Endocrine society hyperparathyroidism guidelines

Primary hyperparathyroidosis (FPT), the most common cause of hypercalcemia, is most common in postmenopausal women. The clinical presentation of PHPT has evolved over the past 40 years to include three different clinical phenotypes, each of which has been studied in detail and has led to the evolution of concepts about the target involvement of the organ, natural history and management. In this review, I present an evidence-based summary of this disorder, as has been studied around the world, citing key concepts and data that helped shape our understanding of the disease. It is now recognized that PHPT includes three clinical phenotypes: direct organ target involvement, mild asymptomatic hypercalcemia and high levels of PTH with consistently normal serum calcium values corrected for albumin. Factors that determine which of these clinical presentations are more likely to prevail in a country include the degree of use of biochemical screening, vitamin D deficiency and whether parathyroid hormone levels are regularly measured when assessing low bone density or outright osteoporosis. The guidelines for parathyroidectomy apply to all three clinical forms of the disease. If surgical guidelines are not met, parathyroidectomy may also be a suitable option if no medical contraindications are present. If either calcium in serum or bone mineral density is of concern and surgery is not an option, pharmacological approaches are available and effective. Advances in our knowledge of PHPT have led to new concepts in diagnostics and management. During the lifetime of many of us, primary hyperparathyroidosis (PHPT), the most common cause of hypercalcemia, appears to change in its clinical presentation regarding the involvement of classical and non-classical target organs. Progress in understanding the disease has also been noted by the use of previously unavailable technologies, which have led to the recognition of a disease that can be widespread even if accidental detection. However, this destructive potential to be widespread, a feature that was realized by the famous aphorism coined by Fuller Albright, as bone disease, stones, moans and groans (1), has a variable natural history that can remain as asymptomatic as it was when it was first discovered or progressed to clinical symptoms. Decades have also given new insights into the surgical and medical management of PHPT, as well as guidelines that have been periodically updated since 1991 (2-5). The disease, which was worthy of reports of cases in the 1930s (6), has now seen a 6,000 published report in the last 20 years. it has generated interest in the PTH molecule itself and its pleotropic cellular and molecular mechanisms of action (7, 8). The disease also catalyzed interest and new ideas into his colleague, but a much more rare disorder disorder parathyroid function, namely hypoparathyroidism (9). The disease gave us a great assessment of the bone as controlled by PTH and other molecular regulators that work according to each other to keep our skeleton and circulating elements under exquisite control under normal conditions. From this perspective, I provide an update on PHPT based on, in part, my experience investigating this disease, which has been spreading for over four decades. The diagnosis of PHPT is associated with abnormal, under-regulated PTH secretion from one or more of the four parathyroid glands (10, 11). In almost all cases, the disorder will be benign with either one adenoma (80%) or multiple glands, usually hyperplastic, disease (20%) Responsibility. PHPT is characterized by hypercalcemia and PTH levels, which are inappropriately high for the hypercalcemia state. Typically, the PTH level is frankly elevated, but it can also be within the normal range. In both situations, detectable or elevated levels of PTH are clearly inappropriate when serum calcium is elevated. The well-documented PHPT was recorded with PTH levels as low as 20 to 25 pg/mL, given the normal range of 10 to 65 pg/mL (12). In almost all other etiologys of hypercalcemia, PTH levels will be frankly suppressed (12). Intervention of substances such as biotin can lead to PTH read low with certain analyses (13). When biotin stops, a re-measurement level of PTH will be more compatible with a PHPT diagnosis if the patient has the disease. Differential diagnosis of pTH-dependent hypercalcemia includes the use of diuretic thiazide or lithium (14, 15). If possible, these medications should be discontinued. Although serum calcium will return to normal in some patients, most of them will demonstrate the preservation of PHPT biochemical traits, namely hypercalcemia and elevated PTH levels. More perplexing to some is the difference between familial hypocalcion hypercalcemia (FHH), a rare disease CASR (calcium receptor gene) and PHPT (16). It is important to recognize that FHH is a rare disease. In addition, FHH has such a high level of foamtrans that virtually all patients will be shown to have hypercalcemia at a young age, at the age of 30. Family history is also usually present. A typical postmenopausal woman who develops phPT biochemical signs in the first decade after menopause is highly unlikely to statistically have FHH. In FHH, the 24-hour calcium secretion in the urine will be very low (lt; 100 mg) and the calcium clearance/creatinine clearance ratio will be zlt;0.01. Due to PTH

calcium preservation of renal actions, low calcium calcium secretion (i.e., calcium clearance / creatinine the ratio of 0.01) can also be compatible with PHPT, especially for patients whose dietary calcium has been limited. Genetic testing for most of the majority The form of FHH (i.e. mutations in CaSR) is readily available if FHH is considered a plausible diagnosis. Normoccalcomic PHPT About 15 years ago, our team recognized the form of PHPT, which was characterized by elevated PTH levels with a consistently normal concentration of albumin-adjusted general and ionized calcium (17). An explanation of why this biochemical phenotype has been discovered and is now quite often relevant to our proactive approach to assessing osteoporosis or low bone syndromes. In these clinical settings, measuring PTH in some centers has become a normal part of the evaluation. With hypercalcemia PHPT calcium in the serum can sometimes be normal; however, with normal-comical PHPT (NPHPT), serum-adjusted calcium levels will be consistently normal. The differential diagnosis of the NPT requires the exclusion of secondary causes of PTH enhancement. Vitamin D deficiency is one of the most important secondary causes to be eliminated. Although this point inevitably leads to a discussion of the normal range of 25-hydroxyvitamin D and immediately resembles the Definition of vitamin D deficiency medicine (18) as a level of zlt;20 ng/ml (50 nmol/L), it is important to understand that the cut of the Institute of Medicine was directed primarily at the normal population without known metabolic bone diseases. In the context of the NPT, it seems reasonable to set a low threshold of 30 ng/ml (75 nmol/l), as some epidemiological studies have linked levels of 30 ng/ml to a progressive increase in PTH (19, 20). In addition, in some situations it is reasonable to aim for an even higher level of 25-hydroxyvitmein D (e.g. 40 ng/ml) to see if PTH levels become normal. Other disorders associated with secondary PTH enlargement, such as renal failure (estimated rate of glomerular filtration of zlt;60 ml/min) and malabsorption syndromes and medications such as diuretics, lithium, bisphosphonates and denosumab, should be excluded before referring to the diagnosis of NPHPT. Even after known causes of secondary PTH heights have been ruled out, the possibility of some unrecognized secondary incentives to account for this presentation will remain in some situations. It is also possible that those whose PTH levels are minimally elevated represent the outer boundary of the normal PTH distribution curve. Approximately 2.5% of the normal population probably have PTH levels in this outer, higher fringe area. Further consideration of the NPT is aimed at observing that analytic such as serum calcium will have much narrower day-to-day excursions in a person than the usual demographic range. It is possible, therefore, that some patients with NPHPT are actually hypercalcemia compared to their historically lower serum calcium values. for example, whose calcium is in the blood serum usually 9.0 mg/dL, can be considered relatively hyperkalemic, but still technically normalocaleptic, if calcium increased to 10 mg/dL. The increase in serum calcium by 1 mg/dL will still be within the normal range of the population, but for this given patient is clearly higher. The patient will represent ostensibly with NPHPT. Although not the subject of the current discussion, it should be noted that the existence of a form of PHPT with normal calcium concentration and PTH serum, which was found only in a pathological examination of abnormal parathyroid tissue, was suggested (21, 22). THE epidemiology of PHPT prevails among women, usually in their postmenopausal years, with the ratio of women to men from 3 to 4:1. Prevalence varies by country and race. In the United States, for example, the prevalence of PHPT was 0.86% (23), with racial bias that seems to favor blacks (24). Much broader estimates of prevalence were recorded under the NPT, from 0.4% to 11% (25-27). Another determinant of the epidemiology of the disease is the extent to which conventional biochemical screening is used in the country. In North America and Western Europe, where biochemical screening has been used since the early 1970s, PGTO has become and remains a relatively common disease (28). In countries such as India, where screening is not common, PHPT is much less common. Overall, however, the incidence and prevalence of PMPT has increased over the past few decades, even in countries where biochemical screening (24) was established decades ago. This could be the result of greater recognition and diagnostic pursuit of mild hypercalcemia and the likelihood that biochemical screening is even more common than before (24, 29, 30). In countries where serum calcium is regularly measured, the incidence of PDS has increased. A good recent example is China, where the incidence has increased due to the increased use of biochemical screening (10, 28, 31). In Latin America, the disease has also seen a change in incidence as screening has become common (32, 33). Etiology and Risk Factors Most patients with PHPT have single adenomatous (80%) or multiply hyperplastic (from 15% to 20%) parathyroid tissue. Multi-glandular disease can also manifest as two, and very rarely, three adenomas. Parathyroid carcinoma is rare, with 1% of all PHPT cases (11). Suspicion of parathyroid cancer should be increased when patients who are usually younger by about one decade are present with much higher levels of calcium in serum and PTH. Invariably, renal and skeletal involvement will be easily obvious. The incidence of parathyroid cancer appears to be increasing in the United States and in (28, 34). More often than not, PHPT is a sporadic disease, with no family history and no evidence for other endocrine glands involved. Genetic Genetic PHPT, which is no more than 10% of the hyperparathyroid population, may be limited to parathyroid glands or be part of multiplanetary endocrine syndrome (10). Mutations of the germline that have been associated with hereditary forms of PHPT are numerous. At least six somatic mutations (35, 36) were also described. Environmental and modifiable risk factors that have been associated with PHPT include chronically low calcium intake, decreased physical activity, higher body weight, furosemide, and hypertension (37-40). External neck irradiation (41, 42) and lithium and thiazide therapy (14, 15) are also classic risk factors. A later experience with thihiside diuretics has shown that hypercalcemia in this environment is likely to expose the underlying state of PHPT and is unlikely to be reversed when diuretic search is stopped (14). The specific aspects of PHPT Signs and Symptoms of PHPT may be associated with hypercalcemia itself, especially when serum calcium is zgt;12 mg/dL and/or if it has increased rapidly. Symptoms include polyuria, polypsia, constipation, anorexia, vomiting, dehydration, arrhythmia, and altered mental state. However, it is most likely that pcPT symptoms are not related to the hypercalcemia itself, but to its key target organs. Renality may take the form of hypercalcyria, nephrolytiasis, nephrochalcinosis and/or decreased kidney function (43). Although the incidence of these external renal manifestations has decreased, in the context of evaluation in many countries of a milder biochemical form of the disease, a later systematic examination of the kidneys among these ampoptite patients showed that stones and/or nephrochalicinosis were actually present in 21% to 55% of patients with asceptomatic PHPT (44, 45). Skeletal symptoms can take the form of any combination of fragility fractures, skeletal deformities and bone pain. In a classic setting, osteost fibrosis cystic describes the radiography features of this presentation, in which brown tumors, lytic lesions, subperoste bone resorbion phalanxes, and bone cysts seen (46, 47). When patients were first described with the amptometic PHPT, in the early 1970s, the absence of these radiographic manifestations is thought to mean that the skeleton has been released or is not yet involved. It took the advent of bone densitometry in the mid-1980s for us to assess the extent to which this mild form of disease did not spare the skeleton. It has been shown that the use of dual energy X-ray absorption (DXA), a disthalic radius of one-third, a patch of cortical bone, is low (48). The lumbar spine, the skeletal site where the trabecular bone predominates, showed a lesser degree of involvement. Areas of the hip joint, a more uniform mixture of trabecular and cortical bone, showed values that were halfway between the relatively well-preserved lumbar spine and the affected distal distal radius of sites. This model, first described in the 1980s, is still the most typical densitometric profile and reinforces the need to measure the dystal forearm in all patients with PHPT. The opposite pattern, however, can also be seen in which the lumbar spine is predominantly reduced (49). The early effects of estrogen deficiency, prior to the onset of PHPT in postmenopausal women, may explain the decrease in lumbar mineral density (BMD) in at least some of these patients. However, any picture of bone loss can be seen in PHPT, ranging from uniformly low missile defense to evenly normal missile defense. The preferential participation of a distal radius of one third in PHPT is consistent with the idea that the catabolic effects of excessive PTH will be seen first on the cortical area. Since DXA is a strong predictor of fracture risk, it was thought that in PHPT, fractures would be more commonly seen in non-vertebrate (i.e. cortical) skeletons. Two reports by Khosla et al. (50) and Vignali et al. (51), however, showed that vertebral fractures were seen with significantly higher frequency than in control populations. To address this obvious paradox, a longer power-resolution imaging technology was needed to allow for a direct assessment of the trabecular bone compartment (52), namely, that the risk of fracture increases in a site that is projected to be relatively protected by DXA results. Even histomorphometry of the bone biopsy of the swirl did not help to solve this problem (53). The technology that made, high-resolution peripheral quantitative tomography (HRp-CT) (54), showed that both cortical and trabecular bone compartments adversely affect PHPT (55-57). In the Stein et al. (55) study, the trabecular microstructure was further analyzed using individual trabecular segmentation analysis. The topology of trabecular indices favored vertically oriented rods, a spatial arrangement that is suboptimal for bone strength. Although HRp-CT is only available in research centers and is thus not evaluated by most clinicians, the trabecular bone score (TBS), which can identify certain aspects of bone quality from the DXA lumbar spine, is available to anyone whose DXA tool is installed with TBS software (58, 59). The TBS concept is comparative, i.e. the degree to which the textural microstructural patterns of the lumbar spine are more comfortable, as better (uniformly) or worse (heterogeneous) bone quality. Using TBS, Silva et al. (60) showed that lower average TBS scores were much more evident in PHPT than in reduced DXA missile defense. Similar data were Romagnoli et al.,61). Such studies reinforced the concept, documented with greater accuracy by HRp-CT, that the trabecular compartment is often involved in PHPT. Applying these new imaging technologies, it is now clear that in PHPT PHPT microstructure in both cortical and trabecular compartments is compromised by observations that are currently being welded with epidemiological studies that have shown an increased risk of fracture of the vertebrae and non-vertebrate sites with the disease. These observations have decision-making implications because the assessment of vertebral fractures and TBS is available to many physicians and can supplement information received only from DXA. Some of the most annoying clinical aspects of PHPT are neurocognitive features that have been well described but are not clearly related to the current form of the disease. Fatigue, anxiety, poor concentration, cognitive decline, and decreased quality of life have all been reported with varying frequency, resulting in some questioning whether the terminology of asymptomatic PHPT is the exact descriptor of these patients. If these complaints may be directly related to the disease, patients so suffer not promptomatic. However, attribution is uncertain. Each of these features can be seen literally in any chronic disease. They lack specificity. Even more problematic is that the demonstration of reversibility after successful parathyroid surgery in carefully conducted clinical trials was inconclusive (62-66). Nervous, cardiovascular, rheumatological and gastrointestinal systems are additional targets of PHPT. When the disease was typically symptomatic, all these systems were described as common manifestations of the disease; however, they are not currently regarded as a clinical problem, with the exception of classic PHPT or in specialized settings (11, 12, 43). Summary of variable clinical expressions PHPT Symptomatic Disorder In an era described between 1930 and 1970, PHPT is generally considered a symptomatic disorder with apparent skeletal and renal complications (67). Radiology, salt and pepper degranulation of the skull, distal narrowing of the collarbone, bone resorbion phalanx, bone cysts, and brown tumors were common. Stones and nephrocalcinosis were renal manifestations. Proximal muscle weakness was caused by impaired function of muscle fibers type 2 (68). Asymptomatic disorder In the 1970s, with widespread biochemical screening, amptometic PHPT became the predominant clinical form. Because PHPT was detected by accident, the open radiological features of PHPT essentially disappeared and the frequency of kidney stones plummeted. Proximal muscle weakness was no longer seen (69). It was reasonable, with tools in our disposable in the 1970s, to describe these subjects with PHPT as amptomatic because they do not have any classic organ signs or symptoms of the disease. Normocalemic Disorder Took another four decades, than the normal-icalemanic variant of PHPT was described in the first decade of the 21st century (17). It was in patients rated for low bone mass or frank osteoporosis (17, 70-75). However, when NPHPT was first described, it was not aritimptomic, but rather related to open bone loss, an observation that spoke of a proactive approach to bone loss syndromes in which PTH became a standard part of the assessment. With early descriptions of NPHPT, the arifmptomatic variant was described when unsuspecting populations are tested with serum calcium and PTH levels (76). Thus, the NPT may be arithmetic or symptomatic (63). These two forms of NPHPT, symptomatic and arifmptomatic, correspond to two forms of the more traditional hypercalcemia variant of the disease. The worldview of how PHPT can present these three different PHPT presentations followed a timeline with a symptomatic form described first and then by the arifmptomic PHPT, and, most recently, NPHPT. While this historical perspective is valuable, it is important to recognize that these three forms of PCPT exist simultaneously in today's world. It can be said that these three forms of PHPT have always coexisted. The preponderance of one option over another would depend on several factors, which tended to vary from country to country. In countries where biochemical screening is still not a regular part of the health care system, symptomatic FTA is probably the most common form of the disease. Since hypercalcemia will only be detected in the context of symptoms, PHPT will be treated in these countries as a rare disease. India may be the best example of this form of PPT (77). In countries where biochemical screening is common, such as in Western Europe, North America and many other parts of the world, there is probably amptomy PTA and will be assessed as a fairly common disease. Parentetically, as noted, the use of the term asymptomatic probably requires some adjustment, if only semantically, because with the large imaging tools applied to this population, it is obvious that such patients can often be shown to have a involvement of the skeleton and/or kidneys. Finally, if PTO is regularly measured when evaluating patients with low AEDT, even in normal people, NPHPT will become the essence. Thus, all three forms of PCPT coexist with the relative incidence of variables, specific countries and practices. The assessment of current patient assessment recommendations using PHPT is summarized in Table 1 (5). Unlike approaches to many bone and mineral metabolism disorders, which measure only the lumbar spine and hip regions, DXA measurements should include a distal radius of one-third (78). In addition to DXA, further assessment of the skeleton is currently recommended due to recent that many patients with asymptomic PHPT have vertebrae involvement. So in addition to DXA, X-rays, rays, fracture assessment, or TBS should be part of a skeletal assessment. In those centres with HRp-CT, the use of HRp-CT should be seriously considered. Additional images should also apply to the kidneys, due to recent evidence that stones and/or nephrocalcinosis are often present among those with PHPT detected by accident. Recommendations include abdominal x-rays, ultrasonography or CT scan (44). A 24-hour calcium test is also highly recommended, with guidelines for a more complete biochemical profiling of the risk of urinary stone if hypercalcyria is present. Table 1.Assessment of patients with primary hyperparathyroidism Is recommended. PTH serum, calcium, phosphate, alkaline phosphate activity, kidney function tests, 25-hydroxyvitamin D 24-hour urine for calcium and creatinine BMD DXA (lumbar spine, hip, distal one-third of radius) Assessment of the vertebrae spine (radiography, CT or VFA from DXA) Stone Risk Profile (if urinary calcium zgt;400 mg/day) Abdominal imaging by radiography, ultrasonography, or CT optional HRp'CT TBS by DXA Bone Turnover Markers Treatment PHPT Surgical Surgery Management in PHPT offers the promise of definitive treatment and should be recommended for those who meet any of the criteria for surgery: hypercalcion kidney stones, hypercalcyria and other stone risk factors; T-rated qlt;2.5 at any site; '50 years' (table) ? surgery can't also be' pursued for those' who do' not meet any of these indications as ' long' as q no medical q contraindications are present and unan It's been reached among the endocrinologist, the surgeon, the surgeon, and the patient about this ' of course of action.' criteria for parathyroidectomy (50 years) is accompanied by a biochemical risk profile of the stone, putting the patient under the qlt;2.5 at any site (lumbar' spine, hip, or distal) one-thirds of the radius) vertebral' fracture by x-ray, qt,'magnetic' resonance or vfa renal' manifestations creatinine clearance'gt; threat of preoperative parathyroid localization It's an axiom in our area, that the most important aspect of paracalciuria imaging is the search for an expert parathyroid surgeon. While this is clearly true, almost all parathyroid surgeons depend on the successful preoperative localization of abnormal parathyroid tissue. Localization recently, however, high-resolution CT and four-dimensional CT have received positive attention. The centers vary depending on what is available. or preferably a combination of conditions (77). As with most procedural endeavors, surgeons who often perform parathyroidectomy and centers that have extensive experience in preoperative localization are likely to have positive results. Success rates among these surgeons and centres exceed 95% (79). Using intraoperative PTH measurements with rapid bandwidth analysis gave confidence in the likelihood of treatment after removing one or multiplying the involvement of parathyroid tissue. Intraoperative reduction of PTH should exceed 50% of the direct preoperative concentration of PTH and should be in the normal range within 15-30 minutes after the procedure. Non-surgical management Given the surgical guidelines, it is clear that those who do not meet such guidelines will not necessarily be encouraged to undergo parathyroidectomy. In these patients who do not have to undergo surgery, a reasonable monitoring protocol includes semi-annual serum calcium testing and PTH; annual or biennial DXA testing (I prefer annual testing); annual measurements of calcium in the urine, as clinically indicated; and further testing of skeletal and renal images as clinically indicated (table 3) (5). If the patient develops a surgical guide, the surgery should be seriously considered. Table 3. Guidelines for Medical Monitoring in Patients with Asymptomatic Primary Hyperparathyroidism Managed Conservative Option. The frequency of the assessment. Calcium Serum Annual Skeletal Triple DXA Every 1-2 Years Imaging Spine to Access a Fractured Vertebra if Clinically Suspected (e.g. Height Loss, Back Pain) Renal Serum Creatinine and eGFR Annually If Kidney Stones Are Clinically Suspected: 24-Hour Biochemical Stone Profile, Imaging Of the Abdominal Cavity with X-Ray, Ultrasonography, or CT Guidelines. The internal logic among many patients and some doctors is to limit calcium intake. Dietary calcium restriction, however, can be perceived as abnormal parathyroid tissue, which still retains some responsiveness to calcium fluctuations in serum, albeit at a higher level, for further increases in PTH levels (80). This does not mean that the calcium level in the serum fluctuates shrewdly as a function of calcium intake, but that parathyroid tissue may well perceive the calcium deficiency of the diet and be additionally stimulated to synthesize and secrete PTH. For these reasons, normal calcium intake, in accordance with the general recommendations of the Institute of Medicine for calcium consumption (18) should be taken by patients with PHPT. Vitamin D. A lot of evidence suggests that vitamin D deficiency in PHPT is factor for further increase in PTH (29, 80-82) and greater expression of disease activity (82-84). In addition, in countries where symptomatic PHPT has been well described, severe vitamin D deficiency is common 86). In PHPT vitamin D deficiency is more likely because PTH stimulates the conversion of 25-hydroxyvitamin D into 1.25-dihydroxyvitamin D. Although it may seem paradoxical, namely that vitamin D deficiency is a clinical problem when 25-hydroxyvitamin D level is low and active vitamin D is normal or high, this is the case. Early cohorts of patients with PHPT typically described vitamin D deficiency. This is undoubtedly because the general population is much more likely to use vitamin D supplements (83, 87). Some studies have even equated seasonal variability of PHPT biochemical indices as a function of seasonal variability in 25-hydroxyvitamin levels D (88). Although clinical observations associated with higher phPT biochemical indices and low 25-hydroxyvitamin D levels, structural skeletal indices measured by TBS (89, 90), quantitative CT (90), or HRp'CT (91) are not so clearly related. To restore vitamin D sufficiency, vitamin D3 or D2 should be used in modest amounts, starting with 1000 IU daily (5). In a randomized clinical trial, Rolighed et al. (92) showed that vitamin D at 2800 IU daily for 6 months resulted in an increase of 25-hydroxyvitamin D from 20 ng/ml to 38 ng/ml. Vitamin D supplements have not been associated with any changes in serum or urinary calcium (92). Pharmacological Guidelines Reasons for Reviewing a Pharmacological Agent for PHPT apply almost always to patients who meet the criteria for surgery but who choose not to undergo parathyroid surgery. Causes of non-parathyroid surgery when guidelines have been met include medical contraception, previous and/or several previous neck surgeries, inability to find abnormal parathyroid tissue, and patient preferences. Low bone density. Bisphosphonate, alendronate, improves the BMD of the lumbar spine without any changes in serum calcium (93-97). It has also been shown that Alendronate increases missile defense in the NPT (98). Very little data on other bisphosphonates in PHPT (99). While increased bone density would be welcome in these patients, alendronate was associated with an increased risk of fracture in a large retrospective cohort study using an insurance database. Comparisons were among those who underwent parathyroidectomy, those who were treated with alendronath, and those who simply observed without any intervention (100). The retrospective nature of this non-randomized survey, the major differences in age, baseline ADS, comorbidities, median T-assessment and frequency of osteoporosis were present among these three groups, concludes uncertain. The bias of the selection may well predetermined who would receive parathyroid surgery or alendronate, or none, and thus influenced the results. More recently, denosumab has been evaluated in a comparative study of older postmenopausal women with PHPT or osteoporosis. After 2 years, the phPT team showed more increase in BMD on the lumbar spine, full hip, and femoral neck than did the group with osteoporosis (101). Gipercalziemia. In patients who are not going to have parathyroid surgery, but who have serum calcium of zgt;1 mg/dL above the norm or symptomatic hypercalcemia present, control of pharmacological remedies may be indicated. Cinacalcet is a calciumimetic agent that can achieve this goal by virtue of its properties to bind to the calcium sensing receptor. Its calcimimetic properties lead to an intracellular effect to reduce PTH synthesis and secretion. The level of calcium in the serum is normalized in 70% of patients (102). Although the main effect of cinacalcet is to affect the synthesis of PTH, circulating levels of PTH will decrease, but only modestly. In a wide range of PHPT clinical presentations from mild to severe illness, cinacalcet has been shown to be effective as a calcium reduction agent (80, 103-105). Data for 5 years did not show any changes in missile defense (105). Hypercalcemia and the reduction of missile defense. Because the medications in PHPT seem to increase BMD or lower levels of calcium in serum, but not both, it seems reasonable to consider combination therapy with alendronath or denosumab and cinacalcet for these patients. With limited experience to date, this approach has demonstrated perspective (106, 107). The natural history of PHPT with and without surgery Long-term outcomes of those who do or do not undergo parathyroid surgery are available for ≤15 years of forward-looking monitoring (5, 64, 65, 78, 108, 109). Among those who did not underwent parathyroid surgery (108), all relevant biochemical indices remained stable, with only a tendency to increase between 13 and 15 years in serum calcium. A MISSILE was stable at all three sites until the age of 8, when the femoral neck and dystal radius of one-third began to decline. These small reductions became more apparent and were noticeable between the age of 10 and 15.Among those undergoing successful parathyroid surgery, biochemical indices quickly normalize and AUS will improve at all sites. The BMD increases first in the lumbar spine, then chronologically improvements in the hip and distal one third of the radius places. Parathyroidectomy also leads to improved skeletal microstructure and bone strength, as defined by HRp-CT and analysis of finite elements (110-112). However, during a relatively short follow-up period, high-resolution images showed improvements, no changes to TBS (110) were found. In a randomized clinical trial (113), a successful parathyroidectomy was bound, bound, only with the improvement of missile defense, but also with a decrease in the incidence of fractures (100, 109, 113). Even in the NPT, when surgical guidelines are applied as recommended, parathyroidectomy has been associated frequently, but not always, with beneficial results such as an increase in AOS (114-116). The renal system appears to be stable over time among those who have not undergone parathyroidectomy, at least in relation to serum creatinine and calcium secretion from the urinary tract. However, recurrence of kidney stones was common (108). Surgery has been associated with a decrease in calcium secretion from the urinary tract and kidney stones (117). Clinically, the risk of kidney stones appears to be significantly reduced after surgery (64, 65, 100, 108, 109). Improvements in skeletal and renal parameters in patients who demonstrate compromise in these two target bodies provide direct evidence of guidelines that recommend surgery for these patients. However, it has not been possible to show with any consistency that neurocognitive and cardiovascular features, if present, improve with surgery (43). Summing up the experience in this area, a recent meta-analysis of both randomized clinical trials and observational studies of amptomy patients with PCPT has shown no improvement in quality of life, neuropsychiatric symptoms or cardiovascular events (118). The lack of evidence for significant improvement in these areas after parathyroidectomy helps substantiate guidelines that do not include these features among the indications of surgery. Over the past 40 years, we have gained an increasing understanding of presentations, the participation of target bodies and the management of PHPT. New imaging technologies have helped to identify involvement among those who were discovered accidentally during biochemical screening. Among those present with classic symptoms, the lack of population biochemical screening, along with vitamin D deficiency, appears to be key determinants. NPHPT can be detected among those who are rated for bone loss, but can also be detected by accident. Although a successful parathyroidectomy cures the disease, the guidelines are useful because of the benign natural history in many who do not meet the criteria for surgery. In those who meet surgical recommendations but who do not have surgery, pharmacological approaches are available to reduce calcium in serum and/or improve BMD. 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