Hyperparathyroidism

John P Bilezikian, Leonardo Bandeira, Aliya Khan, Natalie E Cusano

Primary hyperparathyroidism is a common endocrine disorder of calcium metabolism characterised by hypercalcaemia and elevated or inappropriately normal concentrations of parathyroid hormone. Almost always, primary hyperparathyroidism is due to a benign overgrowth of parathyroid tissue either as a single gland (80% of cases) or as a multiple gland disorder (15–20% of cases). Primary hyperparathyroidism is generally discovered when asymptomatic but the disease always has the potential to become symptomatic, resulting in bone loss and kidney stones. In countries where biochemical screening tests are not common, symptomatic primary hyperparathyroidism tends to predominate. Another variant of primary hyperparathyroidism has been described in which the serum calcium concentration is within normal range but parathyroid hormone is elevated in the absence of any obvious cause. Primary hyperparathyroidism can be cured by removal of the parathyroid gland or glands but identification of patients who are best advised to have surgery requires consideration of the guidelines that are regularly updated. Recommendations for patients who do not undergo parathyroid surgery include monitoring of serum calcium concentrations and bone density.

Published **Online**
September 15, 2017
http://dx.doi.org/10.1016/S0140-6736(17)31430-7

Division of Endocrinology, College of Physicians and Surgeons, Columbia University, New York, NY, USA (Prof J P Bilezikian MD, L Bandeira MD, N E Cusano MD); **Division of Endocrinology and Diabetes, Agamenon Magalhães Hospital, Brazilian Ministry of Health, University of Pernambuco, Medical School, Recife, Brazil** (L Bandeira MD); **and Division of Endocrinology, McMaster University, Hamilton, ON, Canada** (Prof A Khan MD)

Correspondence to:
Prof John P Bilezikian, Department of Medicine, College of Physicians and Surgeons, Colombia University, New York, NY 10032, USA
jpb2@columbia.edu

Introduction

Primary hyperparathyroidism is a common disorder of mineral metabolism that is due to excessive secretion of parathyroid hormone from one or more of the four parathyroid glands. The clinical consequences of abnormally active parathyroid tissue are typically hypercalcaemia and concentrations of parathyroid hormone that are either clearly elevated above the normal range or inappropriately normal in the context of hypercalcaemia.[1] Primary hyperparathyroidism predominantly affects women, with studies reporting a female-to-male ratio of approximately 3–4:1.[2,3] Although several different clinical presentations of primary hyperparathyroidism are now commonly recognised, this was not always the case. In the 1930s, Albright first described the hypercalcaemic state caused by primary hyperparathyroidism as a disease of bones and stones.[4] Although the clinical presentation of primary hyperparathyroidism has changed since the years of Albright, the central target organs for potential complications of this disorder continue to be the skeleton and kidneys. The typical diagnosis of primary hyperparathyroidism is no longer accompanied by overt skeletal and renal involvement. Rather, detection of skeletal or renal involvement requires proactive testing with technologies that were not available in Albright's day. The change in the clinical phenotype of primary hyperparathyroidism has fostered another dilemma—namely, for whom among the large number of individuals with only biochemical abnormalities associated with primary hyperparathyroidism should parathyroid surgery be recommended? The Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, held in 2013, addressed this question and other issues.[5,6]

Clinical presentation

Asymptomatic primary hyperparathyroidism is the most common presentation in countries, such as the USA, Canada, and Germany, where biochemical screening is routinely implemented. Hypercalcaemia is usually not more than 0·25 mmol/L above the upper limit of the normal range (2·10–2·55 mmol/L). Overt kidney stone disease occurs in less than 20% of patients with primary hyperparathyroidism and radiologically evident bone disease is even less common.[7] Conversely, target organ involvement at presentation dominates the clinical landscape of primary hyperparathyroidism in other countries, such as China and India, where biochemical screening is not routine practice.[8] The major presentations of primary hyperparathyroidism as seen throughout the world are summarised in this Seminar. Other forms of hyperparathyroidism (ie, secondary and tertiary hyperparathyroidism) are described in detail elsewhere.[9]

Symptomatic primary hyperparathyroidism

Osteitis fibrosa cystica is the term given to the pathognomonic skeletal features of primary hyperparathyroidism that are evident by routine skeletal radiograph. The radiological features of osteitis fibrosa cystica include salt-and-pepper degranulation of the skull, tapering of the distal clavicle, subperiosteal resorption of the distal phalanges, bone cysts, and brown tumours. These radiological features can be associated with fractures, skeletal deformities, and bone pain.[10] In this symptomatic

Search strategy and selection criteria

We searched PubMed between Jan 1, 2008, and Jan 1, 2016, for the terms "primary hyperparathyroidism", "normocalcemic primary hyperparathyroidism", "parathyroid surgery", "parathyroid localization", and "primary hyperparathyroidism international". The time period for this search covers the years before and after the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism that was held in 2013. We limited the recovered entries to human patients in English. We also based this Seminar on classic literature from before 2008 that was well known to us.

phenotype of primary hyperparathyroidism, the other major target organ, the kidney, can develop kidney stones, nephrocalcinosis, and reduced renal function.[11,12] In the clinically overt phenotype of primary hyperparathyroidism, the neuromuscular system can also be involved with proximal muscle weakness.[13] The gastrointestinal tract might be prone to peptic ulcer disease and pancreatitis.[14] Involvement of the cardiovascular system is typically characterised by hypertension and accelerated atherosclerotic heart disease.[15] Neurocognitive features are also common in symptomatic primary hyperparathyroidism, including anxiety, poor concentrating ability, and cognitive decline.[16,17]

Asymptomatic primary hyperparathyroidism

With the advent of multichannel screening, the most common clinical presentation of primary hyperparathyroidism changed from symptomatic disease to its asymptomatic variant. The term asymptomatic is defined in patients with unequivocal primary hyperparathyroidism, established by laboratory testing, who display no overt signs of the disease or target organ manifestations other than hypercalcaemia.[18] The introduction of widespread screening in the USA in the early 1970s resulted in an increase in incidence of primary hyperparathyroidism by four to five times, which could almost entirely be attributed to patients discovered incidentally and who were asymptomatic.[19]

Normocalcaemic primary hyperparathyroidism

In the early 2000s, the variability of the clinical presentation of the disease broadened further with reports of patients who appeared to have primary hyperparathyroidism on the basis of persistently elevated parathyroid hormone concentrations but whose serum calcium concentrations were persistently within normal range. Early reports came from referral centres in which parathyroid hormone concentration was routinely measured in cases of suspected metabolic bone disease, even if serum calcium was within normal range.[20–23] Secondary causes for increased parathyroid hormone concentration (eg, vitamin D deficiency, malabsorption syndromes, renal insufficiency, primary hypercalciuria, other metabolic bone diseases, lithium, and thiazide diuretics) should be excluded, as these can induce parathyroid hormone stimulation. Some individuals receiving bisphosphonate or denosumab therapies for osteoporosis might also have elevations in parathyroid hormone concentration.[24] When these secondary causes are excluded, a diagnosis of normocalcaemic primary hyperparathyroidism can be made. The work of Parfitt, Rao, and Kleerekoper,[25] in the early 1990s, predicted the existence of this form of primary hyperparathyroidism and its prevalence figures vary widely, from 0·4% to 11%.[26,27]

Patients with normocalcaemic primary hyperparathyroidism often initially present for possible metabolic bone disease, and, probably due to referral bias, show more target organ involvement than patients with asymptomatic hypercalcaemic primary hyperparathyroidism, who are typically discovered incidentally.[20,21] However, when normocalcaemic primary hyperparathyroidism is sought among unselected populations, they too, as expected, are asymptomatic.[28] Thus, patients with the normocalcaemic variant of primary hyperparathyroidism, as with hypercalcaemic primary hyperparathyroidism, can have either symptomatic or asymptomatic disease.[20]

Quality of life

The "moans and groans" of primary hyperparathyroidism, first described by Albright,[4] are also characteristic of hypercalcaemic primary hyperparathyroidism. Although patients have no classic manifestations of target organ involvement,[17] excessive fatigue, difficulty concentrating, and intellectual weariness are often reported.[29] However, whether in the context of the disease identified incidentally, these symptoms can be causally linked to primary hyperparathyroidism, is unclear.[16,30–40]

Epidemiology

North America

In the USA and Canada, primary hyperparathyroidism predominantly presents as an asymptomatic disorder.[21] Overall, the prevalence of primary hyperparathyroidism in the USA was estimated at 0·86% in 2008–09.[41] Consistent with the change in diagnostic strategies, in Southern California the incidence of primary hyperparathyroidism was reported to have tripled between 1995 and 2010.[42] A 60% increase in the incidence of parathyroid cancer over this 15 year period was also reported in the USA.[43] Some differences in incidence between ethnic groups have been reported, with the disease occurring more often in African American populations than in white populations in both men and women.[42]

Europe

Similar to the epidemiology in North America, primary hyperparathyroidism in Europe most often presents as an asymptomatic disorder. Both in Sweden and Denmark, the incidence of primary hyperparathyroidism appears to be increasing, perhaps because of an increase in the use of screening methods.[44,45]

Latin America

Precise information about the prevalence and clinical presentation of primary hyperthyroidism in Latin America is conflicting. One study[46] from Latin America reported about half of patients with primary hyperparathyroidism were asymptomatic, yet another reported that 44% of patients had kidney stones.[47] However, a 2013 study[48] reported that most patients with primary hyperparathyroidism were asymptomatic.

 Published online September 15, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31430-7

Asia

In Asia, primary hyperparathyroidism is more likely to present with more marked hypercalcaemia and target organ involvement than in other regions of the world.[49,50] Nevertheless, this classic presentation is also changing. In Beijing, China several decades ago, primary hyperparathyroidism almost always presented as a symptomatic disorder.[50] More recently, in Shanghai and Hong Kong the presentation of asymptomatic disease has increased.[51–53] In other Asian countries (India, Iran, Pakistan, Saudi Arabia, and Thailand) primary hyperparathyroidism continues to present as a symptomatic disorder.[49,54–58] Thus, prevalence of primary hyperparathyroidism appears to be associated with presentation—ie, in countries where prevalence is higher, primary hyperparathyroidism tends to be more asymptomatic.

Pathophysiology

The secretion and synthesis of parathyroid hormone is controlled by the ambient circulating ionised calcium concentration. Under normal conditions, an increase in circulating ionised calcium concentration, which might not be detected by biochemical methods, will instantly suppress parathyroid hormone secretion. Similarly, an imperceptible reduction in serum calcium concentration will immediately simulate parathyroid hormone secretion. This inverse sigmoidal association between parathyroid hormone and serum calcium concentration is regulated by the calcium-sensing receptor.[59] The other principal regulator of parathyroid hormone secretion is 1,25-dihydroxyvitamin D concentration, which is also inversely associated with parathyroid hormone concentration.[60] Although not considered to be as important as calcium or 1,25-dihydroxyvitamin D, phosphate concentration does bear some association with parathyroid hormone secretion, probably as an indirect factor by influencing calcium concentration.[61] Furthermore, a potential suppressive effect of fibroblast growth factor 23 on parathyroid hormone secretion has been described.[62]

Parathyroid hormone is secreted in three distinct ways: tonic secretion, circadian dynamics (with the highest amount secreted in the morning and lowest in the evening), and a pulsatility that appears to be stochastic (occurring unpredictably, ten or more times a day). Most parathyroid hormone is secreted continuously.[63,64] In bone, parathyroid hormone acts on osteoblasts, osteocytes, and osteoclasts.[65] In the kidney, the effects of parathyroid hormone are targeted to enhance tubular calcium reabsorption, a calcium-conserving property, and enhance phosphate excretion, a phosphaturic property. The logic of this physiology would argue that patients with primary hyperparathyroidism should not have hypercalciuria. Although this argument is logical, and indeed patients with non-parathyroid hormone-dependent hypercalcaemia have greater urinary calcium excretion for a given level of hypercalcaemia than patients with parathyroid hormone-dependent hypercalcaemia, hypercalciuria is also common in primary hyperparathyroidism. Hypercalciuria caused by primary hyperparathyroidism is due to an increased filtered load of calcium that exceeds the conserving capability of the kidney.[6,11] In the context of abnormal parathyroid activity, individual parathyroid cells overproduce parathyroid hormone because they have lost their great sensitivity to the serum calcium concentration (the parathyroid adenoma), or in the context of chronic secondary stimulation or germline or somatic mutations that are normally sensitive to serum calcium concentration, a greater number of parathyroid cells are present (parathyroid gland hyperplasia).

Causes and risk factors

Primary hyperparathyroidism is most commonly due to a single benign parathyroid adenoma (approximately 80% of patients), with multiglandular disease seen in approximately 15–20% of patients.[66] Multiglandular disease usually takes the form of four-gland parathyroid hyperplasia, but multiple parathyroid adenomas have also been described. Parathyroid cancer is rare and accounts for well under 1% of all cases of primary hyperparathyroidism.[9] In most patients with primary hyperparathyroidism, the disease is sporadic, without a personal or family history of primary hyperparathyroidism or other endocrinopathies.[67,68] Risk factors associated with the development of primary hyperparathyroidism include external radiation in childhood[69,70] and exposure to lithium[71] and thiazide diuretics.[72] The genetic syndromes associated with primary hyperparathyroidism are considered major risk factors and include multiple endocrine neoplasia type 1, 2A, and 4, hyperparathyroidism-jaw tumour syndrome, familial isolated primary hyperparathyroidism, familial hypocalciuric hypercalcaemia, and neonatal severe hyperparathyroidism.[68,73,74]

Diagnosis

The albumin-corrected serum calcium concentration is usually elevated. To correct the calcium concentration for serum albumin, the measured serum calcium concentration is adjusted upward by 0·2 mmol/L for every 10 g/L by which the serum albumin is below 40 g/L. Ionised serum calcium concentration can be used for the measurement of serum calcium in centres that are equipped for accurate measurement with an instrument that has a proper ion-sensing electrode, which obviates the need for correction for albumin. Most centres, however, rely on the albumin-corrected total calcium concentration for the measurement of serum calcium. The serum phosphorus concentration is typically in the lower limit of the normal range, which is between 0·97 and 1·13 mmol/L. With clinically useful assays for parathyroid hormone, now available for several decades, the diagnosis of primary

hyperparathyroidism is straightforward. An elevated or inappropriately normal parathyroid hormone concentration essentially establishes the diagnosis of primary hyperparathyroidism.[1] The discussion about how low the concentration of parathyroid hormone can be while remaining consistent with the diagnosis of primary hyperparathryoidism is controversial.[2] Certainly, however, a parathyroid hormone concentration of 20 ng/L or higher in a hypercalcaemic setting is inappropriate and is consistent with a diagnosis of primary hyperparathyroidism.[2]

Familial hypocalciuric hypercalcaemia can be a difficult issue in the differential diagnosis of primary hyperparathyroidism. Familial hypocalciuric hypercalcaemia is an autosomal dominant disorder of the calcium-sensing receptor gene, in which the calcium-to-creatinine clearance ratio is very low (ie, <0·01). A family history of familial hypocalciuric hypercalcaemia might be present and is a very helpful clue to the diagnosis.[75,76] In patients from families in which parathyroid surgery has been unsuccessful, the possibility of familial hypocalciuric hypercalcaemia becomes more probable. Familial hypocalciuric hypercalcaemia is rarely complicated by stone and bone disease or marked hypercalcaemia. The penetrance of familial hypocalciuric hypercalcaemia is so high that almost all individuals who have the genetic mutation will become hypercalcaemic before the age of 30 years. Screening for familial hypocalciuric hypercalcaemia is thus focused on young individuals who present with hypercalcaemia and a very low clearance ratio of calcium-to-creatinine, and have a family history of hypercalcaemia or unsuccessful parathyroid surgery, or both.

Other genetic disorders that should be considered in the differential diagnosis of primary hyperparathyroidism include multiple endocrine neoplasia type 1 or 2. Screening is justified in settings of familial glandular secretory syndromes that involve the pituitary glands and pancreas (ie, multiple endocrine neoplasia type 1), or the thyroid or adrenal glands, or both (ie, multiple endocrine neoplasia type 2). If the patient also has a history suggestive of multiple endocrine neoplasia type 1 or 2, screening for these familial syndromes is important.

The clinical presentation of parathyroid cancer is very different from the presentation of typical primary hyperparathyroidism. Patients with parathyroid cancer tend to be younger by about a decade—namely, between 40 and 50 years—and the prevalence is roughly the same in women and men.[77] Serum calcium and parathyroid hormone concentrations are usually much higher than in typical primary hyperparathyroidism. Overt stone and bone disease are also common. In parathyroid surgery, the parathyroid gland can be adherent to adjacent structures and difficult to remove. Furthermore, local spread of parathyroid cancer can occur.[78] Histologically, parathyroid cancer is suspected when mitotic figures are abundant, cellular atypia is seen, and invasion of adjacent tissue including blood vessels is present.[9,79]

Evaluation

Biochemical and imaging technology are used to determine whether, and the extent to which, primary hyperparathyroidism has involved the bone and kidney. Blood is obtained to analyse concentrations of serum calcium, phosphorus, parathyroid hormone, 25-hydroxyvitamin D, and bone turnover markers (typically one bone formation and one bone resorption index); a 24-h urine test for calcium and creatinine is also done.[1,42]

Skeletal imaging depends on several modalities, the most common being dual energy x-ray absorptiometry (DXA). The classic pattern of skeletal involvement shown in DXA is greatest reduction at the distal third of the radius, a cortical site, followed by lesser degrees of skeletal involvement at the hip and lumbar spine regions endowed with a greater proportion of trabecular bone.[6,80] Although this pattern of skeletal involvement is consistent with the idea that parathyroid hormone is more catabolic at cortical sites, abnormalities can also be readily seen in trabecular bone by the trabecular bone score and high resolution peripheral quantitative tomography.[81–88] The skeletal abnormalities shown with these imaging technologies are consistent with epidemiological studies that show an overall increase in fracture incidence in primary hyperparathyroidism.[89,90] Vertebral fracture assessment, which is an interpretive adaptation of the lumbar spine DXA image, has helped to confirm that the trabecular skeleton is also at risk of fracture in primary hyperparathyroidism. These observations have led to the recommendation that skeletal evaluation in patients with primary hyperparathyroidism should go beyond three-site DXA testing and include vertebral fracture assessment, trabecular bone score, or radiography of the vertebral spine.[5]

Imaging of the kidneys shows the potential effects of primary hyperparathyroidism on its target organ. Although nephrolithiasis has declined as a clinical feature of primary hyperparathyroidism,[6] the incidence of nephrolithiasis and nephrocalcinosis is substantially higher when the kidneys are imaged by radiography, CT, or ultrasound.[90–92] This observation has led to guidance that patients with primary hyperparathyroidism should undergo a more complete analysis for biochemical stone risk constituents as well as renal imaging.[12]

Among the more complex issues related to the evaluation of primary hyperparathyroidism are the non-traditional aspects of neurocognitive and cardiovascular function. However, the fact that these so-called non-traditional features of primary hyperparathyroidism were regularly recognised when the disease presented in a classic symptomatic form, is important to recall. Thus, clear potential exists for neurocognitive and cardiovascular features to show involvement in primary hyperparathyroidism. Nevertheless, to establish unequivocally that neurocognitive and cardiovascular

 Published online September 15, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31430-7

involvement can be reproducibly shown and is reversible after successful parathyroidectomy, has been very difficult.[17,93]

Natural history

Hypercalcaemic primary hyperparathyroidism

The 15-year observational study by Rubin and colleagues[94] indicates that the natural history of asymptomatic hypercalcaemia due to primary hyperparathyroidism can be associated with biochemical and densitometric stability. Many patients who were not candidates for parathyroid surgery at the time of evaluation continued to be stable over the study period. However, a substantial number of patients developed criteria for parathyroid surgery with a tendency for worsening hypercalcaemia and reduced hip and distal radial bone density. These features of increased skeletal involvement became more evident during years 8 and 15 of this observational study.[94,95]

Normocalcaemic primary hyperparathyroidism

The natural history of normocalcaemic primary hyperparathyroidism is much less certain than the hypercalcaemic form of the disease. Normocalcaemic primary hyperparathyroidism progression was observed by Lowe and colleagues[21] in 40% of patients. However, other studies[26,96] have not confirmed these observations.

Management

Acute management

Although primary hyperparathyroidism is considered to be a disorder of mild hypercalcaemia, a presentation of primary hyperparathyroidism with markedly high serum calcium concentrations exists that can be life-threatening. Most often these patients have a history, before their presentation with life-threatening hypercalcaemia, of only mildly elevated serum calcium concentration. Occasionally, patients with life-threatening primary hyperparathyroidism present de novo without any antecedent history of hypercalcaemia. Although the initial consideration of health-care professionals when presented with this medical emergency might be malignancy, the fact that some of the highest reported values of serum calcium concentrations are due to uncontrolled primary hyperparathyroidism is important to consider. If malignancy is suspected, the serum concentration of parathyroid hormone-related protein can indicate acute hypercalcaemia caused by primary hyperparathyroidism.[97,98] Management of acute hypercalcaemia due to primary hyperparathyroidism is not different from management of other causes of life-threatening hypercalcaemia.[97] Hydration is an important treatment, followed by furosemide administration if the clinical situation permits.[9] The use of antiresorptive drugs, such as calcitonin or an intravenous bisphosphonate (pamidronate or zoledronic acid), or both, can be an important adjunct to hydration. Steroids are typically not helpful in the management of acute hypercalcaemia caused by primary hyperparathyroidism, but can be effective in multiple myeloma or hypercalcaemia due to exogenous or endogenous vitamin D production. Cinacalcet (a calcimimetic) would not be used in the setting of acute hypercalcaemia because it requires oral administration and patients with acute hypercalcaemia usually have upper gastrointestinal tract symptoms (nausea and vomiting). Rarely, parathyroidectomy, an acute, life-saving measure, is needed if the diagnosis of primary hyperparathyroidism is secure and all alternative treatments have been exhausted.[98,99]

Standard management and guidelines

Parathyroid surgery in patients with primary hyperparathyroidism, whose parathyroid adenoma has been localised by preoperative imaging, is very straightforward and usually results in cure of the disease.[100,101] Biochemical features of the disease and other outcome measures such as risk of kidney stones, bone mineral density, and risk of fractures, are improved after surgery.[34–36,94,102–104] No controversy exists about patients with symptomatic primary hyperparathyroidism; these patients should undergo parathyroid surgery unless there are extenuating circumstances medically or otherwise that contraindicate this general recommendation.[5,105] Beneficial effects of surgery have also been reported for patients with normocalcaemic primary hyperparathyroidism.[106,107]

What is controversial and has been the focus of four international workshops, is the role of surgery in the management of asymptomatic primary hyperparathyroidism.[5,105,108] A patient with asymptomatic disease might have some signs of target organ disease. Thus, a thorough evaluation is required for all patients with asymptomatic primary hyperparathyroidism to establish whether or not skeletal or renal involvement is present and, thus, would meet current guidelines for surgery. Guidelines were developed on the basis of the Fourth International Workshop on management of asymptomatic primary hyperparathyroidism (panel 1).[5] Note that non-classic manifestations of primary hyperparathyroidism, such as easy fatigability and intellectual weariness, are not part of the current guidelines for surgery because no causal link or reversal of involvement has been established.[12] However, many health-care professionals have had experience with patients who show neurocognitive dysfunction that improves markedly after successful surgery. Yet, many patients with neurocognitive dysfunction cannot be differentiated from patients who improve after surgery and do not notice any improvement after surgery.

Guidelines for normocalcaemic primary hyperparathyroidism were published for the first time in the proceedings of the Fourth International Workshop.[5] Treatment of patients who are hypercalcaemic should comply with the guidelines for patients with hypercalcaemic disease. In patients with normocalcaemic

Panel 1: **Guidelines for surgery in asymptomatic primary hyperparathyroidism[9]**

1 Serum calcium concentration more than 0·25 mmol/L above the upper limit of normal range
2 Skeletal involvement
   a) Reduced bone mineral density as a T score of less than –2·5 at any site (lumbar spine, hip, or distal one-third radius)
   b) Vertebral fracture by radiography, CT, or vertebral fracture assessment
3 Renal involvement
   a) Creatinine clearance less than 60 mL/min
   b) Kidney stone or nephrocalcinosis by ultrasound, CT, or abdominal radiography
4 Hypercalciuria (>400 mg per day) accompanied by a biochemical stone risk profile that places the patient at risk of kidney stones
5 Age less than 50 years

Panel 2: **Guidelines for medical monitoring of patients[9]**

1 Annual assessment of serum calcium.
2 Three-site dual energy x-ray absorptiometry scan every 1–2 years, depending on local standards of care. For a chronic disorder like primary hyperparathyroidism, in which bone density can show slow decline over time, yearly bone mineral density assessment will permit detection of such trends earlier than bone mineral density assessment every 2 years.
3 If the clinical situation changes and an intervening vertebral fracture is suspected (ie, height loss and back pain), radiograph or vertebral fracture assessment should be obtained.
4 Annual assessment of creatinine clearance and serum creatinine.
5 If renal nephrolithiasis or nephrocalcinosis is suspected, abdominal imaging with radiography, CT, or ultrasound is recommended. A 24-h biochemical stone profile might also be indicated.

primary hyperparathyroidism who develop evidence of disease progression (eg, declining bone mineral density, fracture, and kidney stones), parathyroid surgery should be considered.[5]

Surgical management

Minimally invasive parathyroidectomy under local anaesthesia and conscious sedation is the procedure of choice in many centres, based on the assumption that the parathyroid gland or glands have been identified preoperatively. To identify abnormal parathyroid tissue, preoperative localisation approaches use ultrasound, ^{99m}Tc-sestamibi scintigraphy, CT, or four-dimensional CT. Imaging is strongly recommended for patients who are to have parathyroid surgery. The exact modality used depends on technological availability.[109] CT or four-dimensional CT with or without ^{99m}Tc-sestamibi scintigraphy is used in major medical centres, but high-resolution ultrasound is also routinely used. The standard approach in centres that are not equipped to perform CT or four-dimensional CT is ultrasound or sestamibi scintigraphy, or both. Other approaches include MRI and PET. The minimally invasive parathyroidectomy approach also requires the capability to measure parathyroid hormone concentrations intraoperatively.[110] The parathyroid hormone concentration should decrease by more than 50% into the normal range within 10 min after removal of the diseased parathyroid gland or glands, which is the sign that cure has been achieved. Cure rates with parathyroidectomies are more than 98% in patients operated on by experienced parathyroid surgeons.[100,101] Although parathyroid surgery is generally reserved for patients with symptomatic primary hyperparathyroidism and for patients with asymptomatic disease who meet the surgical guideline criteria, parathyroid surgery can also be done on patients who do not meet any criteria and are free from complications of primary hyperparathyroidism. As long as no medical contraindications exist, and patients and their physicians have made an informed and agreed decision, no reason remains why parathyroid surgery cannot proceed.[5,110]

Guidance from the Fourth International Workshop is also offered to patients who do not have parathyroid surgery (panel 2).[5] If a patient meets one or more criteria in the guidelines for surgery during monitoring and no medical contraindications are found, surgery should be recommended.

Nutritional guidelines and medical management

Many patients with asymptomatic primary hyperparathyroidism do not have parathyroid surgery but are, instead, managed conservatively. Nutritional guidelines are important for all patients to consider.[111] One notion that should be dispelled is that patients with primary hyperparathyroidism should restrict their intake of calcium. Conversely, restriction of calcium intake could provide a further stimulus to abnormal parathyroid tissue to produce parathyroid hormone. National guidelines[112] recommended that calcium intake should also pertain to patients with primary hyperparathyroidism. Another important nutritional element is adequate vitamin D intake. Experimental evidence shows that patients with low vitamin D concentrations, as measured by circulating 25-hydroxyvitamin D, are at risk of more active disease.[50] Low vitamin D concentration could lead directly to further parathyroid hormone secretion from abnormal parathyroid tissue and indirectly by reduced absorption of dietary calcium. The plasma 25-hydroxyvitamin D concentration should be higher than 50 nmol/L, but some experts recommend concentrations of higher than 75 nmol/L.[5,113]

 Published online September 15, 2017 http://dx.doi.org/10.1016/S0140-6736(17)31430-7

Pharmacological approaches

Oestrogen was the first pharmacological approach to primary hyperparathyroidism and, at high doses, was associated with a reduction in serum calcium concentrations.[114–116] Cinacalcet binds to regions of the calcium-sensing receptor complex, thereby enhancing sensitivity to the ambient calcium concentration. The cinacalcet-amplified calcium signal is transmitted to the parathyroid cell and thus reduces parathyroid hormone synthesis and secretion. Cinacalcet is approved for use in primary hyperparathyroidism and parathyroid cancer.[117,118] Clinical trials[119,120] with cinacalcet show that normalisation of serum calcium concentration occurs in most patients and parathyroid hormone concentrations decrease modestly. Continued use of cinacalcet for up to 5 years provides long-term control of serum calcium concentration.[121–124] Furthermore cinacalcet does not appear to have any effect on bone mineral density. The use of the bisphosphonate, alendronate, has also been studied in primary hyperparathyroidism. In contrast to cinacalcet, the serum calcium concentration does not change but bone mineral density improves, particularly in the lumbar spine, in both women and men.[125–129] A beneficial effect of alendronate has also been reported in patients with normocalcaemic primary hyperparathyroidism.[130] Not surprisingly, the combination of cinacalcet and alendronate for primary hyperparathyroidism treatment has been of interest. Although data are not yet conclusive, this combination appears to be associated with an increase in bone density and reductions in serum calcium concentration.[131] Other antiresorptive agents have not been studied in detail in primary hyperparathyroidism. Use of the receptor activator of nuclear factor kappa-B ligand inhibitor, denosumab, is an interesting approach because it inhibits a pathway that is important in the catabolic actions of parathyroid hormone.[132]

Controversies and uncertainties

Normocalcaemic primary hyperparathyroidism

The classification of normocalcaemic primary hyperparathyroidism as a primary disorder could be questioned because of the uncertainty related to an unknown secondary stimulus that might foster raised concentrations of parathyroid hormone. Furthermore, consideration of the normal distribution range for any analyte is important. The so-called normal range of parathyroid hormone spans two standard deviations about the mean (eg, 10–65 ng/L), and some patients with normocalcaemic primary hyperparathyroidism might be healthy, but are just on the fringe of the normal distribution curve for parathyroid hormone. Patients could be three standard deviations away from the mean and still be healthy, which is improbable but possible. Another point to consider is the possibility that a patient's normal serum calcium concentration might not actually be within the normal range for the population. The variance about the mean of a given circulating element is generally narrower in an individual than the population variance for that element. A patient, for example, whose serum calcium is 2·25 mmol/L on average could be hypercalcaemic if their serum calcium concentration increases to 2·45 mmol/L. The patient's increased serum calcium concentration, however, is still within the normal population range and thus the patient would be diagnosed with normocalcaemic primary hyperparathyroidism, although they actually are hypercalcaemic considering their clinical history. The vexing issue here is that the patient's average serum calcium concentration before they developed normocalcaemic primary hyperparathyroidism, is often not known (panel 3).

***Panel 3:* Outstanding research questions**

In this Seminar, we have embedded questions for which more research is needed to clarify areas of uncertainty, which are summarised as follows. This list was adapted from discussions among the expert panel at the time of the Fourth International Workshop on the management of asymptomatic primary hyperparathyroidism.[5]

1. Normocalcaemic primary hyperparathyroidism: natural history, pathophysiology, and incidence throughout the world.
2. Vitamin D: improved understanding of the optimal nutritional and therapeutic value of 25-hydroxyvitamin D in the medical management of primary hyperparathyroidism.
3. Neurocognitive features of primary hyperparathyroidism: before and after parathyroid surgery and in patients who are followed up long-term without surgery.
4. Microstructure of bone in primary hyperparathyroidism, before and after successful surgery: these studies should include the use of high resolution peripheral quantitative tomography with the most sophisticated approaches to microstructural analysis. Trabecular bone score and reference point indentation are additional state-of-the-art approaches that need more complete investigation in primary hyperparathyroidism. Can these approaches be used to predict fracture risk before and fracture risk reduction after parathyroid surgery?
5. Is the fracture risk assessment tool sufficient to predict fracture risk in primary hyperparathyroidism? What risk factors contribute to fracture risk in primary hyperparathyroidism that are not included in the fracture risk assessment tool?
6. To what extent is a complete biochemical stone risk analysis helpful to predict stone risk in primary hyperparathyroidism? What is the incidence of kidney stones and nephrocalcinosis in patients with this history before successful parathyroidectomy?
7. Are there beneficial effects to using denosumab as a pharmacological approach to primary hyperparathyroidism?

Vitamin D

Individuals exist who have developed primary hyperparathyroidism after years of a secondary stimulus for parathyroid hormone secretion. In severe malabsorption syndromes or renal failure, secondary hyperparathyroidism has given way, at times, to the selection of a clone of parathyroid cells that takes over and becomes an adenoma.[133] This observation raises the possibility that primary hyperparathyroidism in some individuals could be due to years of unrecognised vitamin D deficiency (panel 3). However, most experts do not view vitamin D deficiency as an aetiological feature of primary hyperparathyroidism.[134] The viewpoint against vitamin D having a primary role in the pathogenesis of primary

hyperparathyroidism comes from observations that average 25-hydroxyvitamin D concentration has increased among patients with primary hyperparathyroidism over the past 10 years,[135] but the incidence of primary hyperparathyroidism has also increased.[42]

Neurocognition in primary hyperparathyroidism

Whether the non-specific neurocognitive elements of primary hyperparathyroidism are causally associated with the disease is unclear. Studies[136] so far have not definitively established this association. Furthermore, some specific neurocognitive features of primary hyperparathyroidism might exist while other neurocognitive features cannot. Further research is necessary to gain more insight into this issue (panel 3).

Fracture risk and recovery after successful surgery

Epidemiology and microstructural data support the idea of a global increase in fracture risk at all sites in primary hyperparathyroidism.[85,137] However, whether fracture risk can be accounted for by low bone mineral density and other risk factors, as described in the fracture risk assessment tool, or whether other skeletal features of primary hyperparathyroidism, such as the micro-architectural abnormalities in both cortical and trabecular compartments are important in the assessment of fracture risk, is not known. How microskeletal features change after successful parathyroid surgery and whether they are related to reduced fracture risk are further areas of uncertainty (panel 3).

Who needs surgery and who can be safely monitored?

Although the guidelines are helpful to direct the endocrinologist, surgeon, and patient in decision making, the matter is still controversial. Natural history studies clearly give support to the idea that some individuals can be safely monitored over long periods of time (panel 3).[95] The natural history studies also give support to another natural history in which the disease progresses in as many as 40% of subjects followed up for up to 15 years.[94] How these different natural histories can be sorted out in individuals who do not meet surgical guidelines at the time they are evaluated, is unclear.

Conclusion

In this Seminar, we have provided an updated account of the new concepts related to the presentation, cause, and management of primary hyperparathyroidism. The disorder presents ongoing challenges as features of its clinical recognition continue to evolve. These changes require regular access to new investigative tools with particular reference to target and off-target manifestations as well as reconsideration of concepts of surgical and non-surgical management.

Contributors

JPB conceived, organised, and wrote the Seminar. NEC, AK, and LB assisted in writing. All authors provided editorial revisions.

Declaration of interests

We declare no competing interests.

References

1 Bandeira F, Griz L, Chaves N, et al. Diagnosis and management of primary hyperparathyroidism—a scientific statement from the Department of Bone Metabolism, the Brazilian Society for Endocrinology and Metabolism. *Arq Bras Endocrinol Metabol* 2013; **57:** 406–24.

2 Yu N, Donnan PT, Murphy MJ, Leese GP. Epidemiology of primary hyperparathyroidism in Tayside, Scotland, UK. *Clin Endocrinol (Oxf)* 2009; **71:** 485–93.

3 Gasser RW. Clinical aspects of primary hyperparathyroidism: clinical manifestations, diagnosis, and therapy. *Wien Med Wochenschr* 2013; **163:** 397–402.

4 Albright F, Aub JC, Bauer W. Hyperparathyroidism: a common and polymorphic condition as illustrated by seventeen proved cases from one clinic. *J Am Med Assoc* 1934; **102:** 1276–87.

5 Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *J Clin Endocrinol Metab* 2014; **99:** 3561–69.

6 Silverberg SJ, Bilezikian JP. Asymptomatic primary hyperparathyroidism. In: Bilezikian JP, Marcus R, Levine M, Marcocci C, Silverberg SJ, Potts JT, eds. The parathyroids, 3rd edn. USA: Elsevier, 2015: 317–27.

7 Bilezikian JP. Primary hyperparathyroidism. In: De Groot LJ, Chrousos G, Dungan K, et al, eds. Endotext. South Dartmouth: MDText.com Inc, 2017.

8 Bandeira F, Correia A. Clinical presentation of primary hyperparathyroidism: a global perspective. In: Bilezikian J, Marcus R, Levine MA, Marcocci C, Silverberg SJ, Potts JT Jr, eds. The parathyroids, 3rd edn. USA: Elsevier, 2015: 309–14.

9 Cetani F, Marcocci C. Parathyroid carcinoma. In: Bilezikian JP, Marcus R, Levine MA, Marcocci C, Silverberg SJ, Potts JT Jr, eds. The parathyroids, 3rd edn. USA: Elsevier, 2015: 409–22.

10 Bandeira F, Cusano NE, Silva BC, et al. Bone disease in primary hyperparathyroidism. *Arq Bras Endocrinol Metabol* 2014; **58:** 553–61.

11 Lila AR, Sarathi V, Jagtap V, Bandgar T, Menon PS, Shah NS. Renal manifestations of primary hyperparathyroidism. *Indian J Endocrinol Metab* 2012; **16:** 258–62.

12 Silverberg SJ, Clarke BL, Peacock M, et al. Current issues in the presentation of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab* 2014; **99:** 3580–94.

13 Patten BM, Bilezikian JP, Mallette LE, Prince A, Engel WK, Aurbach GD. Neuromuscular disease in primary hyperparathyroidism. *Ann Intern Med* 1974; **80:** 182–93.

14 Abboud B, Daher R, Boujaoude J. Digestive manifestations of parathyroid disorders. *World J Gastroenterol* 2011; **17:** 4063–66.

15 Fitzpatrick LA, Bilezikian JP, Silverberg SJ. Parathyroid hormone and the cardiovascular system. *Curr Osteoporos Rep* 2008; **6:** 77–83.

16 Walker MD, McMahon DJ, Inabnet WB, et al. Neuropsychological features in primary hyperparathyroidism: a prospective study. *J Clin Endocrinol Metab* 2009; **94:** 1951–58.

17 Walker MD, Rubin M, Silverberg SJ. Nontraditional manifestations of primary hyperparathyroidism. *J Clin Densitom* 2013; **16:** 40–47.

18 Silverberg SJ, Walker MD, Bilezikian JP. Asymptomatic primary hyperparathyroidism. *J Clin Densitom* 2013; **16:** 14–21.

19 Heath H 3rd, Hodgson SF, Kennedy MA. Primary hyperparathyroidism. Incidence, morbidity, and potential economic impact in a community. *N Engl J Med* 1980; **302:** 189–93.

20 Cusano N, Silverberg SJ, Bilezikian J. Normocalcemic PHPT. In: Bilezikian J, Marcus R, Levine MA, Marcocci C, Silverberg SJ, Potts JT Jr, eds. The parathyroids, 3rd edn. USA: Elsevier, 2015: 331–37.

21 Lowe H, McMahon DJ, Rubin MR, Bilezikian JP, Silverberg SJ. Normocalcemic primary hyperparathyroidism: further characterization of a new clinical phenotype. *J Clin Endocrinol Metab* 2007; **92:** 3001–05.

22 Amaral LM, Queiroz DC, Marques TF, Mendes M, Bandeira F. Normocalcemic versus hypercalcemic primary hyperparathyroidism: more stone than bone? *J Osteoporos* 2012; **2012:** 128352.

23 Charopoulos I, Tournis S, Trovas G, et al. Effect of primary hyperparathyroidism on volumetric bone mineral density and bone geometry assessed by peripheral quantitative computed tomography in postmenopausal women. *J Clin Endocrinol Metab* 2006; **91:** 1748–53.

24 Nakamura Y, Kamimura M, Ikegami S, et al. Changes in serum vitamin D and PTH values using denosumab with or without bisphosphonate pre-treatment in osteoporotic patients: a short-term study. *BMC Endocr Disord* 2015; **15:** 81.

25 Parfitt AM, Rao DS, Kleerekoper M. Asymptomatic primary hyperparathyroidism discovered by multichannel biochemical screening: clinical course and considerations bearing on the need for surgical intervention. *J Bone Miner Res* 1991; **6** (suppl 2)**:** S97–124.

26 Kontogeorgos G, Trimpou P, Laine CM, Oleröd G, Lindahl A, Landin-Wilhelmsen K. Normocalcaemic, vitamin D-sufficient hyperparathyroidism—high prevalence and low morbidity in the general population: a long-term follow-up study, the WHO MONICA project, Gothenburg, Sweden. *Clin Endocrinol (Oxf)* 2015; **83:** 277–84.

27 Vignali E, Cetani F, Chiavistelli S, et al. Normocalcemic primary hyperparathyroidism: a survey in a small village of Southern Italy. *Endocr Connect* 2015; **4:** 172–78.

28 Cusano NE, Maalouf NM, Wang PY, et al. Normocalcemic hyperparathyroidism and hypoparathyroidism in two community-based nonreferral populations. *J Clin Endocrinol Metab* 2013; **98:** 2734–41.

29 Cope O. The study of hyperparathyroidism at the Massachusetts General Hospital. *N Engl J Med* 1966; **274:** 1174–82.

30 Amstrup AK, Rejnmark L, Mosekilde L. Patients with surgically cured primary hyperparathyroidism have a reduced quality of life compared with population-based healthy sex-, age-, and season-matched controls. *Eur J Endocrinol* 2011; **165:** 753–60.

31 Caillard C, Sebag F, Mathonnet M, et al. Prospective evaluation of quality of life (SF-36v2) and nonspecific symptoms before and after cure of primary hyperparathyroidism (1-year follow-up). *Surgery* 2007; **141:** 153–60.

32 Pasieka JL, Parsons LL, Demeure MJ, et al. Patient-based surgical outcome tool demonstrating alleviation of symptoms following parathyroidectomy in patients with primary hyperparathyroidism. *World J Surg* 2002; **26:** 942–49.

33 Veras A, Maia J, Mesquita P, Eufrazino C, Bandeira F. Lower quality of life in longstanding mild primary hyperparathyroidism. *Arq Bras Endocrinol Metabol* 2013; **57:** 139–43.

34 Rao DS, Phillips ER, Divine GW, Talpos GB. Randomized controlled clinical trial of surgery versus no surgery in patients with mild asymptomatic primary hyperparathyroidism. *J Clin Endocrinol Metab* 2004; **89:** 5415–22.

35 Ambrogini E, Cetani F, Cianferotti L, et al. Surgery or surveillance for mild asymptomatic primary hyperparathyroidism: a prospective, randomized clinical trial. *J Clin Endocrinol Metab* 2007; **92:** 3114–21.

36 Bollerslev J, Jansson S, Mollerup CL, et al. Medical observation, compared with parathyroidectomy, for asymptomatic primary hyperparathyroidism: a prospective, randomized trial. *J Clin Endocrinol Metab* 2007; **92:** 1687–92.

37 Perrier ND, Balachandran D, Wefel JS, et al. Prospective, randomized, controlled trial of parathyroidectomy versus observation in patients with "asymptomatic" primary hyperparathyroidism. *Surgery* 2009; **146:** 1116–22.

38 Rolighed L, Rejnmark L, Sikjaer T, et al. No beneficial effects of vitamin D supplementation on muscle function or quality of life in primary hyperparathyroidism: results from a randomized controlled trial. *Eur J Endocrinol* 2015; **172:** 609–17.

39 Aberg V, Norenstedt S, Zedenius J, et al. Health-related quality of life after successful surgery for primary hyperparathyroidism: no additive effect from vitamin D supplementation: results of a double-blind randomized study. *Eur J Endocrinol* 2015; **172:** 181–87.

40 Webb SM, Puig-Domingo M, Villabona C, Munoz-Torres M, Farrerons J, Badia X. Development of a new tool for assessing health-related quality of life in patients with primary hyperparathyroidism. *Health Qual Life Outcomes* 2013; **11:** 97.

41 Press DM, Siperstein AE, Berber E, et al. The prevalence of undiagnosed and unrecognized primary hyperparathyroidism: a population-based analysis from the electronic medical record. *Surgery* 2013; **154:** 1232–38.

42 Yeh MW, Ituarte PH, Zhou HC, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *J Clin Endocrinol Metab* 2013; **98:** 1122–29.

43 Lee PK, Jarosek SL, Virnig BA, Evasovich M, Tuttle TM. Trends in the incidence and treatment of parathyroid cancer in the United States. *Cancer* 2007; **109:** 1736–41.

44 Abood A, Vestergaard P. Increasing incidence of primary hyperparathyroidism in Denmark. *Dan Med J* 2013; **60:** A4567.

45 Dalemo S, Hjerpe P, Bostrom Bengtsson K. Diagnosis of patients with raised serum calcium level in primary care, Sweden. *Scand J Prim Health Care* 2006; **24:** 160–65.

46 Bandeira F, Griz L, Caldas G, Bandeira C, Freese E. From mild to severe primary hyperparathyroidism: the Brazilian experience. *Arq Bras Endocrinol Metabol* 2006; **50:** 657–63.

47 Spivacow FR, Martinez C, Polonsky A. Primary hyperparathyroidism: postoperative long-term evolution. *Medicina* 2010; **70:** 408–14 (in Spanish).

48 Eufrazino C, Veras A, Bandeira F. Epidemiology of primary hyperparathyroidism and its non-classical manifestations in the city of Recife, Brazil. *Clin Med Insights Endocrinol Diabetes* 2013; **6:** 69–74.

49 Pradeep PV, Jayashree B, Mishra A, Mishra SK. Systematic review of primary hyperparathyroidism in India: the past, present, and the future trends. *Int J Endocrinol* 2011; **2011:** 921814.

50 Bilezikian JP, Meng X, Shi Y, Silverberg SJ. Primary hyperparathyroidism in women: a tale of two cities—New York and Beijing. *Int J Fertil Womens Med* 2000; **45:** 158–65.

51 Zhao L, Liu JM, He XY, et al. The changing clinical patterns of primary hyperparathyroidism in Chinese patients: data from 2000 to 2010 in a single clinical center. *J Clin Endocrinol Metab* 2013; **98:** 721–28.

52 Liu JM, Cusano NE, Silva BC, et al. Primary hyperparathyroidism: a tale of two cities revisited—New York and Shanghai. *Bone Res* 2013; **1:** 162–69.

53 Lo CY, Chan WF, Kung AW, Lam KY, Tam SC, Lam KS. Surgical treatment for primary hyperparathyroidism in Hong Kong: changes in clinical pattern over 3 decades. *Arch Surg* 2004; **139:** 77–82.

54 Gopal RA, Acharya SV, Bandgar T, Menon PS, Dalvi AN, Shah NS. Clinical profile of primary hyperparathyroidism from western India: a single center experience. *J Postgrad Med* 2010; **56:** 79–84.

55 Malabu UH, Founda MA. Primary hyperparathyroidism in Saudi Arabia: a review of 46 cases. *Med J Malaysia* 2007; **62:** 394–97.

56 Prasarttong-Osoth P, Wathanaoran P, Imruetaicharoenchoke W, Rojananin S. Primary hyperparathyroidism: 11-year experience in a single institute in Thailand. *Int J Endocrinol* 2012; **2012:** 952426.

57 Hamidi S, Soltani A, Hedayat A, Kamalian N. Primary hyperparathyroidism: a review of 177 cases. *Med Sci Monit* 2006; **12:** CR86–9.

58 Biyabani SR, Talati J. Bone and renal stone disease in patients operated for primary hyperparathyroidism in Pakistan: is the pattern of disease different from the west? *J Pak Med Assoc* 1999; **49:** 194–98.

59 Brown EM. Role of the calcium-sensing receptor in extracellular calcium homeostasis. *Best Pract Res Clin Endocrinol Metab* 2013; **27:** 333–43.

60 Segersten U, Correa P, Hewison M, et al. 25-hydroxyvitamin D (3)-1alpha-hydroxylase expression in normal and pathological parathyroid glands. *J Clin Endocrinol Metab* 2002; **87:** 2967–72.

61 Naveh-Many T, Rahamimov R, Livni N, Silver J. Parathyroid cell proliferation in normal and chronic renal failure rats. The effects of calcium, phosphate, and vitamin D. *J Clin Invest* 1995; **96:** 1786–93.

62 Ben-Dov IZ, Galitzer H, Lavi-Moshayoff V, et al. The parathyroid is a target organ for FGF23 in rats. *J Clin Invest* 2007; **117:** 4003–08.

63 Herfarth K, Schmidt-Gayk H, Graf S, Maier A. Circadian rhythm and pulsatility of parathyroid hormone secretion in man. *Clin Endocrinol (Oxf)* 1992; **37:** 511–19.

64 Schmitt CP, Schaefer F, Bruch A, et al. Control of pulsatile and tonic parathyroid hormone secretion by ionized calcium. *J Clin Endocrinol Metab* 1996; **81:** 4236–43.

65 Silva BC, S Kousteni. Cellular actions of PTH. Osteoblasts, osteoclasts, and osteocytes. In: Bilezikian JP, ed. The parathyroids, 3rd edn. USA: Elsevier, 2015: 127–37.

66 Baloch ZW, Livolsi VA. Parathyroids: Morphology and Pathology. In: Bilezikian JP, Marcus R, Levine MA, Marocci C, Silverberg SJ, Potts JT Jr, eds. The parathyroids, 3rd edition. USA: Elsevier, 2015: 23–36.

67 Bandeira L, Bilezikian J. Primary hyperparathyroidism. *F1000Res* 2016; published online Jan 4. DOI:10.12688/f1000research.7039.1.

68 Marx SJ. Hyperparathyroid and hypoparathyroid disorders. *N Engl J Med* 2000; **343:** 1863–75.

69 Cohen J, Gierlowski TC, Schneider AB. A prospective study of hyperparathyroidism in individuals exposed to radiation in childhood. *JAMA* 1990; **264:** 581–84.

70 Boehm BO, Rosinger S, Belyi D, Dietrich JW. The parathyroid as a target for radiation damage. *N Engl J Med* 2011; **365:** 676–78.

71 Szalat A, Mazeh H, Freund HR. Lithium-associated hyperparathyroidism: report of four cases and review of the literature. *Eur J Endocrinol* 2009; **160:** 317–23.

72 Griebeler ML, Kearns AE, Ryu E, et al. Thiazide-associated hypercalcemia: incidence and association with primary hyperparathyroidism over two decades. *J Clin Endocrinol Metab* 2016; published online Jan 11. DOI: 10.1210/jc.2015-3964.

73 Friedman E, Sakaguchi K, Bale AE, et al. Clonality of parathyroid tumors in familial multiple endocrine neoplasia type 1. *N Engl J Med* 1989; **321:** 213–18.

74 Thakker RV, Bouloux P, Wooding C, et al. Association of parathyroid tumors in multiple endocrine neoplasia type 1 with loss of alleles on chromosome 11. *N Engl J Med* 1989; **321:** 218–24.

75 Varghese J, Rich T, Jimenez C. Benign familial hypocalciuric hypercalcemia. *Endocr Pract* 2011; **17** (suppl 1)**:** 13–17.

76 Eastell R, Brandi ML, Costa AG, D'Amour P, Shoback DM, Thakker RV. Diagnosis of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab* 2014; **99:** 3570–79.

77 Shane E. Clinical review: parathyroid carcinoma. *J Clin Endocrinol Metab* 2001; **86:** 485–93.

78 Marcocci C, Cetani F, Rubin MR, Silverberg SJ, Pinchera A, Bilezikian JP. Parathyroid carcinoma. *J Bone Min Res* 2008; **23:** 1869–80.

79 Al-Kurd A, Mekel M, Mazeh H. Parathyroid carcinoma. *Surg Oncol* 2014; **23:** 107–14.

80 Bandeira F, Cassibba S. Hyperparathyroidism and bone health. *Curr Rheumatol Rep* 2015; **17:** 48.

81 Nishiyama KK, Shane E. Clinical imaging of bone microarchitecture with HR-pQCT. *Curr Osteoporos Rep* 2013; **11:** 147–55.

82 Silva BC, Bilezikian JP. Trabecular bone score: perspectives of an imaging technology coming of age. *Arq Bras Endocrinol Metabol* 2014; **58:** 493–503.

83 Silva BC, Leslie WD, Resch H, et al. Trabecular bone score: a noninvasive analytical method based upon the DXA image. *J Bone Miner Res* 2014; **29:** 518–30.

84 Silva BC, Boutroy S, Zhang C, et al. Trabecular bone score (TBS)—a novel method to evaluate bone microarchitectural texture in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2013; **98:** 1963–70.

85 Stein EM, Silva BC, Boutroy S, et al. Primary hyperparathyroidism is associated with abnormal cortical and trabecular microstructure and reduced bone stiffness in postmenopausal women. *J Bone Miner Res* 2013; **28:** 1029–40.

86 Hansen S, Beck Jensen JE, Rasmussen L, Hauge EM, Brixen K. Effects on bone geometry, density, and microarchitecture in the distal radius but not the tibia in women with primary hyperparathyroidism: a case-control study using HR-pQCT. *J Bone Miner Res* 2010; **25:** 1941–47.

87 Silva BC, Walker MD, Abraham A, et al. Trabecular bone score is associated with volumetric bone density and microarchitecture as assessed by central QCT and HRpQCT in Chinese American and white women. *J Clin Densitom* 2013; **16:** 554–61.

88 Romagnoli E, Cipriani C, Nofroni I, et al. "Trabecular Bone Score" (TBS): an indirect measure of bone micro-architecture in postmenopausal patients with primary hyperparathyroidism. *Bone* 2013; **53:** 154–59.

89 Vignali E, Viccica G, Diacinti D, et al. Morphometric vertebral fractures in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2009; **94:** 2306–12.

90 Cipriani C, Biamonte F, Costa AG, et al. Prevalence of kidney stones and vertebral fractures in primary hyperparathyroidism using imaging technology. *J Clin Endocrinol Metab* 2015; **100:** 1309–15.

91 Cassibba S, Pellegrino M, Gianotti L, et al. Silent renal stones in primary hyperparathyroidism: prevalence and clinical features. *Endocr Pract* 2014; **20:** 1137–42.

92 Suh JM, Cronan JJ, Monchik JM. Primary hyperparathyroidism: is there an increased prevalence of renal stone disease? *AJR Am J Roentgenol* 2008; **191:** 908–11.

93 McMahon DJ, Carrelli A, Palmeri N, et al. Effect of parathyroidectomy upon left ventricular mass in primary hyperparathyroidism: a meta-analysis. *J Clin Endocrinol Metab* 2015; **100:** 4399–407.

94 Rubin MR, Bilezikian JP, McMahon DJ, et al. The natural history of primary hyperparathyroidism with or without parathyroid surgery after 15 years. *J Clin Endocrinol Metab* 2008; **93:** 3462–70.

95 Silverberg SJ, Shane E, Jacobs TP, Siris E, Bilezikian JP. A 10-year prospective study of primary hyperparathyroidism with or without parathyroid surgery. *N Engl J Med* 1999; **341:** 1249–55.

96 Garcia-Martin A, Reyes-Garcia R, Munoz-Torres M. Normocalcemic primary hyperparathyroidism: one-year follow-up in one hundred postmenopausal women. *Endocrine* 2012; **42:** 764–66.

97 Bilezikian JP. Management of acute hypercalcemia. *N Engl J Med* 1992; **326:** 1196–203.

98 Fitzpatrick LA. Acute primary hyperparathyroidism. In: Bilezikian J, Marcus R, Levine MA, Marcocci C, Silverberg SJ, Potts JT Jr, eds. The parathyroids, 3rd edn. USA: Elsevier, 2015; 401–07.

99 Schwarz P, Body JJ, Cap J, et al. The PRIMARA study: a prospective, descriptive, observational study to review cinacalcet use in patients with primary hyperparathyroidism in clinical practice. *Eur J Endocrinol* 2014; **171:** 727–35.

100 Udelsman R, Lin Z, Donovan P. The superiority of minimally invasive parathyroidectomy based on 1650 consecutive patients with primary hyperparathyroidism. *Ann Surg* 2011; **253:** 585–91.

101 Van Udelsman B, Udelsman R. Surgery in primary hyperparathyroidism: extensive personal experience. *J Clin Densitom* 2013; **16:** 54–59.

102 Vestergaard P, Mosekilde L. Cohort study on effects of parathyroid surgery on multiple outcomes in primary hyperparathyroidism. *BMJ* 2003; **327:** 530–34.

103 Vestergaard P, Mosekilde L. Parathyroid surgery is associated with a decreased risk of hip and upper arm fractures in primary hyperparathyroidism: a controlled cohort study. *J Intern Med* 2004; **255:** 108–14.

104 Mollerup CL, Vestergaard P, Frokjaer VG, Mosekilde L, Christiansen P, Blichert-Toft M. Risk of renal stone events in primary hyperparathyroidism before and after parathyroid surgery: controlled retrospective follow up study. *BMJ* 2002; **325:** 807.

105 Bilezikian JP, Khan AA, Potts JT, Jr. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the third international workshop. *J Clin Endocrinol Metab* 2009; **94:** 335–39.

106 Koumakis E, Souberbielle J-C, Payet J, et al. Individual site-specific bone mineral density gain in normocalcemic primary hyperparathyroidism. *Osteoporos Int* 2014; **25:** 1963–68.

107 Koumakis E, Souberbielle J-C, Sarfati E, et al. Bone mineral density evolution after successful parathyroidectomy in patients with normocalcemic primary hyperparathyroidism. *J Clin Endocrinol Metab* 2013; **98:** 3213–20.

108 Bilezikian JP, Potts JT Jr, Fuleihan Gel H, et al. Summary statement from a workshop on asymptomatic primary hyperparathyroidism: a perspective for the 21st century. *J Bone Miner Res* 2002; **17** (suppl 2)**:** N2–11.

109 Khan AA, Hanley DA, Rizzoli R, et al. Primary hyperparathyroidism: review and recommendations on evaluation, diagnosis, and management. A Canadian and international consensus. *Osteoporos Int* 2017; **28:** 1–19.

110 Udelsman R, Akerstrom G, Biagini C, et al. The surgical management of asymptomatic primary hyperparathyroidism: proceedings of the Fourth International Workshop. *J Clin Endocrinol Metab* 2014; **99:** 3595–606.

111 Marcocci C, Bollerslev J, Khan AA, Shoback DM. Medical management of primary hyperparathyroidism: proceedings of the fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism. *J Clin Endocrinol Metab* 2014; **99:** 3607–18.

112 Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. Dietary reference intakes for calcium and vitamin D. Washington, DC: The National Academies Press, 2011.

113 Rolighed L, Rejnmark L, Sikjaer T, et al. Vitamin D treatment in primary hyperparathyroidism: a randomized placebo controlled trial. *J Clin Endocrinol Metab* 2014; **99:** 1072–80.

114 Marcus R, Madvig P, Crim M, Pont A, Kosek J. Conjugated estrogens in the treatment of postmenopausal women with hyperparathyroidism. *Ann Intern Med* 1984; **100:** 633–40.

115 Selby PL, Peacock M. Ethinyl estradiol and norethindrone in the treatment of primary hyperparathyroidism in postmenopausal women. *N Engl J Med* 1986; **314:** 1481–85.

116 Grey AB, Stapleton JP, Evans MC, Tatnell MA, Reid IR. Effect of hormone replacement therapy on bone mineral density in postmenopausal women with mild primary hyperparathyroidism. A randomized, controlled trial. *Ann Intern Med* 1996; **125:** 360–68.

117 Sensipar FDA approved label. Highlights of prescribing information. 2011. http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/021688s017lbl.pdf (accessed March 22, 2017).

118 European Medicines Agency. Mimpara cinacalcet EPAR summary for the public. 2009. http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Summary_for_the_public/human/000570/WC500028901.pdf (accessed March 2, 2016).

119 Peacock M, Bilezikian JP, Klassen PS, Guo MD, Turner SA, Shoback D. Cinacalcet hydrochloride maintains long-term normocalcemia in patients with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2005; **90:** 135–41.

120 Khan A, Bilezikian J, Bone H, et al. Cinacalcet normalizes serum calcium in a double-blind randomized, placebo-controlled study in patients with primary hyperparathyroidism with contraindications to surgery. *Eur J Endocrinol* 2015; **172:** 527–35.

121 Iglesias P, Ais G, Gonzalez A, et al. Acute and one-year effects of cinacalcet in patients with persistent primary hyperparathyroidism after unsuccessful parathyroidectomy. *Am J Med Sci* 2008; **335:** 111–14.

122 Cetani F, Saponaro F, Banti C, et al. Cinacalcet efficacy in patients with moderately severe primary hyperparathyroidism according to the European Medicine Agency prescription labeling. *J Endocrinol Invest* 2012; **35:** 655–60.

123 Luque-Fernandez I, Garcia-Martin A, Luque-Pazos A. Experience with cinacalcet in primary hyperparathyroidism: results after 1 year of treatment. *Ther Adv Endocrinol Metab* 2013; **4:** 77–81.

124 Peacock M, Bolognese MA, Borofsky M, et al. Cinacalcet treatment of primary hyperparathyroidism: biochemical and bone densitometric outcomes in a five-year study. *J Clin Endocrinol Metab* 2009; **94:** 4860–67.

125 Rossini M, Gatti D, Isaia G, Sartori L, Braga V, Adami S. Effects of oral alendronate in elderly patients with osteoporosis and mild primary hyperparathyroidism. *J Bone Miner Res* 2001; **16:** 113–19.

126 Parker CR, Blackwell PJ, Fairbairn KJ, Hosking DJ. Alendronate in the treatment of primary hyperparathyroid-related osteoporosis: a 2-year study. *J Clin Endocrinol Metab* 2002; **87:** 4482–89.

127 Chow CC, Chan WB, Li JK, et al. Oral alendronate increases bone mineral density in postmenopausal women with primary hyperparathyroidism. *J Clin Endocrinol Metab* 2003; **88:** 581–87.

128 Khan AA, Bilezikian JP, Kung AW, et al. Alendronate in primary hyperparathyroidism: a double-blind, randomized, placebo-controlled trial. *J Clin Endocrinol Metab* 2004; **89:** 3319–25.

129 Khan AA, Bilezikian JP, Kung A, Dubois SJ, Standish TI, Syed ZA. Alendronate therapy in men with primary hyperparathyroidism. *Endocr Pract* 2009; **15:** 705–13.

130 Cesareo R, Di Stasio E, Vescini F, et al. Effects of alendronate and vitamin D in patients with normocalcemic primary hyperparathyroidism. *Osteoporos Int* 2015; **26:** 1295–302.

131 Faggiano A, Di Somma C, Ramundo V, et al. Cinacalcet hydrochloride in combination with alendronate normalizes hypercalcemia and improves bone mineral density in patients with primary hyperparathyroidism. *Endocrine* 2011; **39:** 283–87.

132 Camozzi V, Luisetto G, Basso SM, Cappelletti P, Tozzoli R, Lumachi F. Treatment of chronic hypercalcemia. *Med Chem* 2012; **8:** 556–63.

133 Ludvigsson JF, Kämpe O, Lebwohl B, Green PHR, Silverberg SJ, Ekbom A. Primary hyperparathyroidism and celiac disease: a population-based cohort study. *J Clin Endocrinol Metab* 2012; **97:** 897–904.

134 Silverberg SJ, Shane E, Dempster DW, Bilezikian JP. Vitamin D insufficiency in primary hyperparathyroidism. *Am J Med 1999*; **107:** 561–67.

135 Walker MD, Cong E, Lee JA, et al. Low vitamin D levels have become less common in primary hyperparathyroidism. *Osteoporos Int* 2015; **26:** 2837–43.

136 Walker MD, Silverberg SJ. Non-traditional manifestations of primary hyperparathyroidism. In: Bilezikian JP, Marcus R, Levine MA, Marocci C, Silverberg SJ, Potts JT Jr, eds. The parathyroids, 3rd edition. USA: Elsevier, 2015: 469–80.

137 Khosla S, Melton LJ 3rd, Wermers RA, Crowson CS, O'Fallon WM, Riggs BL. Primary hyperparathyroidism and the risk of fracture: a population based study. *J Bone Min Res 1999*; **14:** 1700–07.