Primary hyperparathyroidism: Skeletal and non-skeletal effects, diagnosis and management

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ABSTRACT

Primary hyperparathyroidism (PHPT) is the third most common endocrinopathy seen today, and is most frequently found in the 6th to 7th decade of life. PHPT can present with various degrees of symptoms, and can affect many organ systems, including the skeletal, renal, central nervous system and cardiovascular system. Despite this, the most common presentation of hyperparathyroidism is “asymptomatic” with the diagnosis being made incidentally with the initial finding of hypercalcemia on routine laboratory studies, leading to further investigation. Surgical versus medical management is usually based on factors such as age and complications related to hyperparathyroidism (i.e. the presence of renal stones, renal insufficiency and bone loss and significant increases in serum calcium). Treatment options include parathyroidecomy, bisphosphonates, calcitonin and calcimetics.

In this review, we discuss primary hyperparathyroidism in detail with a focus on clinical manifestations particularly in the elderly population. We highlight the indications for surgical versus medical management and compare some of the uses of newer therapeutic agents relative to traditional ones.

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1. Introduction

Primary hyperparathyroidism is a common endocrine disorder of the 6th to 7th decade of life. Recent research reveals that parathyroid hormone (PTH), besides its well described effect on mineral metabolism and bone, also affects different organs, including the nervous and cardiovascular system. In this article, we will review the current data on the clinical implication of “asymptomatic” hyperparathyroidism, its presentation and management.

2. Definition

Primary hyperparathyroidism is due to increased intrinsic activity of the parathyroid gland, altering the secretion of parathyroid hormone, in the absence of a known or recognized stimulus (affecting calcium homeostasis).

3. Epidemiology

Primary hyperparathyroidism (PHPT) is the 3rd most common endocrine disorder after diabetes and thyroid disorders. It is the most common cause of hypercalcaemia in the outpatient population, and along with malignancy associated hypercalcaemia accounts for over 90% cases of hypercalcaemia. This disorder affects 1 in 500 women and 1 in 2000 men > 40 years of age, with a peak incidence in post menopausal women (50–60 years) [1].

The prevalence depends on populations studied and the detection methods used. Biochemical screening established the prevalence at 1 per 1000 (USA). An estimation of the true incidence is difficult, but overall figures (UK, USA, and Sweden) are consistent with 27 and 30 per 100,000 person-years [1–3]. The introduction of the automated serum calcium measurement was associated with a dramatic increase in early 1970s (1974–1982 annual rate was 82.5 per 100,000), with a progressive decline in the incidence thereafter [1].

In sporadic cases, primary hyperparathyroidism results from a single enlarged gland (adenoma) in 80–85 percent cases, usually involving the lower pole of the gland and tends to consist of chief cells. Multiple gland hyperplasia accounts for approximately 10–15 percent, double adenomas for an additional 2–5 percent and parathyroid carcinoma for about 1 percent of cases of primary hyperparathyroidism [4,5]. In heritable disorders, primary hyperparathyroidism is more frequently associated with multiple abnormal parathyroid glands and a higher risk of persistent or recurrent disease [6].

4. Physiology

Calcium homeostasis relies in large part on the actions of parathyroid hormone (PTH). PTH is an 84 amino acid polypeptide that is secreted solely from the parathyroid gland. It acts primarily on bone and kidneys via PTH receptors. Serum calcium, phosphorus and Vitamin D metabolites help to regulate release of PTH [8] and are summarized in Fig. 1. PTH release is almost immediate in the setting of hypocalcemia, reaching peak values within 4–10 min with an apparent half-life of 3 min [9]. Approximately 99% of total body calcium is located in bone [9], and is the major reservoir for replenishment of serum calcium deficits. Movement of calcium in and out of the body is regulated by the intestines and kidneys while movement of calcium between extracellular fluid and bone is regulated mainly by bone itself [7]. PTH that is secreted into the circulation acts primarily on the PTH1R receptors (a G protein-coupled receptor that responds to both PTH and PTHrP) located throughout the kidneys and bone [11]. PTHrP is an important calcium regulating hormone during fetal development. In the mid-1990s, it was discovered that in bone, PTH stimulates PTH1 receptor activator of nuclear factor kβ ligand (RANKL) on the osteoblasts which in turn, promotes osteoclast differentiation and increased osteoclast activity, promoting bone resorption of calcium, further increasing serum calcium levels [10].

In the kidney, PTH acts on the PTH1R receptors located on the renal tubules which acts to increase reabsorption of calcium from urine, mostly in the thick ascending loop of Henle and distal tubules [10,11].

Furthermore, PTH acts on the kidneys to stimulate the release of alpha-hydroxylase, an enzyme that converts 25 hydroxyvitamin D, to the more active form of 1,25 hydroxyvitamin D. 1,25 hydroxyvitamin D contributes to calcium homeostasis by enhancing the absorption of calcium in the intestine from dietary intake

![Fig. 1. Secretion of PTH is controlled mainly by serum calcium through negative feedback. The G-protein coupled calcium sensing receptors located on parathyroid cells are activated when extracellular calcium is low. Whereas elevated extracellular calcium results in activation of the Gq G-protein coupled cascade via phospholipase C (PLC). This signaling inhibits the secretion of preformed PTH from storage granules in the parathyroid gland. PTH functions to raise calcium via bone resorption and renal calcium reabsorption. In the kidney, it also stimulates the metabolism of Vitamin D to its active hormonal form, 1,25(OH)2Vitamin D which in turn enhances calcium absorption from the gut. PTH also inhibits renal phosphate reabsorption Excessive PTH (in hyperparathyroidism), breaks the feedback loops.](image-url)
[10,11]. Also, 1,25 hydroxyvitamin D further increases serum calcium levels by increasing the production of osteoclasts from stem cells [13].

In 1993, Brown et al. [7,119] discovered calcium sensing receptors (CaSR), which are G protein-coupled receptor made up of 1078 amino acid residues [7,12] and are located on various tissues, including parathyroid, thyroidal C cells, intestines, bone and kidneys. These receptors respond mostly to Ca++ stimulus but can also respond to Type 1 agonists as di- or tri-valent cations (i.e. magnesium or gadolinium, or other positively charged organic molecules) and Type 2 agonists (includes various L-amino acids; yet requires some level of Ca++ as well. Activation of the CaSR located on the parathyroid by ionized Ca++ inhibits PTH secretion [7,10] and this principle underlies the targeted calcimimetic treatment to lower serum PTH in hyperparathyroidism.

CaSRs are located throughout the nephron. In the proximal convoluted tubule, the CaSR are partially responsible for excretion of inorganic phosphate, and according to some studies, may in part, help to regulate the synthesis and actions of 1,25 hydroxyvitamin D. In the thick ascending loop on Henle and distal convoluted tubules, CaSRs may help in regulating calcium absorption and excretion in hypercalcemic states as well [7].

In bone, recent evidence shows expression of CaSRs on osteoclast precursors and mature cells as well as in preosteoblasts and osteoblasts. Especially in preosteoblasts, CaSR has mitogenic properties and upon stimulation may promote cellular differentiation and enhance bone formation [7]. As a result, high calcium levels promote formation of bone while inhibiting bone resorption in the normal circumstance (Fig. 2).

5. Etiology

Abnormalities in key controlling genes, protooncogenes or tumor suppressor genes are responsible for the development of parathyroid tumors.

20–40 percent of sporadic parathyroid adenomas over express cyclin D1 [14–17], resulting in parathyroid cell proliferation. Transgenic mice in which cyclin D1 was over expressed had parathyroid cell proliferation and abnormal control of PTH secretion [18–19].

The MEN1 gene is a tumor suppressor gene also associated with sporadic nonfamilial parathyroid adenomas. Somatic inactivating mutation in the MEN1 gene was found in 12–13 percent subjects with true sporadic tumors [20–21].

Familial hyperparathyroidism is associated with gain of function of RET mutations similar to those in MEN 2A or 2B.

HRPT2 gene inactivating mutations have been described in familial hyperparathyroidism, the hyperparathyroidism-jaw tumor syndrome and associated with an increased risk of parathyroid cancer [22].

Hereditary forms of hyperparathyroidism are rare. Primary hyperparathyroidism is the earliest and most common manifestation of MEN1 (80–100 percent) with mutation in MEN-1 gene (menin) present with hypercalcemia by 40 years of age.

In contrast, primary hyperparathyroidism is associated only in 20 percent with MEN 2A, generally less severe, with inherited mutation of RET proto-oncogene.

Radiation exposure. In a retrospective analysis of patients treated with radiation for tuberculous adenitis, risk of developing an adenoma was almost zero at doses below 300 rad, but exceeded 50 percent at doses above 1200 rad [23].

Irradiation for acne could have accounted for a 2–3 fold increase in disease and a 4-fold increase was noted in atomic bomb survivors [24,25].

<table>
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<th>Table 1</th>
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<td><strong>Clinical manifestation of hypercalcemia.</strong></td>
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<td><strong>Cardiovascular</strong></td>
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<td>Arrhythmia</td>
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<td>Hypertension</td>
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<td>EKG abnormalities: prolongation of QT interval</td>
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<td><strong>Gastroenterological</strong></td>
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<td>Pancreatitis</td>
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<td>Peptic ulcer disease</td>
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<td>Abnormal peristalsis: constipation</td>
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<td>Nephrolithiasis</td>
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<td>Nephrocalcinosis</td>
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<td>Tubular injury: distal renal tubular acidosis, polyuria, nephrogenic DI</td>
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<td><strong>Acute or chronic renal failure</strong></td>
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<td><strong>Neuro-psychiatric</strong></td>
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<td>Confusion</td>
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<td>Fatigue</td>
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<td>Stupor, coma</td>
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<td>Cognitive: decreased concentration and ability to learn</td>
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<td>Depression</td>
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<td>Anxiety</td>
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<td>Muscle-skeletal</td>
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<td>Osteoporosis and osteopenia</td>
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<td>Muscle weakness</td>
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Present doses of radioactive iodine for thyrotoxicosis do not increase the incidence of primary hyperparathyroidism [26].

6. Diagnosis

Primary hyperparathyroidism is diagnosed with elevation of parathyroid hormone (PTH) (or lack of suppression) in the context of hypercalcemia. Single elevations of serum calcium level, should be confirmed by repeating the test and corrected for any factors that may influence serum calcium measurement (e.g. serum albumin level, acid-base status) [27]. PTH in human is a peptide of 84 amino acids (1–84 PTH). The standard measurement of parathyroid hormone (PTH) is the intact PTH (iPTH) immunoassay, which is very specific for 1–84 PTH. This assay can also interact with other truncated fragments of non-1–84 PTH (e.g. 7–84 PTH) in 20–60% of cases. This is clinically relevant mostly in dialysis patients, when attempting to establish the diagnosis of PHPT, in whom PTH may thus be falsely elevated [28]. Also, Familial Hypocalciuric Hypercalcaemia (also known as FHH) must be ruled out. In FHH there is a loss-of-functional mutation of the calcium-sensing receptor on the parathyroid cells. Reflecting this physiological change, the urinary fractional calcium excretion is usually less than 0.1 in FHH, whereas in PHPT, it is greater than 0.2 [120]. The clinical importance of distinguishing these entities is that PHPT is usually treated whereas hypercalcemia is usually mild in FHH and requires no specific treatment as it is not associated with complications. Furthermore, parathyroidectomy does not alter this mild hypercalcemia.

To localize a parathyroid adenoma, Sestimibi scanning can be used. Adenomas appear as an increased area of uptake following a washout of 99mTc-sestamibi. False-negatives are not infrequent and are more common with multigland hyperplasia. A negative scan is not a reason to not seek a surgical referral.

7. Clinical manifestations

7.1. Clinical presentation

The most common presentation of PHPT today is asymptomatic hypercalcemia, found routinely on blood test. The symptoms can range from nonspecific calcium homeostasis disturbances to acute presentation of hypercalcemia crisis (Table 1). In the past renal
stones, osteoporosis, and diffuse symptoms of hypercalcemia such as acute pancreatitis, peptic ulcer were the classic and common presentation [29,30], but with the use of more sensitive serum calcium assays, and more routinely prescribed biochemistry screening, this is a very rare presentation today. Out of all of these classical complications, nephrolithiasis is the most common today and seen in up to 20% [31–33] of hyperparathyroid cases. This change in the clinical spectrum over the last several decades have grown to include patients with minimal objective symptoms. These patients have been referred to as “asymptomatic.” Despite this, as many patients may suffer from minimal objective symptoms such as fatigue, constipation, polyuria, hypertension and neuropsychiatric complications. If PHPT is untreated for long periods, it leads to deterioration of the bone mineral density (BMD) and increased risk of fracture [87–90]. It is worth mentioning that clinical presentations and the degree of hypercalcemia differ between different geographic areas and may in part be explained by differences in endemic vitamin D nutrition [34–36]. The degree of hypercalcemia may be less pronounced, but the combined effect on mineral metabolism, bone mass and stone formation may be more evident in combination of PHPT and vitamin D deficiency [35,36].

7.2. Survival

Symptomatic PHPT has been linked with increase mortality of all causes [37–40]. In recent years, however, more research has focused on the effect of asymptomatic PHPT on other organs especially the cardiovascular system. It has been reported that patients suffering from chronic hyperparathyroidism are more likely to have higher all-cause mortality with a standardized mortality ratio of 2.62 [41]. The leading cause of this increased mortality in PHPT is cardiovascular followed by malignancy [41,42] as found in large cohort European studies [39,41,42]. In contrast, this was not reported in Northern American populations [43]. Even mild PTH has been reported to be associated with cardiovascular and metabolic abnormalities including diabetes mellitus, hypertension, renal diseases [41,42]. It is still unclear whether hypercalcemia, PTH or the calcium/phosphate product contributes to the worse outcomes in patients with PHPT. Elevated serum calcium itself correlated negatively with survival in a 25 year case control follow up study [40]. One large cohort study [37] revealed that PHPT itself (its duration and severity) was a risk factor in increased mortality. The effect is thought to be related to impaired renal function, which is not always detected by the serum creatinine level. In this study, other
independent risk factors contributing to mortality in PHPT were age, sex, diabetes, underlying cardiovascular disease, and weight of the diseased parathyroid removed at surgery [37]. During the Third International Workshop on asymptomatic PHPT, it was indicated that the PTH level may be a risk factor for death [34].

7.3. Effect of PTH on cardiovascular system

Cardiovascular (CVD) complications are associated with increased mortality among PHPT patients. Reported abnormalities include: hypertension, disturbances in the pressor hormones system, cardiac arrhythmias, metabolic abnormalities as well as structural and functional alterations in the cardiac and vascular wall. These include diastolic dysfunction, LVH, changes in endothelial function as well as increased vascular stiffness [44–51].

7.3.1. Cardiac function

Abnormal cardiac function, both systolic and diastolic, have been identified across the spectrum of disease severity in hyperparathyroidism, although its causality and reversibility in mild disease is controversial [52–56]. Therefore current guidelines do not include CVD complications as an indication for parathyroid surgery. It is difficult to draw firm conclusions since most data is derived from cohort studies which did not exclude pre-existing CVD risk factors. Studies which included healthy subjects with PHPT without preexisting CVD risk factors, showed no improvement of cardiac function after parathyroidectomy [55,57]. The severity of the PHPT seems to play an important role in the incidence of cardiac complications [56,57] and is consistent with data on survival [41]. PTH and calcium both have direct positive inotropic effects on the myocardium [57,58]. Patients with mild PHPT without any other known cardiovascular risk factors have a higher systolic myocardial performance at baseline, which seems to be associated with the level of PTH and Ca++. Theoretically, such a chronic inotropic effect might promote cardiac hypertrophy and explain the apparent paradox of increase mortality in PHPT. Also duration of the disease seems to influence the CVD morbidity and reversibility of the disease, suggesting early surgical intervention might be curative in the mild or early stage of the disease, prior to the occurrence of irreversible structural cardiac changes [59].

7.3.2. Hypertension and vascular smooth muscle

Hypertension (HTN) has long been associated with PHPT and is more prevalent in patients with PHPT than in the general population [60,61,72].

Large observational studies have linked elevated blood PTH levels to elevations in blood pressure. [62]. The effect initially was thought to be purely the result of elevated PTH, but recent data from NHANES revealed independent associations between low vitamin D, high PTH and hypertension [63].

The underlying mechanism of PHPT on HTN is not fully understood, PTH binds to PTH/PTHrp endothelium receptor on vascular smooth muscle cells, which activates the cAMP and reduces Ca influx in vitro settings [64–66]. This is believed to have vasodilating effect on vasculature in a physiological state. However, in the hyperparathyroid state the response of the endothelium to PTH may be altered explaining the paradox of elevated BP in PHPT. Several studies showed decreased endothelium-dependent vasodilation in patients with PHPT [67,68], which was reversed after parathyroid surgery however, this was not confirmed by other studies [69]. Of note, most of the studies did not exclude subjects with preexisting CVD risk factors such as essential hypertension and smoking, which may contribute to discordant results.

Another possible explanation for causal relation between PHPT and HTN, could be its effect on regulating hormones. Although the inverse association of vitamin D on the renin-angiotensin-aldosterone system is well established, a few small studies have reported only a weak effect of PTH on the renin-angiotensin-aldosterone system, and the topic remains open for debate [51,70,71].

Gennari showed elevated pressor hormones and vascular response to epinephrine as well as free cytosolic calcium in platelets of hypertensive PHPT patients as compared to normotensive PHPT and control patients [51]. The authors also found reversibility of these changes seen with parathyroidectomy.

In aggregate, these studies suggest that the vascular response to PHPT may depend on the underlying state of the vasculature. Whether this is a result of longstanding HTN leading to irreversible vascular changes is not known.

Thus, the question whether there is any causal relationship between HTN and PHPT remains unanswered and controversial as the reversibility of HTN by parathyroidectomy can be demonstrated in only 50% of patients [72–74]. Therefore, current guidelines do not recommend parathyroidectomy for treatment of HTN in PHPT patients.

7.4. Neuropsychiatric system

Severe hypercalcemia may result in psychosis, confusion, coma even death. In recent decades, however, research has focused on emotional or cognitive aspect of “asymptomatic” PHPT. Neuropsychiatric symptoms are mostly vague and nonspecific, particular in elderly patients, such as asthenia, anxiety, depression, irritability, mood swings, amnestic and cognitive disturbances. The prevalence of the symptoms may be as high as 12% [75], and is higher in elderly patients. It is still controversial whether PHPT with mild hypercalcemia is a cause of such symptoms and whether neuropsychiatric symptoms should be included into criteria for medical/surgical intervention.

7.4.1. Quality of life

Several prospective case-controlled, including some randomized studies were conducted in PHPT patients who underwent parathyroidectomy to assess quality of life changes. Most of this work was done by Pasieka et al. [76,77]. He developed a parathyroid assessment of symptoms (PAS) questionnaire consisting of 13 items which included physical, emotional and pain symptoms to assess changes in PHPT patients. In his 2002 multi-center prospective study, Pasieka [77] evaluated the impact of parathyroidectomy on QOL in 203 patients and showed that parathyroidectomy improved overall scores of QOL and reduced symptoms of PHPT. Another structured questionnaire, the Medical Outcomes Short Form 36 of QOL (SF-36), consisting of 8 domains of health status and function (general health, physical function, physical role limitation, mental health, emotional role limitation, social function, bodily pain, and energy/fatigue) demonstrated improvement in most or all domains after parathyroidectomy, in both symptomatic and asymptomatic patients independently of serum calcium level [78–80]. Recently, Mihai et al. [81] compared these 2 questionnaire scores (PAS and SF-36) in 101 patients who underwent parathyroidectomy and found that both correlated well with one another. Thus, the authors concluded that the PAS (a simpler system) should be used as a tool to assess changes in QOL and as a possible indicator for symptomatic disease and a reason for parathyroidectomy.

7.4.2. Cognitive function

Improvement has also been shown for neurocognitive symptoms in post-parathyroidectomy patients in several studies some of which revealed improvement of cognitive function in elderly patients. Using structured psychological testing, the ability to concentrate under stress and retentiveness, was studied in 20 patient who underwent parathyroidectomy at 6 and 12 months.
after surgery [82]. Patients' concentration and ability to memorize numbers improved significantly post-operatively. In another prospective trial [83], 41 patients who underwent parathyroid surgery showed improvement in their learning efficiency.

7.4.3. Depression

Wilhelm et al. [83] concluded a 1-year cost-effectiveness of parathyroidectomy in patients with depression. He retrospectively analyzed 360 patients who underwent parathyroidectomy using DSM-IV-R diagnostic criteria for depression. More than a half of those with pre-op depression showed improvement in their QOL and 54% reduced or discontinued their anti-depressive medications.

In conclusion, in recent decades, there is growing evidence that PHPT is associated with neuro-psychiatric changes. Parathyroidectomy showed modest improvement in these symptoms in small studies. This raises the question whether neuro-psychiatric evaluation should be implemented into the assessment of symptomatic disease and to be one of the indications for surgical or medical treatment for the condition. Larger prospective studies are needed in this area.

7.5. Bone and mineral metabolism

Bone and mineral metabolism symptoms in PHPT have changed over last decades in developed countries from classic symptoms of ostitis fibrosa cystica and kidney stones to a disease with none to few symptoms. As mentioned earlier, of all the classic presentations, nephrolithiasis is the most common nowadays and may complicate up to 20% of the PHPT cases [31–33]. However, even in “asymptomatic” disease the endogenous excess of PTH increases bone turnover leading to an insidious reversible loss of cortical (forearm and femur) and trabecular bone (axial skeleton, verte-brae/pelvis) [83]. Quantitative histomorphometric studies from iliac crest biopsies from PHPT patients after intravenous double-labelling with tetracycline have revealed a 50%-60% increase in bone turnover leading to increased extension of resorption [86–88] at the endosteal surface.

Most studies reported decreased bone mineral density (BMD) in PHPT, in both symptomatic and asymptomatic patients [89–94]. The initial studies indicated that bone loss occurred mostly in the cortical bone while sparing the trabecular bone [92]. In contrast, a very recent prospective study of 36 PHPT female patients, assessing volumetric bone mineral density [95] with peripheral quantitative computed tomography, revealed negative effect of excess PTH on both bone types.

Parathyroidectomy has been shown to halt bone deterioration, improve BMD and reduce risk of fracture in patients with PHPT [96–98].

In a well designed study by Rao et al. [97], 216 patients with PHPT were observed (108 who underwent parathyroidectomy and 108 who did not) for 52 months and 47 months, respectively. Cessation of bone loss was demonstrated (using DEXA scanning) among the patients who underwent surgery, with corresponding Z-scores became significantly less negative over the observational period. In the longest follow-up study of bone density (15 years) DAX scanning showed that in asymptomatic PHPT 37% of patients showed progression at any point [99]. Interestingly, having surgical criteria at baseline was not predictive of progression of one loss. In a 2006 retrospective study by VanderWalde et al. [96] of a large population database, patients with PHPT who underwent parathyroidectomy compared with those who did not had reduced risk of fracture regardless of age, calcium, or parathyroid hormone level. A large cohort study [98], reported an increased risk of fracture in both cortical (forearm HR: 4.0) and trabecular (vertebra HR: 3.5) bone in 674 patients with PHPT (median age 61) followed at least 10 years prior to and 10 years after parathyroidectomy. The risk of fracture returned to normal after surgery. Based on these and other evidence, the most recent guidelines in 2009 recommended parathyroidectomy for patients with T-score less (−2.5) on BMD at any location and/or previous fracture fragility [34].

8. Therapy

With the advent of automated screening for calcium and large increase in asymptomatic, often older patients, the question of what constitutes optimal treatment arises. Several long-term and other studies informed an expert panel, The Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, which published revised guidelines for surgical and medical treatment in 2009 [34].

8.1. Surgical management

In patients with PHPT who have any one of the following criteria should undergo surgical management in order to prevent progression.

- Serum calcium >1.0 mg/dl (0.25 mmol/l).
- A reduction in CrCl <60 ml/min.
- T-score <−2.5 at any site on BMD and/or previous fracture fragility.
- Age <60 years.

- Surgery may also be indicated in patients whose medical surveillance is neither desired nor possible.
- Some physicians still use the older indication of 24h calcium excretion of >400 mg as an indication for surgery; however, it has lost favor because it is only one of many factors that play a role in renal stone formation. In addition, although those with stones do tend to have elevated calcium excretion, patients with higher urinary calcium without stones have not been shown to be associated with stone formation. Lastly, other mitigating factors that play a role in calcium excretion include age, sex, race, diet, renal function and vitamin D level, hence, making the arbitrary number of 400 mg of little value [34,110].

8.2. Medical management

8.2.1. The guidelines

For patients who do not undergo surgery, the absence of clear compelling evidence, the most recent recommended guidelines for follow-up of patients includes:

- Annual serum calcium.
- Annual serum creatinine.
- Bone density every 1–2 years (three sites).

Of interest is a recent report that among the elderly with clear criteria for surgical treatment, the likelihood of parathyroidectomy decreased linearly with age [110].

Among the PHPT patients who are not candidates for surgery, the only approved medical therapy is calcimimetic drugs. The use of
bisphosphonates, estrogens and SERMS (Selective Estrogen Receptor Modulators) are not currently approved for asymptomatic PHPT. Bisphosphonates are frequently used and this practice is supported by several clinical trials. As with most acute hypercalcemia, bisphosphonates are also effective in PHPT. Table 2 shows the effect of surgical and medical treatment on key clinical markers on calcium and bone metabolism.

### 8.2.2. Bisphosphonates

Bisphosphonates are potent inhibitors of bone resorption and may be useful in long-term control of osteopenia in asymptomatic PHPT. Since a high percentage of patients are post-menopausal women, treatment targeting improvement in bone mineral density should be considered.

Intravenous (iv) pamidronate causes an acute transient decrease in calcium, urine calcium and bone turnover indicators; however, an increase in parathyroid hormone and 1,25-dihydroxyvitamin D follows, which can restrict effectiveness [100]. An improved functional independence measure was noted in elderly patients after iv pamidronate [101].

Oral alendronate is promising as seen in four studies including 119 postmenopausal women and 24 men treated up to 2 years, which reported significant increase in lumbar spine and femoral neck bone mineral density, with no substantial change in radial bone mineral density [102–105]. There was no significant effect on serum calcium and urinary calcium but significant decrease in parathyroid hormone and bone turnover markers.

In one study a fall in urine deoxypyridinoline was seen within the first month of treatment, while a fall in serum alkaline phosphatase and osteocalcin became significant only after 3 months of treatment; thereafter all other bone turnover markers remained consistently suppressed for duration of treatment [102].

Also noted in another study was lower serum bone specific alkaline phosphate activity, a decrease in osteocalcin and urinary N-telopeptide. These markers of bone turnover increased 24 weeks after treatment was withdrawn [104].

However, there has been no documentation of benefit of bisphosphonate therapy as being sustained and accompanied by a decrease in fracture incidence.

The effect of prior bisphosphonate therapy on post-surgical bone mineral density improvement is unknown. Since bone remodeling is necessary, bisphosphonates which decrease bone turnover, may prevent post-parathyroidectomy increase in bone mass as noted in observational and randomized trials.

Hence, the widespread use of bisphosphonates in patients with primary hyperparathyroidism may not be optimal in candidates for surgery. However bisphosphonates may be used in patients who do not meet the criteria for surgery, are unwilling to have, or are unsuitable for surgery.

### 8.2.3. Cinacalcet

One of the newest targeted medical treatment options, cinacalcet, was recently approved by the US FDA (2011) and the European EMA (2008) for the treatment of primary hyperparathyroidism. Cinacalcet is a calcimimetic, that acts on the calcium-sensing receptors expressed on the parathyroid cells and sensitizes them to extracellular calcium. This results in decreased serum PTH levels, which consequently leads to a decrease in serum calcium levels [106,107].

Calcimimetics can cause modest reductions in PTH levels (about 20%), as well as stabilization of normocalcemia, it does not appear to have a significant impact on BMD [106–109]. Thus, in patients with normal BMD, cinacalcet can be a good medical therapy to reduce PTH and calcium levels, reducing the risk of other possible complications associated with primary hyperparathyroidism.

### 8.3. Vitamin D replacement in PHPT

Vitamin D deficiency is more common in PHPT than in general population, especially in frail elderly patients [111,112]. Current guidelines recommend measurement and replacement of vitamin D if the pre-parathyroidectomy vitamin D level is less than 20 ng/ml (50 nmol/l) [34]. The major complication of low vitamin D levels after parathyroidectomy is hypocalcemia due to “hungry bone syndrome” [113]. Although most of the physicians supplement vitamin D prior to parathyroidectomy surgery, the safety of this practice is not known. Several small studies on patients with mild hypercalcemia (less than 12 mg/dl or 3.0 mol/l) showed that supplementation of vitamin D in PHPT patients is safe and did not cause significant worsening of hypercalcemia [114–118], even with use of high doses of vitamin D (50,000 IU). Some studies showed improvement in bone density in PHPT patients, however other did not [115,116]. The potential risk of replacing vitamin D includes hypercalcemia [115,117]. There are no prospective randomized studies, confirming that supplementation of vitamin D is safe and effective in patients with PHPT, especially elderly patients.

### 9. Conclusions

There is ample evidence that excessive parathyroid secretion has a negative effect on multiple tissues of the body in addition to the traditional targets of bone and kidney [121]. Hyperparathyroidism is associated with higher mortality due to cardiovascular and possibly oncologic and has neuropsychiatric complications. The full extent of PHPT’s effect on the cardiovascular system is not known. There seems to be strong evidence that PHPT has a negative effect on quality of life (QOL), especially in the elderly. QOL questionnaires should be considered part of the clinical evaluation on these patients. More studies on cardiovascular and neuropsychiatric evaluation should be conducted.
The diagnosis of PHPT is fairly straightforward although it is imperative to identify FHH in which surgery is not indicated. Due to the increase in prevalence and mostly asymptomatic presentation especially in the elderly, evidence and expert opinion-based national guidelines for surgical treatment have been developed. Patients who are not surgical candidates can be treated medically with targeted therapy such as calcimimetics and adequate hydration. Bisphosphonates, although used clinically in asymptomatic PHPT and supported by clinical studies showing benefit for bone density are not approved for use by regulatory agencies or the International expert panels [34]. Vitamin D replacement in the context of PHPT should be undertaken cautiously.

Contributors

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