 mg/dL) from the state of Minnesota, USA, subjects with PHPT were not more likely to develop acute pancreatitis than age-, sex- and year of registration-matched controls.[204] Some studies have reported a greater prevalence of cholelithiasis in severe PHPT than in general population, particularly among older women.[199,205] The association between peptic ulcer disease and sporadic PHPT is not clear, but it is evident in PHPT associated with multiple endocrine neoplasia type 1 (MEN1) and Zollinger-Ellison syndrome (ZES).[197,206,207] Patients with ZES may also present diarrhea and steatorrhea.[207] In this context, hypercalcemia is related to hypergastrinemia and the correction of hypercalcemia by PTX clearly improves the gastric acid hypersecretion and the ZES.[207,208]

Mortality

We identified nine studies of PHPT patients,[68,209-216] and three studies on patients with hypercalcemia identified from an outpatient registry with a presumed diagnosis of PHPT,[217-219] assessing mortality risk (Table 5).[68,210-217] Severe classical PHPT is associated with increased mortality, whereas the impact of milder PHPT on survival is uncertain. Increased mortality, even in the presence of mild hypercalcemia, mostly from cardiovascular disease (CVD), but also cancer, was reported in studies from Northern Europe, the UK, and Australia,[209-213,217,218] with a reported relative risk [RR] of 1.2 to 1.6,[211-213] compared to a control population. These findings were however not confirmed in the US cohort.[214,215] Mortality was predicted by elevations in serum calcium levels,[68,214,216] although not consistently,[212,217] disease severity or gland size,[210,215] and PTH levels,[68,212,215,216] the latter being a possible surrogate of low 25(OH)D and frailty.[68] Age was a predictor of mortality in patients with PHPT in several studies; however, no controls were included in the multivariate model available to dissect the specific effect of disease itself, as opposed to aging, on mortality.[68,214-216] The study of Palmér and colleagues[217] did so but his population consisted of hypercalcemic subjects (SCa 2.72 mmol/L or 10.8 mg/dL) presumed to have PHPT from an outpatient registry. Interestingly, that study noted that the effect of age on mortality was not linear. It was only significant on subjects with age <70 years, with an interaction between age and calcium levels. Important

Table 5. Summary of Studies on All-Cause Mortality in Patients with Hypercalcemia and PHPT and Its Predictors*

Source, Country	Setting Population	*n*	Gender (% women)	Age (years)	Follow up years	Death rate (%)	Predictors of mortality on multivariate analysis
Palmér and colleagues[217] (1987) Sweden	Mild to moderate hyperCa[a] in health screening in 1969 Control: normocalcemic cohort matched for sex, age and date of screening	172[a]	85[a]	59.3 (12.1)	14	HyperCa: 33 Controls: 22.7 ($p = 0.0135$, log rank)	Data derived from HyperCa and control cohorts: Age β 1.51 (p = NA) (calculated HR 4.52) Gender (reference being men) β −1.07 (p = NA) (calculated HR 0.34) Calcium β 4.97 (p = NA) (only at age <79 years) (calculated HR 144) PTH NA
Hedbäck and Odén[210] (1995) Sweden	Single institution, PHPT with single adenoma, surgical cohort (1953–1982)	713	74	57.8 (12.9)	10.3 (5.6)	PHPT 33	Data derived from PHPT cohort: Age β 0.1 (p = NA) (calculated HR 1.1) Gender (reference being men) β −0.63 (p = NA) (calculated HR 0.53) Calcium,[b] PTH NA
Söreide and colleagues[215] (1997) Rochester	Single institution, PHPT, surgical cohort (1980–1984) Control: matched patient population from the upper Midwest	1052	73	Median 59 (range 12–89)	Median 12 (0–15)	PHPT 24 Risk of death similar PHPT versus control	Data derived from PHPT cohort: Age[c] RR 2.17 (1.86; 2.54) Men RR 2.07 (1.48; 2.88) Calcium NA PTH >100 µLEq/mL RR 1.48 (1.09; 2.02)
Hedbäck and Odén[211] (1998) Sweden	National patient registry, PHPT surgical cohort (1987–1994) Control: general population, to derive expected death, using the Swedish Central Bureau of Statistics.	4461	79	Range of means 61.3–64.7	3.6	11.3 RR of death 1.53 (PHPT versus control) (p = NA)	Data derived from PHPT cohort, by gender: Age: significant predictor, risk was significantly increased for both categories: age >65 years or <65 years Calcium, PTH NA
Wermers and colleagues[214] (1998) Rochester	Population-based, PHPT surgical and nonsurgical cohort (1965–1992) Control: Minnesota white residents matched for age and gender	435	76	56.1 (range 15.8–89.4)	Up to 20	NA Observed versus expected death: no difference ($p = 0.23$)	Data derived from PHPT cohort: Age (per 10 years increase) HR 2.6 (2.2, 3.1) Gender NS Highest calcium (per mg/dL increase) HR 1.3 (1.1, 1.6) PTH NA
Yu and colleagues[213,216] (2011 and 2013) Scotland	Population based[d] PHPT nonsurgical cohort (1997–2006) Control: general population matched for age, gender, calendar year of PHPT diagnosis	2097	70	68 (13.7)	3.5 (max 10)	31 HR for mortality 1.64 (1.43–1.87) PHPT versus control	Data derived from PHPT cohort: Age HR 1.04 (1.03; 1.05) Gender (reference men) HR 0.81 (0.68; 0.97) PTH HR 1.46 (1.25; 1.71) for ≤1000 days; HR 3.13 (2.37; 4.14) for >1000 days Ca HR 1.21 (1.11; 1.31) for <1000 days; HR 0.71 (0.57–0.85) for >1000 days

(Continues)

Table 5. Continued

Source, Country	Setting Population	*n*	Gender (% women)	Age (years)	Follow up years	Death rate (%)	Predictors of mortality on multivariate analysis
							Data derived from PHPT and control cohorts: Age and gender: matching terms Ca and PTH: NA
Clifton and colleagues[212] (2015) Australia	Single institution PHPT surgical and nonsurgical cohort (1961–1994) Control: Australian population at large matched for age, sex, the year observation began, duration of observation	561	NA	Range of means 52.9–55.5	10	22 Survival rate in PHPT versus control: 86.8% (84.9;86.2)	Data derived from PHPT cohort: Surgically treated ($n = 448$): Age NA; Gender, Calcium, PTH: NS Non-surgically treated ($n = 113$): Age NA; Gender, Calcium: NS PTH HR 1.59 (1.20; 2.11)
Reid and colleagues[68] (2019) Edinburg, Scotland	Single institution PHPT surgical and nonsurgical cohort (2006–2014)	611	82	Range of means 61–69 (49–77)	Median 6.2	16	Data derived from PHPT cohort: Age HR 1.05 (1.02;1.08) Gender NA Calcium HR 8.584 (1.68; 44.95) PTH NS[e]

μLEq = microliter equivalent; HyperCa = hypercalcemia.

[a]Data on mortality were derived from the nationwide Swedish Address Registry. Data presented in Table is relevant to the hypercalcemia group, presumed but not diagnosed to have PHPT (18 patients had parathyroid surgery, and 15 had a single parathyroid adenoma). The multivariate analysis results included hypercalcemic and normocalcemic patients. The β-values "show the change in the logarithm of the hazard function as the variable x increases by 1 unit, given that the other variables are unchanged".

[b]"The correlation coefficients were 0.45 for the peak serum calcium level and 0.43 for the mean level. When the influence of the adenoma weight was eliminated, neither of the serum calcium values showed any significant relationship to the risk of death ($p = 0.12$ and $p = 0.11$, respectively)".

[c]"Overall survival for the study population was compared with an expected survival for a matched patient population from the upper mid-west. Survival was calculated by the Kaplan–Meier product-limit method and comparisons of survival by the log-rank test; The overall survival rate in the study population did not differ from the expected survival rate of a matched mid-west population". On multivariate analysis, PTH and gender were significant only in patients without kidney stone, while age was significant for those with and without kidney stone. In patients with kidney stone, for age RR 2.74 (2.05–3.68).

[d]Tayside is a National Health Service Board in Scotland with a stable population of approximately 400,000, representative to the Scottish and UK population in terms of age, sex and social; the included PHPT were not surgically treated.

[e]Findings for age, calcium and PTH were similar for the overall cohort and the nonsurgical cohort.

*Adjustments in multivariate models: Palmér and colleagues[217]: age, gender, calcium, serum glucose, systolic and diastolic blood pressure, serum uric acid, serum cholesterol; Hedbäck and Odén[210]: adenoma weight, age, gender; Söreide and colleagues[215]: age, gender, PTH; Hedbäck and Odén[211]: age, time since surgery, calendar year; analysis done by gender; Wermers and colleagues[214]: age, highest calcium level, presence of complications, the time period of diagnosis (before or after 1974); Gender was not included in the multivariate analysis, although at the univariate analysis, *p* was 0.2; Yu and colleagues[213]: multiple deprivation index, history of bisphosphonates prescription, history of hospital admitted CVD, cerebrovascular disease, hypertension, renal failure, renal stones, psychiatric disease, fractures, cancer and diabetes; Yu and colleagues[216]: age, gender, SIMD, Ca, PTH, Creatinine, alkaline phosphatase, co-morbidities; Clifton and colleagues[212]: diabetes, kidney stones, congestive heart failure, coronary heart disease, hypertension, PTH, Paget's disease, cerebrovascular accident, calcium, fracture, ulcer, gender, smoking, pancreatitis, cholesterol, cancer; Reid and colleagues[68]: age, Scottish index of multiple deprivation, PTH, calcium, creatinine, vitamin D deficiency, surgery.

limitations of these studies is the fact that only one was population-based covering the country at large,[211] and the majority were conducted before the 1990s (see Table 5).[68,210-217]

Causality between PHPT and CVD mortality remains uncertain due to lack of consistent reversibility of mortality risk post-PTX.[209,217] Furthermore, observed associations between serum calcium with either CV or cancer mortality in subjects without PHPT, with calcium levels within the normal range, shed further doubt on disease causality.[219] Conversely, the enduring effect of PHPT on mortality post-PTX may also be explained by irreversible structural and functional damage of the CV system. Attempts to assess secular trends and geographic variability in the incidence of mortality in PHPT are limited by the heterogeneous nature and limitations of data available Acute PHPT is a life-threatening condition, with an estimated mortality of 59% in series prior to 1970, that however was substantially lower (6%) in the latest largest review of 48 cases.[220]

Knowledge gaps and research agenda

The shift in the presentation of PHPT over the last decades from a predominantly symptomatic to an asymptomatic disease has presented several challenges. The evidence available today suffers from several drawbacks including the poor definition of the various phenotypes of PHPT, the lack of adequate controls, blinding, scarce and small RCTs, and relatively short follow-up. The clinical course of mild asymptomatic disease, with its two phenotypes, mild and silent disease (without any end-organ damage), and mild subclinical (with end-organ damage) is unclear. Its management is also controversial. Furthermore, many, but not all, observational and cross-sectional studies continue to show associations between PHPT of varying severity and nonclassical manifestations, namely CV or neurologic abnormalities. RCTs, however, have not demonstrated a consistent long-term benefit of PTX versus observation on such manifestations, except for suggestive improvement in VPBs and on limited specific domain of QoL, both of which require confirmation. We identified the following gaps in general and by topic/organ system involvement.

Gaps/research agenda

- Investigate the natural history of the disease in patients with NPTH, with asymptomatic PHPT phenotypes (with or without target organ involvement), with regard to skeletal, renal, CV, neurologic (neuromuscular, neuropsychiatric, and QoL) manifestations
- Identify predictors of deterioration in renal or skeletal complications, in its various phenotypes to provide evidence for surgical interventions in NPHPT and in PHPT without evidence of end-organ damage
- Gain insights for causality of nonclassic manifestations through evidence for reversal post-PTX
- Establish a global registry for patients with PHPT

Global presentation

- Identify factors that account for the high prevalence of symptomatic PHPT in Asia and Latin America

Clinical manifestations

- Develop models to predict the complications of NPHPT, and of mild asymptomatic PHPT, with or without target organ involvement at diagnosis, and allow intervention at earlier stages

Normocalcemic PHPT

- Revise the current definition of NPHPT using strict criteria. We would recommend more robust estimates of reference intervals for albumin-adjusted calcium, ionized calcium, and PTH.

Skeletal manifestations

- Develop models to predict fracture risk based on biochemical markers and bone imaging information (TBS, FRAX)
- Investigate vertebral fracture risk in patients with asymptomatic PHPT, without end-organ involvement, followed without any intervention, compared to controls

Renal manifestations

- Elucidate natural history of silent nephrocalcinosis and nephrolithiasis
- Investigate biochemical markers and radiological novel tools to better diagnose the presence of nephrolithiasis and nephrocalcinosis
- Develop a disease specific index to predict the risk of stone formation and nephrocalcinosis
- Develop an algorithm based on combining prerenal comorbidities (eg, hypertension, diabetes, previous kidney disease) and renal (creatinine clearance) factors to predict deterioration in kidney function

Neuromuscular, neurobehavioral, QoL

- Evaluate current disease-specific QoL questionnaires
- Conduct large trials (surgery versus observation) in patients with neurologic manifestations and no end-organ involvement to assess the impact of surgery on neurologic symptoms as endpoints. Observation would be in patients with silent disease or those who decline surgery and medical therapy

CV manifestations

- Conduct large trials (surgery versus observation) with CV events as outcomes
- Observation would be in patients with silent disease or those who decline surgery and medical therapy

Mortality

- Establish a global registry or registries for patients with PHPT to determine the effect of mild disease on major outcomes, including CV and cancer mortality, investigate their predictors (for eg, disease severity, chronicity), and their reversibility post-PTX.

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Authors' roles: Project Administration and Supervision: GEHF and CM. Software and Resources: GEHF. Conceptualization, data curation, validation, visualization, writing original draft, writing-review and editing all co-authors.

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Conflicts of Interest

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Ethical Approval

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 manuscript are available in PubMed, MEDLINE, EMBASE, and the Cochrane databases.

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