J Endocrinol Invest (2015) 38:577–593
DOI 10.1007/s40618-015-0261-3

CONSENSUS STATEMENT

Italian Society of Endocrinology Consensus Statement: definition, evaluation and management of patients with mild primary hyperparathyroidism

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Received: 6 November 2014 / Accepted: 16 February 2015 / Published online: 28 March 2015

Introduction

Over the last 50 years, the spectrum of clinical presentation of primary hyperparathyroidism (PHPT) has shifted from a symptomatic disorder, characterized by symptoms of hypercalcemia, nephrolithiasis, and overt bone disease, toward a less symptomatic or asymptomatic disorder [1]. The recognition of the asymptomatic variant of PHPT has markedly increased following the inclusion of serum calcium measurement in the multichannel biochemical screening.

Parathyroidectomy (PTX) is the only definitive cure of PHPT. PTX is appropriate to consider in all patients with PHPT and should be recommended in patients with the symptomatic variant. The question of whether patients with asymptomatic PHPT should undergo surgery, as it is recommended in the symptomatic counterpart, has been the focus of four International Workshops. The latest has been held in Florence on September 19–21, 2013. The guidelines for surgery in patients with asymptomatic PHPT and monitoring for those who do not undergo surgery have been recently published and are reported in Table 1 [2]. Nowadays, approximately half of the patients with asymptomatic PHPT do not meet the surgical indications. The clinical profile of these patients is characterized by mild hypercalcemia (albumin-adjusted serum calcium lower than 1 mg/dL with respect to the upper normal limit) and no involvement of the classic target organs. These patients are often recognized by chance and could be classified as having a "mild" PHPT. For the purpose of the present Statement, the diagnostic criteria of mild PHPT are listed in Table 2.

This Consensus Statement will focus on how patients with hypercalcemia should be investigated to recognize those with mild PHPT, and how the latter patients should be evaluated, treated and monitored. Summary of recommendations is presented in Tables 3 and 4.

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Table 1 2014 Guidelines for surgery in patients with asymptomatic PHPT and guidelines for monitoring for those who do not undergo surgery

Guidelines for surgery	Guidelines for monitoring
Parameter	Parameter
Serum calcium: 1 mg/dL (0.25 mmol/L) > upper limit of normal	Serum calcium annually
BMD by DXA: *T* score < −2.5 at lumbar spine, femoral neck, total hip, or distal 1/3 radius	BDM by DXA every 1–2 years at lumbar spine, hip or distal 1/3 radius
Detection of vertebral fractures by X-rays, VFA, MRI or CT	Spine X-rays or VFA when clinically indicated (e.g., back pain, height loss)
Serum creatinine Estimated creatinine clearance (eGFR) <60 mL/min	Serum creatinine annually Creatinine clearance (eGFR) annually
24-h urine: Daily urinary calcium excretion >400 mg/day and increased stone risk by the urinary biochemical stone risk profile	24-h urinary biochemical stone profile if renal stones suspected
Presence of nephrolithiasis or nephrocalcinosis (by X-ray, ultrasound or CT)	Renal imaging (X-rays, ultrasound or CT) if renal stones suspected
Age <50 years	

Adapted from Ref. [2]

BMD bone mineral density, *DXA* dual-energy X-ray absorptiometry, *VFA* vertebral fracture assessment (by DXA), *MRI* magnetic resonance imaging, *eGFR* estimated glomerular filtration rate, *CT* computed tomography

Table 2 Definition of mild PHPT

Albumin-corrected serum calcium concentration lower than 1 mg/dL (0.25 mmol/L) above the upper limit of normal
Bone mineral density by DXA: *T* score ≥ −2.5 at lumbar spine, femoral neck, total hip, or distal 1/3 radius
No evidence of vertebral fractures (X-ray, VFA, MRI or CT)
Estimated creatinine clearance (or eGFR) >60 mL/min
24-h urinary calcium excretion ≤400 mg/day and low renal stone risk by the urinary biochemical stone risk profile
Absence of nephrolithiasis or nephrocalcinosis (by X-ray or ultrasound)
Absence of relevant symptoms and complications directly attributable to either hypercalcemia or excess PTH secretion
Age ≥ 50 years

DXA dual-energy X-ray absorptiometry, *VFA* vertebral fracture assessment (by DXA), *MRI* magnetic resonance imaging, *CT* computed tomography, *eGFR* estimated glomerular filtration rate

Methods

Literature search

The major source of data acquisition included PubMed search strategies. Papers published in the last 35 years were screened. In addition, the bibliographies of relevant citations and chapters of major textbooks were evaluated for any additional appropriate citation.

Grading

The GRADE system was used to make recommendations and express the quality of the evidence [3]. The task force used the following coding system: (1) indicates a strong recommendation and is associated with the sentence "we recommend"; (2) denotes a weak recommendation and is associated with the sentence "we suggest". Evidence grading: ØOOO denotes very low quality evidence; ØØOO, low quality; ØØØO, moderate quality; ØØØØ, high quality. The task force admits that, due to the limited availability of randomized clinical trials, the strength and quality of evidence are mostly low/moderate.

1. How should the differential diagnosis of hypercalcemia be approached?

Several diseases increase calcium concentrations, the most common being PHPT and cancer. Clinical presentation of PHPT has changed, being oligo-asymptomatic in up to 80 % of subjects when serum calcium is routinely determined [1, 4]. Other causes of hypercalcemia

Table 3 Summary of recommendations for clinical evaluation

Recommendation number	Statement	Strength and level of evidence
1	Hypercalcemia should be confirmed in repeated measures, possibly including the measurement of ionized serum calcium	1 ØØØØ
2	Plasma PTH measurement in all confirmed cases of hypercalcemia	1 ØØØØ
3	Serum 25OHD measurement in all patients with confirmed diagnosis of mild PHPT	1 ØØØØ
4	Reevaluation of hypercalcemia after withdrawal of thiazide diuretics (3–4 weeks) when plasma PTH is elevated or in the upper normal range	1 ØØOO
5	Reevaluation of hypercalcemia after withdrawal of lithium therapy, when feasible according to the psychiatric conditions of the patient	2 ØØOO
6	The use of albumin-corrected serum calcium measurement at initial evaluation. The measurement of ionized calcium could be useful in selected cases	1 ØØØO
7	Measurement of serum 25OHD in all patients with PHPT and in normocalcemic subjects with elevated PTH levels	1 ØØØO
8	The diagnosis of mild PHPT should NOT be applied to patients aged less than 50 years	1 ØØOO
9	Measurement of CCCR on the 2nd fasting morning urine sample following vitamin D deficiency correction	1 ØØØO
10	Genetic analysis of the *CASR* gene when there is a clinical suspicion of FHH and the CCCR result is in the 0.01–0.02 interval. This test could also be considered in apparently sporadic PHPT patients whose CCCR is <0.01. Mutational analysis of the *GNA11* and *AP2S1* genes could be considered in kindreds with FHH and no mutation of the *CASR* gene	2 ØOOO
11	Against routinely genetic screening for mutations of the susceptibility genes of parathyroid tumorigenesis	1 ØØOO
12	A completely workout investigating family history and syndrome-related clinical and biochemical features in young (less than 45 years of age) mild PHPT patients	2 ØØOO
13	Measurement of serum creatinine, phosphate, total alkaline phosphatase activity and creatinine clearance or alternatively eGFR measurement	1 ØØOO
14	Measurement of serum 25OHD in all patients and vitamin D replacement if serum 25OHD levels are lower than 20 ng/mL	1 ØØØO
15	Kidney ultrasound imaging to detect asymptomatic kidney stones and evaluate kidney morphology	1 ØØOO
16	Measurement of 24-h urinary calcium excretion	1 ØØØO
17	To evaluate the urinary stone risk profile (possibly by measurement of all parameters) when 24-h urinary calcium excretion is >400 mg	2 ØOOO
18	BMD measurements at lumbar spine, hip and distal one-third radius in all patients with mild PHPT	1 ØØØØ
19	Looking for vertebral fractures by morphometry (possibly by DXA rather than X-ray) particularly in postmenopasal women, individuals older than 65 years and/or with reduced BMD (T score < -2.5) at any site, as well as when a vertebral fracture is clinically suspected (back pain, height loss)	1 ØØØO
20	Against instrumental cardiovascular evaluation (echocardiogram, carotid intima-media thickness) in all patients with mild PHPT	1 ØØOO
21	Against psychometric or cognitive evaluation routinely in all patients with mild PHPT	1 ØØOO
22	To evaluate clinical CV measures such as blood pressure and heart rate as well as metabolic parameters such as BMI, blood glucose and lipid levels in all patients with mild PHPT accordingly to the standard clinical practice	2 ØOOO

are overtreatment with vitamin D medication, sarcoidosis, kidney disease, lithium and diuretic treatment, and skeletal diseases; a careful investigation of patients with increased calcium levels is therefore of utmost importance, since the majority of these patients will turn out to have an underlying disorder during a 10-year follow-up period [4]. Hypercalcemia should be confirmed in repeated measurements, including measurement of ionized calcium if available. If hypercalcemia is confirmed the next step should be the measurement of plasma PTH. The finding of hypercalcemia associated with abnormally elevated PTH or levels in the upper half of the normal range strongly suggests PHPT. Familial hypocalciuric hypercalcemia (FHH) and lithium therapy should be considered in the differential diagnosis. Vitamin D status should also be evaluated by measurement of serum 25-hydroxyvitamin D (25OHD). Patients with PHPT and vitamin D deficiency may have serum calcium in the upper normal range. Vitamin D supplementation may decrease serum PTH and increase serum calcium up to hypercalcemic values, thus allowing a better

Table 4 Summary of recommendations for management

Recommendation number	Statement	Strength and level of evidence
23	PTX is appropriate to consider in all patients with mild PHPT	1 ØØØO
24	Patients with mild PHPT be informed on the benefits and risks of PTX, on the stability of biochemical and densitometric parameters for a period of years, and on the possibility that a progression of the disease might occur in up to 25 % of patients not undergoing surgery	1 ØØØO
25	Performing noninvasive localization studies when PTX has been planned in patients with mild PHPT	1 ØØOO
26	Patients considered for PTX be referred to an experienced endocrine surgeon	1 ØØØØ
27	Against using imaging studies for diagnostic purposes	1 ØØØØ
28	Surgery should be considered as the first therapeutic option to patients with mild PHPT, provided that an experience surgeon is available and that the surgical risk is low	2 ØØOO
29	Surgery could be postponed if imaging studies are negative	2 ØOOO
30	Considering PTX in patients with mild PHPT and increased cardiovascular risk, if the surgical risk is low	2 ØOOO
31	Against PTX in patients with mild PHPT because of associated neurocognitive disorders	1 ØØOO
32	An intake of calcium appropriate for the age and sex as in the general population	1 ØØOO
33	Against restriction of dietary calcium intake	1 ØØOO
34	Correcting vitamin D deficiency in all patients with PHPT. Schedule using a daily dose of 800–1000 IU of vitamin D (weekly or monthly doses calculated on this daily dose) should be adopted	1 ØØOO
35	Increasing serum 25OHD values at >20 ng/mL and to aim to the target established for the general population	1 ØØOO
36	Against the use of cinacalcet in patients with mild PHPT. The current information does not indicate that patients with PHPT and mild hypercalcemia might benefit for a decrease of serum calcium	1 ØØØO
37	Alendronate might be an option for patients with low BMD who are not candidate for PTX	2 ØØØO
38	Serum calcium and creatinine measurements (and eGFR) annually	1 ØØØO
39	BMD measurements every 2 years and X-ray or VFA of the spine in the suspicion a vertebral fracture	1 ØØØO
40	Renal imaging and 24-h urinary biochemical stone profile if renal stones are suspected	1 ØØOO
41	Against routine annual renal imaging to discover asymptomatic renal lithiasis	1 ØOOO
42	PTX should be recommended if relevant changes occur during monitoring (see text)	1 ØØOO
43	The majority of pregnant women with mild PHPT be managed conservatively	1 ØOOO
44	PTX in very selected pregnant women with mild PHPT and deterioration of hypercalcemia	2 ØØOO
45	Patients with syndromic and familial forms of PHPT be evaluated for detecting associated disorders	1 ØØØØ

discrimination between patients with PHPT and those with secondary hyperparathyroidism [5]. Additional biochemical and imaging studies should be performed in patients with hypercalcemia and low-undetectable plasma PTH, to identify causes of PTH-independent hypercalcemia, including hypercalcemia of malignancy.

1.a. How should a hypercalcemic patient taking thiazide diuretics or lithium be evaluated?

Hypercalcemia is observed in 7–8 % of patients treated with thiazide diuretics, which block the thiazide-sensitive NaCl transporter in the distal convoluted tubule, thus decreasing calcium excretion [6, 7]. In a population-based study in Olmsted County, Minnesota, about 2/3 of the patients who discontinued thiazide had persistence of hypercalcemia, suggesting that PHPT is common in patients who develop hypercalcemia while taking thiazide diuretics [8]. In patients with hypercalcemia and concomitant thiazide therapy, serum calcium should be retested after withdrawal of therapy for 3–4 weeks.

Lithium can influence calcium homeostasis by increasing urinary calcium absorption [9], altering the calcium sensing receptor set point (lack of PTH suppression by hypercalcemia) [10] and directly stimulating PTH secretion [11]. Hypercalcemia with short-term use of lithium usually resolves upon treatment discontinuation. On the other hand, hypercalcemia persists in approximately 10–15 % of chronic lithium users (for more than 10 years), thus indicating a diagnosis of PHPT. The prevalence of lithium-induced hypercalcemia is higher in patients with renal failure, in whom urinary excretion of calcium is reduced. Thus, monitoring of serum creatinine and calcium levels in patients on lithium treatment is highly recommended [11].

Recommendations

- **1. We recommend** hypercalcemia be confirmed in repeated measures, possibly including the measurement of ionized serum calcium (1 ØØØØ).
- **2. We recommend** plasma PTH measurement in all confirmed cases of hypercalcemia (1 ØØØØ).
- **3. We recommend** serum 25OHD measurement in all patients with confirmed diagnosis of mild PHPT (1 ØØØØ).
- **4. We recommend** reevaluation of hypercalcemia after withdrawal of thiazide diuretics (3–4 weeks) when plasma PTH is elevated or in the upper normal range (1 ØØØØ).
- **5. We suggest** reevaluation of hypercalcemia after withdrawal of lithium therapy, when feasible according to the psychiatric conditions of the patient (2 ØØOO).

2. Should ionized calcium be measured in all cases to confirm the diagnosis of hypercalcemia or we suggest calculating the albumin-corrected serum calcium value?

In blood, about 50 % of calcium is bound to proteins, primarily albumin (40 %), while the remainder is ionized or 'free'. Some calcium exists in the blood as complexes with anions such as phosphate or sulfate. It is advisable to calculate the corrected calcium using the formula: corrected calcium = serum calcium in mg/dL + [0.8 × (4-serum albumin in g/dL)]. The measurement of ionized calcium could be useful in selected cases, such as in patients with hyperalbuminemia, thrombocytosis, Waldenström macroglobulinemia and myeloma. In these instances, hypercalcemia may be present with normal ionized serum calcium [12, 13]. Several studies have shown discrepancies between serum total or corrected and ionized calcium levels [14]. Whether acute illness leads to calcium measurement unreliability is still debatable. Acidosis causes a rise in the ionized fraction, while metabolic alkalosis can decrease the ionized calcium concentration as much as 0.36 mmol/l [14].

Recommendations

- **6. We recommend** the use of albumin-corrected serum calcium measurement at initial evaluation. The measurement of ionized calcium could be useful in selected cases (1 ØØØO).

3. Should 25OHD be measured at initial evaluation or only once the diagnosis of mild PHPT has been established?

The measurement of 25OHD should be obtained in all patients since many of them show a vitamin-deficient status [15]. This is important not only to document the state of hypovitaminosis, but also to tailor the supplementation on the basis of the actual and desired target values. Furthermore, it is well established that hypovitaminosis D might result in increased PTH values [16] and that hypovitaminosis D might mask a more significant elevation of serum calcium, because of reduced calcium absorption [17].

Recommendations

- **7. We recommend** measurement of serum 25OHD in all patients with PHPT and in normocalcemic subjects with elevated PTH levels (1 ØØØO).

4. Is there an age limit for the diagnosis of mild PHPT?

The Fourth International Workshop on Asymptomatic Primary Hyperparathyroidism confirms that patients aged less than 50 years should be surgically treated [2]. Age has been shown to be predictive of disease progression: PHPT patients younger than 50 years of age were approximately three times as likely to have a worsening of the disease [18].

Recommendations

- **8. We recommend** that the diagnosis of mild PHPT should not be applied to patients aged less than 50 years. All patients with PHPT aged less than 50 years, independently of the calcium levels and symptoms, should be candidate to surgery (1 ØØOO).

5. Is mild PHPT distinguishable from FHH in individual cases?

The main diagnostic challenge consists to distinguish mild PHPT and FHH, as both conditions are often, not invariably, asymptomatic. Nonetheless, this distinction is mandatory since asymptomatic FHH does not need follow-up or treatment. However, it should be highlighted that cases of coexisting PHPT and FHH have been recently described [19].

5.a. Is there a role of the medical history?

Medical history may help in the differential diagnosis: the family history should be investigated to identify siblings affected by FHH. FHH is often missed at diagnosis; therefore, the endocrinologist should invite relatives of the PHPT patient to have their serum calcium measured.

5.b. Do vitamin D-deficient patients be replete before approaching this differential diagnosis?

Vitamin D deficiency is associated with increased PTH secretion, impairment of urinary calcium excretion, and reduced sensitivity of urinary calcium-to-creatinine clearance ratio (CCCR) measurement in the differential diagnosis between mild PHPT and FHH [20]. The CCCR is calculated as follows: [UCa × SCr]/[SCa × UCr], where UCa is the urinary calcium concentration, SCr is the serum creatinine, SCa is the serum calcium concentration, and UCr is the urinary creatinine concentration, all in mg/dL.

Therefore, serum 25OHD levels should be tested and vitamin D deficiency should be corrected with adequate cholecalciferol supplements.

5.c. Which tests should be performed?

FHH patients have lower serum PTH and 1,25-dihydroxy-vitamin D levels than PHPT patients, while serum calcium and 25OHD levels are similar [21]. Furthermore, FHH patients show higher BMD *Z* score when compared to PHPT patients at the total forearm, the mid forearm and the ultradistal forearm; nonetheless, these differences are less sensitive than the CCCR value as a diagnostic tool to separate FHH from PHPT [22]. These biochemical and clinical differences, even if suggestive, do not successfully discriminate between FHH and PHPT.

Patients with mild PHPT should be evaluated to exclude FHH by measuring the CCCR. A CCCR less than 0.01 is highly suggestive for FHH diagnosis, whereas a ratio higher than 0.02 excludes FHH diagnosis. Values between 0.01 and 0.02 should be carefully evaluated, since values in this range might be due to minimal renal impairment or incorrect urine collection. The CCCR is the consensus biochemical test to differentiate between FHH and PHPT. Due to the difficulties to obtain reliable 24 h urine collection in particular in outpatient setting, the 2nd fasting morning urine sample collected over about 2 h can be used [23]. It is advisable to drink some distilled water to facilitate bladder emptying. Blood is drawn at the midpoint of the urine. However, the definitive diagnosis of FHH requires genetic testing [24]. There are three genetic variants of FHH determined by inactivating mutations of the *CASR* gene (FHH type 1) [25], of the *GNA11* gene (FHH type 2) [26] and of the *AP2S1* gene (FHH type 3) [27]. About 2/3 of kindreds with FHH harbor inactivating mutation of the *CASR*. In the remaining cases, mutations in the noncoding region of the CASR gene may be present. Mutations of the *GNA11* gene and *AP2S1* gene have been described in few kindreds.

Recommendations

- **9. We recommend** CCCR on the 2nd fasting morning urine sample following vitamin D deficiency correction (1 ØØØO).
- **10. We suggest** genetic analysis of the *CASR* gene when there is a clinical suspicion of FHH and the CCCR result is in the 0.01–0.02 interval. This test could also be considered in apparently sporadic PHPT patients whose CCCR is <0.01. Mutational analysis of the *GNA11* and *AP2S1* genes could be considered in kindreds with FHH and no mutation of the *CASR* gene (2 ØOOO).

6. Is there a role for genetic testing in a patient with mild PHPT?

Mild PHPT might develop as clinical feature of PHPT-related syndromes.

Asymptomatic Multiple Endocrine Neoplasia type 1 (MEN1)-related PHPT is more likely to occur in young (<30 years) patients, often diagnosed with PHPT during biochemical and hormonal screening of relatives of MEN1-affected probands identified by *MEN1* gene mutation screening. Hypercalcemia is frequently associated with PTH levels in the normal range. Nonetheless, evaluation of bone and kidney complications should be carefully performed, as these features are more frequent in early-onset MEN1-related than in sporadic PHPT patients [28].

Inactivating mutations of the *CDKN1B* gene, coding for the p27 protein, have been shown to be associated with MEN4 syndrome that is characterized by pituitary adenomas and PHPT with a presentation that in the few patients so far described is similar to that observed in MEN1-related PHPT [29–31].

Patients with Multiple Endocrine Neoplasia type 2A (MEN2A), harboring mutations of the *RET* oncogene involving codon 634 in exon 11, may develop PHPT in 20 % of cases. PHPT is usually due to parathyroid hyperplasia and is classically reported as mild or asymptomatic [32].

Germline-inactivating *HRPT2/CDC73* gene mutations are associated with the hyperparathyroidism–jaw tumor (HPT–JT) syndrome, characterized by parathyroid carcinomas or adenomas. Three relatives out of six reported patients with *HRPT2/CDC73* mutations presented with serum calcium levels lower than 1 mg/dL over the upper limit of the normal range and with typical adenoma or atypical adenoma [33].

Genetic analysis for *CASR* gene mutation should be performed in all patients with CCCR less than 0.02 as it can help to distinguish FHH from PHPT (21). Nonetheless, it should be kept in mind that patients harboring inactivating mutations of the *CASR* gene and surgically proven PHPT (as demonstrated by normalization of hypercalcemia after surgery), have been described. These cases account for up to 3 % of PHPT patients [34].

Mutations of the *CDC73* gene have been detected in approximately 20 % of patients with familial isolated hyperparathyroidism (FIHP) [35]. Therefore, gene deletion analysis should be extended to all FIHP as well as HPT–JT patients without *CDC73* mutations. Mutations in the *MEN1* gene and, rarely, in the *CASR* gene may also occur in FIHP [36, 37].

In a recent study in a large sample of patients with PHPT aged less than 45 years and no history suggestive of familial PHPT, germline-inactivating mutations in susceptibility genes have been found in 24 out of 102 (23.5 %) patients, including 15 *MEN1,* 4 *RET*, 3 *CASR* and 2 *HRPT2/CDC73* mutations [38].

Recommendations

- **11. We recommend** against routine genetic screening for mutations of the susceptibility genes of parathyroid tumorigenesis (1 ØØOO).
- **12. We suggest** a complete workout investigating family history and syndrome-related clinical and biochemical features in young (less than 45 years of age) mild PHPT patients (2 ØØOO).

7. How should a patient with a biochemical diagnosis of PHPT and mild hypercalcemia be evaluated to reach the clinical diagnosis of mild PHPT?

The term "mild" defines a PHPT with hypercalcemia lower than 1 mg/dL above the upper limit of the normal range, while the term "asymptomatic" should be used to indicate a condition of PHPT not associated with typical and/or atypical PHPT symptoms, independently of the serum calcium level. Typical PHPT symptoms are considered kidney stones and bone disease. Asymptomatic renal disease should be ruled out by performing kidney ultrasound. BMD should be evaluated by DXA at lumbar spine, hip and distal one-third radius site. Osteoporosis occurred at lumbar spine in 48 %, at femoral neck in 20 %, at one-third radius in 71 % of mild PHPT patients. The presence of symptomatic vertebral fractures should be evaluated. Vertebral fractures, mostly mild morphometric vertebral fractures, were detected in 11 % of postmenopausal women with PHPT [39].

Atypical features of PHPT include cardiovascular morbidities and neuropsychological symptoms. Neither of them are currently indications for recommending PTX [2].

7.a. Should additional biochemical tests be performed?

In PHPT, vitamin D insufficiency is more common than that in general population [40]. Daily supplementation with a high vitamin D dose (2800 IU) safely improves vitamin D status and decreases plasma PTH in patients with PHPT [41]. Moreover, the treatment with vitamin D is accompanied by reduced bone resorption and improved BMD [41, 42]. Therefore, serum 25OHD levels should be measured in all patients with a diagnosis of PHPT.

Serum creatinine and creatinine clearance, phosphate, alkaline phosphatase activity, and 24-h urinary calcium should also be measured. If 24-h urinary calcium >400 mg, the risk of nephrolithiasis should be determined by evaluating the urinary stone risk profile[1] [2]. The urinary stone risk profile may be derived from the measurements of several urinary parameters, in addition to calcium (sodium, potassium, magnesium, phosphate, citrate, oxalate, chloride, pH and urine volume) [43].

7.a.1. Should bone turnover markers be measured?

Bone turnover markers have been considered to have a poor role. Nonetheless, serum total alkaline phosphatase (ALP), and more specifically bone alkaline phosphatase (BALP), should be obtained at the time of diagnosis to identify significant increases suggestive for Paget's disease, that in 2.2–6.0 % of cases is known to be associated with mild PHPT [44].

7.a.2. Should metabolic parameters be evaluated?

A number of epidemiologic and clinical studies suggest an increased risk for cardiovascular morbidity and mortality in patients with PHPT; nonetheless, up to now there is no convincing evidence to justify the need to evaluate metabolic parameters.

7.b. How should renal involvement be evaluated?

Most studies indicate rates of 16–17 % of chronic kidney disease in PHPT. Renal function should be evaluated for the following reasons: (1) the Fourth International Workshop panel recommends PTX for PHPT patients with

[1] Stone risk profile can be evaluated as indicated by Marangella et al. [46] using an electronic algorithm or may also be obtained by commercial laboratories.

CKD (eGFR < 60 mL/min/1.73 m^2) or overt hypercalciuria and increased risk of nephrolithiasis [2]; (2) impaired renal function might modify the biochemical presentation of PHPT: PTH levels might be further increased and serum phosphate levels might be inappropriately normal [45].; (3) recurrent nephrolithiasis due to idiopathic hypercalciuria might induce a secondary hyperparathyroidism that in some cases may progress to tertiary hyperparathyroidism, which is often characterized by serum calcium levels at the upper limit of the normal range.

Renal involvement should be evaluated by kidney ultrasound and measurement of the eGFR (based on serum creatinine) and 24-h urinary calcium excretion and stone risk profile if the latter is >400 mg [46].

7.c. How should bone involvement be evaluated?

Patients with mild PHPT may show a reduction in BMD, particularly at cortical skeletal sites, such as the distal one-third radius, with relative preservation of BMD at the lumbar spine. Some but not all studies have reported an increase in fracture risk in patients with PHPT. Much less is known regarding the relationship between BMD and fracture risk in mild PHPT.

At present, bone involvement in mild PHPT should be evaluated by performing:

7.c.1. Dual-energy X-ray absorptiometry (DXA)

In both symptomatic and asymptomatic PHPT, BMD is reported reduced at the distal radius while the lumbar spine is relatively preserved and the hip region shows BMD that is intermediate between axial and appendicular sites [23, 47]. However, as PHPT commonly occurs in postmenopausal women, many patients show skeletal effects that reflect both PHPT and estrogen deficiency-related osteoporosis, thus reduced lumbar spine BMD can be prevalent. Therefore, it is standard to measure BMD at 3 skeletal sites (hip, lumbar spine and distal one-third radius) [48]. Moreover, BMD can be influenced by some PHPT-related factors such as renal function. A slight decrease in renal function is associated with more pronounced bone loss and altered bone remodeling, independent of age, body mass index, and PTH levels. This association is also present in asymptomatic PHPT [49, 50].

7.c.2. Vertebral morphometry

It can be performed both with X-ray and DXA. Spine X-ray examination is the gold standard to detect vertebral fractures; however, vertebral fracture assessment (VFA) by DXA has been recognized as an acceptable alternative. The latter is more convenient compared with the standard vertebral spine x-ray because it is performed at the same time as BMD measurement by DXA with less radiation exposure [39, 48].

In PHPT, an increased rate of vertebral fractures has been reported, including non-clinical vertebral fractures [39]. Moreover, it has been recently reported an inverse relationship between morphological vertebral fracture incidence and serum calcium levels suggesting the opportunity to screen routinely patients with mild PHPT for vertebral fractures [2, 51].

7.c.3. Trabecular bone score (TBS)

This evaluation has been recently proposed as an indirect measure of bone micro-architecture. TBS seems to indirectly reflect an alteration of bone micro-architecture in postmenopausal women with PHPT [52].

7.d. Should the patient be evaluated for the presence of nonclassical manifestations of PHPT?

Among nonclassical manifestations, cardiovascular disease and neuropsychological symptoms are part of the modern phenotype of PHPT [47].

7.d.1. Cardiovascular and metabolic manifestations

There is considerable interest regarding the cardiovascular effects of PHPT, with continuous data coming out concerning their extent and clinical significance. Studies have investigated the association with hypertension, cardiac and vascular abnormalities, as well as mortality [53].

Other cardiovascular risk factors have also been shown to be more prevalent in patients with both ‘mild’ and ‘severe’ PHPT, such as dyslipidemia and diabetes [53].

The increased cardiovascular morbidity and mortality observed in patients with severe PHPT has not been definitively demonstrated in patients with a more mild disease (studies from Scandinavia in contrast to American study in Rochester Minnesota) [1]. However, a recent retrospective population-based observational study in patients with mild PHPT indicated that both cardiovascular morbidity and mortality ratios were increased compared with those without PHPT [54].

Results from observational studies that have assessed the effect of PTX on cardiovascular health have been conflicting. The single randomized clinical trial (RCT) in this area did not demonstrate that PTX was beneficial [55]. Despite recent progress in these areas, more data from rigorously designed studies are needed to better inform the clinical management of patients with asymptomatic PHPT.

7.d.2. Neuropsychological symptoms

A number of observational studies suggest that mild PHPT may be associated with depression, decreased quality of life, and changes in cognition, but limited data from RCTs have not indicated consistent benefits after PTX [55–58].

A recent prospective nonrandomized study including patients with mild PHPT indicates that patients with asymptomatic PHPT have clinical improvement of their symptoms (including psychological symptoms) postoperatively even after 1 year. Younger patients and those with higher preoperative calcium levels showed the best improvement [59].

7.d.3. Other nonclassical manifestations

Impairment of muscle function has also been reported. Muscle impairment may be present in patients with mild PHPT. In a recent study, analyses of ''asymptomatic'' PHPT patients showed significantly lower muscle strength at knee extension and flexion and impaired postural stability than in matched controls. The impaired muscle function might contribute to the increased fracture risk independently of BMD [41].

Recommendations

- **13. We recommend** measurement of serum creatinine, phosphate, total alkaline phosphatase activity and creatinine clearance or alternatively eGFR measurement in all patients with mild PHPT (1 ØØOO).
- **14. We recommend** measurement of serum 25OHD in all patients and vitamin D replacement if serum 25OHD levels are lower than 20 ng/mL (1 ØØØO).
- **15. We recommend** kidney ultrasound imaging to detect asymptomatic kidney stones and evaluate kidney morphology in all patients with mild PHPT (1 ØØOO).
- **16. We recommend** measurement of 24-h urinary calcium excretion in all patients with mild PHPT (1 ØØØO).
- **17.We suggest** to evaluate the urinary stone risk profile (possibly by measurement of all parameters) when 24-h urinary calcium excretion is >400 mg (2 ØOOO).
- **18. We recommend** BMD measurements at lumbar spine, hip and distal one-third radius in all patients with mild PHPT (1 ØØØØ).
- **19. We recommend** looking for vertebral fractures by morphometry (possibly by DXA rather than X-ray) particularly in postmenopausal women, individuals older than 65 years and/or with reduced BMD (T score < -2.5) at any site, as well as when a vertebral fracture is clinically suspected (back pain, height loss) (1 ØØØO).
- **20. We recommend against** instrumental cardiovascular evaluation (echocardiogram, carotid intima-media thickness) in all patients with mild PHPT (1 ØØOO).
- **21. We recommend against** psychometric or cognitive evaluation routinely in all patients with mild PHPT (1 ØØOO).
- **22. We suggest** to evaluate clinical cardiovascular measures such as blood pressure and heart rate as well as metabolic parameters such as BMI, blood glucose and lipid levels in all patients with mild PHPT accordingly to the standard clinical practice (2 ØOOO).

8. How should a patient with mild PHPT be managed?

According to the current guidelines, patients with mild PHPT could safely be followed without surgery at least a number of years [2]. To properly address this question, several issues should be considered.

8.a. What do we know about the natural history of mild PHPT?

Randomized clinical trial data do not demonstrate significant deleterious effects of observation in asymptomatic patients over a short (1–2 years) period of observation [55, 57, 58, 60]. However, though long-term randomized trial data are not available, observational studies report that more than one-third of patients develop new guidelines for surgery if observed for up to 15 year [60]. Very recently, a an extension up to 5 years of one of these prospective RCTs in patients with asymptomatic PHPT has shown that even though new vertebral fractures occurred only in the observation group, the frequency was not significantly different from that in patients who had been cured by surgery [61].

Bone density is stable over the first years of observation but begins to decline particularly at the cortical sites (hip and forearm) after 8 year of follow-up [60].

Limited data are available concerning renal function in patients with mild PHPT, while a progressive deterioration is common in patients with symptomatic PHPT. Serum creatinine significantly decreased ($P < 0.01$) over 5 years in patients with asymptomatic PHPT followed without surgery [61]. Renal stone can be present in up to 11.4 % of patients with asymptomatic PHPT [62] and the risk of renal colic requiring hospital admission remains increased for at least 10 year after surgical cure of PHPT [63].

8.b. Do patients with mild PHPT benefit from surgery?

Information concerning whether patients with mild PHPT might benefit from surgery can be obtained from three RCTs, with a duration ranging between 1 and 3.5 years [55,

57, 58]. These studies enrolled women (about 85 %) and men aged >50 years, with inclusion criteria comparable to those we used to define herein mild PHPT (namely mild hypercalcemia and no indication for PTX according to the guidelines available when patients were enrolled). Longitudinal data were obtained on biochemical, densitometric and quality-of-life changes.

Normalization of serum calcium, PTH and other biochemical parameters followed PTX. Patients submitted to PTX, compared to patients followed without surgery, showed a significant increase in BMD at the lumbar spine [56, 58], femoral neck and total hip [57, 58], whereas no benefit was observed at the forearm. The study of Ambrogini et al. [64] (in which patients with BMD *Z* score < −2 by DXA were not included because this was a criterion for surgery according to the 1990 guidelines) showed that the densitometric improvement at the lumbar spine and total hip occurred independently of whether patients were classified as osteoporotic or not on the basis of the *T* score (a T score of <−2.5 at any site has become a criterion for PTX since 2002 [65]).

Patients included in the surgical groups also showed some benefit on quality of life and psychological functioning, but the results were inconsistent despite the use of the same tool (Short Form-36 general health survey) [55, 57, 58]. A more recent study evaluated a cohort of 36 postmenopausal women with mild PHPT patients at baseline and after PTX [66]. At baseline PHPT patients, compared with non-PHPT controls, showed higher scores for depression and anxiety and a worse performance of verbal memory and nonverbal abstraction. Scores for depressive symptoms, verbal memory and nonverbal abstraction improved after PTX and did no longer differ from those of controls.

8.c. Should surgery be considered in all patients?

Guidelines for management of patients with asymptomatic PHPT suggest PTX is appropriate to be considered in all patients, and that surgery is recommended in patients who met well-defined criteria such as age, serum calcium levels and the degree of renal and bone impairment [2]. Successful PTX is followed by several beneficial effects, which may also occur in patients with mild PHPT. As a matter of fact, parathyroid surgery is followed by improvement in BMD even in patients with mild PHPT and a BMD *T* score > −2.5 [56–58, 67]. Thus surgery could be considered also for patients with mild sporadic PHPT, independently of the presence of criteria for PTX. On the other hand, PTX could be postponed in patients with MEN1-associated PHPT or FIHP, since multiglandular disease, occasionally with asynchronous involvement, is more frequent than in sporadic PHPT and may account for operative failure and increased recurrence rates. Moreover, preoperative (99 m) Tc-sestamibi scan is less sensitive in patients with mild PHPT, being positive in no more than 64 % of cases [68].

When performed by skilled neck surgeons, parathyroid surgery is safe, cost-effective, and associated with very low perioperative morbidity [69]. Younger patients and those with higher preoperative calcium levels (>10.4 mg/dL) show the best improvement [59]. However, it is important to consider that PTX, particularly if performed by unexperienced neck surgeons, may be complicated by side effects, which could be invalidating and not acceptable in a subject with a mild disease associated with a good quality of life.

8.d. Is there a role of parathyroid imaging in the decision-making process?

The diagnosis of PHPT is biochemical, and therefore, imaging studies are not needed for the diagnosis. Imaging studies should only be performed in patients who will undergo PTX [69]. Noninvasive localization studies including color Doppler cervical ultrasound and sestamibi scan are usually employed for focused explorations such as minimally invasive PTX. However, false-positive and false-negative results are possible and the diagnostic performance of imaging studies may vary between different centers [70, 71]. Negative imaging studies do not preclude parathyroid surgery, but the decision to perform PTX in a patient with mild PHPT might be reconsidered if imaging studies are negative [23]. More extensive surgical procedures than minimally invasive PTX may be required in these cases.

8.e. Which is the appropriate surgical approach?

The gold standard surgical approach, namely bilateral neck exploration identification of all four parathyroid glands and excision of the diseased one(s), is less frequently performed nowadays at initial surgery. Minimally invasive surgical approach is usually adopted, when the abnormal parathyroid is preoperatively identified. This approach should be associated with the intraoperative quick PTH monitoring. The standard approach is usually chosen for patients with familial diseases (more likely to have multiglandular involvement) and in the case of remedial surgery.

Recommendations

- **23.** PTX is appropriate to consider in all patients with mild PHPT (1 ØØØO).
- **24. We recommend** that patients with mild PHPT be informed on the benefits and risks of PTX, on the stability of biochemical and densitometric parameters for a period of years, and on the possibility that a progression of the disease might occur in up to 25 % of patients not undergoing surgery (1 ØØØO).

- **25. We recommend** performing noninvasive localization studies when PTX has been planned in patients with mild PHPT. Negative imaging studies could influence the decision process (see below) (1 ØØOO).
- **26. We recommend** that patients considered for PTX be referred to an experienced endocrine surgeon (1 ØØØØ).
- **27. We recommend against** using imaging studies for diagnostic purposes (1 ØØØØ).
- **28. We suggest** that surgery **should be considered** as the first therapeutic option to patients with mild PHPT, provided that an experience surgeon is available and that the surgical risk is low. Moreover, PTX should be performed in patients who are unwilling to be followed without surgery (provided that the surgical risk is low) (2 ØØOO).
- **29. We suggest** that surgery could be postponed if imaging studies are negative (2 ØOOO).

9. Are there comorbidities that might influence the management of a patient with mild PHPT?

Cardiovascular disease and neuropsychiatric disorders have been associated to PHPT.

PHPT and severe hypercalcemia have been associated with the increase of mortality and morbidity mainly due to cardiovascular disease (CVD) [54, 72], but the association of mild PHPT with CVD is uncertain, consequently, the present data do not suggest PTX aiming to improve CVD risk in patients with mild PHPT. Turning the question, considering for example, a patient of middle age with metabolic syndrome, CVD and a mild PHPT, could PTX be indicated since PHPT could affect CVD and increase the risk of death? There are no studies designed for answering such a question and a case-finding approach could be suggested to plan PTX in a patient with mild PHPT and low surgical risk.

Neurocognitive disorders have been associated with PHPT. Depression [73] as well as neuropsychological symptoms [74] has been reported to improve after PTX in mild PHPT patients. Although depression and anxiety seem to improve after PTX [66] the data are not robust enough to suggest PTX in mild PHPT. Turning the question, considering for example, a patient of middle age with mild PHPT and neuropsychological symptoms, could PTX be indicated since PHPT could affect such a disease over time? There are no studies designed for answering such a question and we suggest a case-finding approach.

Recommendations

- **30. We suggest** considering PTX in patients with mild PHPT and increased cardiovascular risk, if the surgical risk is low (2 ØOOO).
- **31.** We **recommend against** PTX in patients with mild PHPT because of associated neurocognitive disorders (1 ØØOO).

10. How should patients not undergoing surgery be monitored/managed?

General principles for monitoring patients with PHPT not undergoing surgery have been recently published [2].

10.a. Should the dietary calcium intake be reduced?

A number of studies have examined the effect of calcium intake in patients with PHPT, even though these investigations do not directly focus on individuals with mild PHPT. Results obtained have been inconsistent; Insogna and coworkers found that calcium intake of 1000 mg per day suppresses mean fasting levels of PTH by 19 % among 18 PHPT participants [75]. Similar results were obtained by Jorde and co-workers [76], by giving calcium supplementation. However, Locker and colleagues [77] found no significant effect of dietary calcium intake on serum PTH. Differences in the results obtained so far and the lack of studies in patients with mild PHPT preclude suggestions based on evidence; however, a calcium intake similar to that desirable for the general population at different ages is appropriate until prospective studies addressing this issue will be carried out [78]. Furthermore, the long-term safety of a low-calcium diet has been questioned; in addition, low-calcium diets can increase urinary oxalate excretion because low-calcium concentration in the intestinal lumen leaves more oxalate in the unbound state to be absorbed.

10.b. Should patients with vitamin D deficiency/insufficiency be treated? Which is the target serum 25OHD value?

A number of investigations have shown that hypovitaminosis D in patients with PHPT is associated with higher PTH values, larger adenomas, more compromised skeletal health and increased incidence of hungry bone syndrome after PTX compared with vitamin D replete or vitamin sufficient patients [17]. Vitamin D deficiency should be corrected in all patients aiming at serum levels of 25OHD >20 ng/mL. The attainment of higher values (>30 ng/mL) might also be considered because there is some evidence that these levels may be associated with a greater reduction in PTH. Despite these convincing demonstrations, there is still uncertainty about treatment of vitamin D depletion in patients with PHPT. Recent papers favor the corrections of hypovitaminosis D [42, 79]. However, studies carried out in a population of patients mild PHPT are lacking, so that specific

guidelines do not exist. Such studies are needed, and should be of long duration defining the amount and modalities of refilling body stores in this particular gland disorder. In the meantime, it seems prudent to suggest targeting vitamin D threshold according to the guidelines of different scientific societies [80, 81], because this might reduce the severity of the disease with no safety concerns.

Recommendations

- **32. We recommend** an intake of calcium appropriate for the age and sex as in the general population (1 ØØOO).
- **33. We recommend against** restriction of dietary calcium intake (1 ØØOO).
- **34. We recommend** correcting vitamin D deficiency in all patients with PHPT. Schedule using a daily dose of 800–1000 IU of vitamin D (weekly or monthly doses calculated on this daily dose) should be adopted (1 ØØOO).
- **35. We recommend** increasing serum 25OHD values at >20 ng/mL and to aim to the target established for the general population (1 ØØOO).

11. Is there a role for medical management?

11.a. Antiresorptive therapy

Antiresorptive agents such as bisphosphonates and estrogen therapy are effective in decreasing bone turnover and improving BMD in patients with PHPT. The magnitude of the effects of bisphosphonates and estrogen on BMD is comparable to that which occurs after successful PTX [78, 82, 83]. The best evidence is with the use of alendronate. Of note, none of these agents significantly lowers serum calcium or PTH levels. No fracture data are available with either treatment in patients with mild PHPT.

11.b. Calcimimetics

The calcimimetic cinacalcet has been shown to decrease and often normalize serum calcium concentration over a wide range of serum calcium levels in patients with PHPT [78]. Cinacalcet is also effective in increasing serum phosphate, whereas it has only a modest effect to reduce PTH concentration and no effect on BMD [78]. No data are available of other disease-associated manifestations.

The use of cinacalcet has been approved by the EMA "for the reduction of hypercalcemia in patients with PHPT, for whom PTX would be indicated on the basis of serum calcium levels (as defined by relevant treatment guidelines), but in whom PTX is not clinically appropriate or is contraindicated" [84]. The FDA has approved the use of cinacalcet for the management of severe hypercalcemia in patients with PHPT unable to undergo PTX [85]. Recent reports, published afterwards have included also patients whose serum calcium was below the approved cutoffs, and show that cinacalcet treatment, at rather low dosage (30–60 mg daily), was associated with normalization of serum calcium concentrations in most, if not all patients [78, 86, 87].

The question of whether the decrease of slightly increased serum calcium in patients with mild PHPT treated with cinacalcet will result in a benefit on potential hypercalcemia-associated features (mortality, neuropsychological and cognitive abnormalities, cardiovascular abnormalities, nephrolithiasis etc.) remains to be established.

Recommendations

- **36. We recommend against** the use of cinacalcet in patients with mild PHPT. The current information does not indicate that patients with PHPT and mild hypercalcemia might benefit from a decrease of serum calcium (1 ØØØO).
- **37. We suggest** that alendronate might be an option for patients with low BMD who are not candidate for PTX (2 ØØØO).

12. How should patients not undergoing surgery be monitored?

The recently revised guidelines have extended the recommendation for PTX in patients with asymptomatic PHPT, including those with mild PHPT [2]. However, patients who do not meet the surgical criteria as well as those who refuse surgery or have comorbidities which contraindicate surgery can be followed safely at least for some years.

All patients not undergoing surgery should be replete in vitamin D (serum levels of 25OHD >20 ng/mL).

Patients should be monitored by the measurement of serum calcium, creatinine and creatinine clearance/eGFR every year; periodic assessment (every 2 years) of BMD by DXA at the three sites should also be performed. X-ray or VFA of the spine should be performed in the suspicion of a vertebral fracture (back pain, high loss). If nephrolithiasis is suspected (renal colic episodes, kidney gravel, recurrent urinary infections), a 24-h urinary biochemical stone profile should be obtained and renal imaging performed.

Recommendations

- **38. We recommend** serum calcium and creatinine measurements (and eGFR) annually (1 ØØØO).
- **39. We recommend** BMD measurements every 2 years and X-ray or VFA of the spine in the suspicion a vertebral fracture (1 ØØØO).

- **40. We recommend** renal imaging and 24-h urinary biochemical stone profile if renal stones are suspected (1 ØØOO).
- **41. We recommend** against routine annual renal imaging to discover asymptomatic renal lithiasis (1 ØOOO).

13. What does represent a clinically relevant change for recommending PTX during monitoring?

- **42.** PTX should **be recommended** if relevant changes occur during monitoring [2] (1 ØØOO):
- An increase of serum calcium greater than 1 mg/dL above the upper limit of normal range.
- A reduction of creatinine clearance below 60 mL/min.
- The occurrence of kidney stones or nephrocalcinosis.
- A BMD *T* score at any site lower than −2.5 or a significant decrease of the BMD at any site greater than the least significant change as defined by the International Society for Clinical Densitometry (even if the *T* score is greater than −2.5).
- The occurrence of a clinical fragility fracture.
- The detection of a morphometric vertebral fracture, even if asymptomatic.

14. How should a pregnant woman with mild PHPT be evaluated and managed?

The evaluation of a pregnant woman with PHPT is not different from that carried out in the occasional patient. However, at least three points should be considered: firstly, since normal pregnancy is associated with hemodilution related to extravascular fluid expansion and sometimes with gestational hypo-albuminemia, it would be preferable to measure serum ionized calcium. Secondly, neck ultrasound plays a major role in the localization of hyper-functioning parathyroid tissue; other techniques such as for example, scintigraphy or computed tomography should be avoided. Thirdly, given the young age of pregnant women, hereditary forms of the disease should be excluded [88]. Patients with modest elevations of serum calcium can be managed with conservative therapy, mainly intensive hydration. If there is a worsening of hypercalcemia, PTX during the second trimester [88, 89] and cinacalcet [90] can also be considered.

Recommendations

- **43. We recommend** that the majority of pregnant women be managed conservatively (1 ØOOO).
- **44. We suggest** PTX in very selected pregnant women with mild PHPT and deterioration of hypercalcemia (2 ØØOO).

15. How should a patient with a syndromic form of mild PHPT be evaluated/managed?

Patients with a syndromic form of mild PHPT should be evaluated for detecting other manifestations of the disease. Patients with MEN1-associated PHPT or carriers of germline *MEN1* mutations should undergo a biochemical evaluation including a complete gastrointestinal hormonal profile (gastrin, insulin associated with fasting glucose, chromogranin A, pancreatic polypeptide, glucagon, VIP, prolactin and IGF-I) [91]. Imaging investigation should include abdominal MRI or CT or endoscopic ultrasounds for the detection of pancreatic neuroendocrine tumors and adrenal tumors, pituitary MRI for adenomas and chest CT (or MRI) for the detection of thymic and bronchial carcinoids. Patients with germline *HRPT2/CDC73* mutations should be evaluated for the presence of jaw tumors, kidney tumors and gonadal tumors.

Familial history should be carefully investigated to identify relatives affected by PHPT and/or diseases associated with PHPT in the syndromic forms: pituitary tumors, adrenal neoplasia, thyroid carcinomas, jaw tumors, kidney tumors, gonadal tumors and pancreatic neuroendocrine tumors. Physical examination might reveal neck mass, arterial blood hypertension, signs of pituitary hyper- or hypofunction.

Recommendations

- **45. We recommend** that patients with syndromic and familial forms of PHPT be evaluated for detecting associated disorders (1 ØØOO).

Conflict of interest The authors declare they have no conflict of interest.

Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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