Primary Hyperparathyroidism

22

Francisco Bandeira, Lívia Amaral, Paula Aragão, and Alyne Layane Pereira Lemos

Epidemiology

Primary hyperparathyroidism is not a rare disease [1–4]. The prevalence ranges from 0.4 to 82 cases per 100,000. In the study by Eufrazino et al., a prevalence of 0.78% was found, of which 81.8% were asymptomatic [5]. In addition, in recent years, there has been an increase in the diagnosis of PHPT, explained in part by the increase in requests for serum PTH. Yeh et al., observed a threefold increase in PHPT prevalence between 1995 and 2010 [6]. It is more common in subjects over 50 years of age and in postmenopausal women.

Etiology

The solitary parathyroid adenoma appears in 85–90% of the cases [3, 7]. Hyperfunction in several parathyroid glands associated with hyperplasia and multiple adenomas occurs in most other cases [1]. In this context, it is important to mention that the disorder in multiple glands represents the most usual finding in subjects who have the primary hyperparathyroidism (PHPT) familial syndromes, corresponding to about 10% of cases [7]. On the other hand, parathyroid carcinoma occurs rarely, accounting for 0.7% of all cases [3]. Furthermore familial PHPT is related to several pathological entities, such as multiple endocrine neoplasia type 1 (MEN1), type 2A (MEN2A), and type 4 (MEN4), familial hypocalciuric hypercalcemia, familial hypercalciuric hypercalcemia, jaw tumor hyperparathyroidism syndrome, familial isolated hyperparathyroidism, and neonatal severe hyperparathyroidism [8–10] (Table 22.1).

MEN1 can be considered a rare cause of PHPT, the incidence of MEN1 being about 2–4% of PHPT cases. However, PHPT is the most common endocrinopathy in the MEN1 syndrome: it is found in almost 100% of the patients over 50 years of age and constitutes the first sign of the disease in most carriers in their 20s [8]. The diagnosis of PHPT in young adults should therefore include the search for MEN1. The search for MEN1 should also be conducted in the immediate family. The prevalence of PHPT in MEN2 is lower than in MEN1 and is found in 20–30% of cases. Furthermore, the majority of patients with PHPT present clinical manifestations that are more discrete than the clinical signs demonstrated by MEN1 carriers [11].

The jaw tumor hyperparathyroidism syndrome is a rare disease. Evidence shows that bone tumors of the jaw related

Table 22.1 The genetic syndromes associated with primary hyperparathyroidism

Familiar syndrome	Clinical features	Genes
Multiple endocrine neoplasia type 1 (MEN1)	PHPT, pituitary adenomas, pancreatic adenoma tumors	*MEN1*
Multiple endocrine neoplasia type 2A (MEN2A)	PHPT, medullary thyroid cancer, pheochromocytoma	*RET*
Multiple endocrine neoplasia type 4 (MEN4)	PHPT, anterior pituitary tumors, pancreatic neuroendocrine tumors	*CDKN1B (p27)*
Familial isolated hyperparathyroidism	Isolate PHPT	*MEN1 CASR GCM2*
Hyperparathyroidism—Jaw tumor syndrome	PHPT, often parathyroid carcinoma, jaw tumors	*CDC73*

Adapted from Ref. [9]

F. Bandeira
Division of Endocrinology, Agamenon Magalhães Hospital, University of Pernambuco Medical School, Recife, PE, Brazil
e-mail: francisco.bandeira@upe.br

L. Amaral
Universidade Federal de Alagoas (UFAL), Algoas, AL, Brazil

P. Aragão · A. L. P. Lemos (✉)
Division of Endocrinology and Diabetes, Agamenon Magalhães Hospital, University of Pernambuco Medical School, Recife, Pernambuco, Brazil

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to PHPT can be outlined [12]. Parathyroid cancer has been also detected in more than 15% of cases [12].

Parathyroid carcinoma is a rare disease, accounting for less than 1% of cases. It may occur in young patients and usually presents with severe hypercalcemia and much greater PTH levels when compared to classic primary hyperparathyroidism. Severe disease such as *osteitis fibrosa cystica*, osteoporosis and multiple fractures are common. The histopathological diagnosis is difficult, due to its similarity to the adenoma. Presence of mitoses, cellular pleomorphism, vascular invasion, and invasion of adjacent tissue may facilitate differentiation [9, 10]. The genetic pathogenesis of PHPT is unclear in most cases. Some genes have been identified and are shown in Table 22.1.

Diagnosis

In familial isolated hyperparathyroidism, cases of PHPT are diagnosed in the immediate family in the absence of other endocrinopathies; this characterizes the phenotype as a hidden syndrome, such as MEN1 and MEN2 [1].

Hypercalcemia and an increase in PTH levels constitute the biochemical markers of PHPT. In normal conditions of hypercalcemia, there is an inhibition of the parathyroid glands. This inhibition is translated by low levels of PTH [7].

The majority of patients with PHPT present slightly increased levels of PTH, but up to 10% of the cases can exhibit normal to upper normal levels of PTH [13, 14]. Nevertheless, these levels are inappropriately high because of the hypercalcemia. Hypercalcemia is found in most of the cases of PHPT, but one has to consider the possibility of fluctuations in the levels of serum calcium, which could explain the normal levels of calcemia [13].

Diagnosis includes the evaluation of serum concentrations for calcium, phosphorus, albumin, alkaline phosphatase, intact PTH, 25 (OH)-D vitamin, and renal function [13, 14]. 24-h urinary calcium and the serum levels of creatinine must be evaluated in order to rule out the possibility of familial hypocalciuric hypercalcemia [15, 16].

About 40% of serum calcium is linked to albumin. Serum levels must be adjusted according to the following equation: corrected calcium = serum calcium (mg/dL) + [0.8 × (4 − serum albumin)]. The measurement of the ionized calcium can be useful in specific cases, such as subjects with hyperalbuminemia, thrombocytosis, Waldenstrom's macroglobulinemia, and myeloma, since in these subjects there is hypercalcemia with normal ionized serum calcium (artifactual hypercalcemia) [15, 17].

In a retrospective cohort with 6982 subjects, the serum ionized and total calcium were compared in patients with hypercalcemia. PTH-dependent hypercalcemia was set as total serum calcium (corrected by albumin) equal to or greater than 10.2 mg/dL or ionized calcium (technique of specific ion electrode) equal to or greater than 1.32 mmol/L with the PTH >5 pmol/L (35 pg/mL; reference values 0.9–9 pmol/L). Among these subjects, 343 had high ionized calcium, and 156 (45%) had high total calcium. In a second cohort with 203 subjects, 143 presented histologically confirmed PHPT: high ionized serum calcium was present in 141 cases (98%) and, lastly, increased total serum calcium in 108 (76%), demonstrating a greater diagnostic accuracy when ionized serum calcium was used [18].

A cohort study, based on the population of Tayside in Scotland, used the following criteria to diagnose primary hyperparathyroidism: (1) serum calcium corrected for albumin >10.22 mg/dL (reference values: 8.4–10.22 mg/dL) on at least two occasions, with serum PTH >13.5 ng/L (reference values: 4.5–31.05 ng/L), or (2) serum calcium corrected for serum albumin >10.22 mg/dL on one occasion with serum PTH >31.05 ng/L [19]. These values of serum PTH correspond to 20 pg/mL for assays with reference values between 10 and 65 pg/mL.

The causes of secondary hyperparathyroidism that can increase the serum levels of parathormone, such as the use of thiazide diuretics [14] and lithium, deficiency of vitamin D, and the use of bisphosphonates, must be excluded. Concerning tertiary hyperparathyroidism due to renal failure, genetic causes such as familial hypocalciuric hypercalcemia also need to be sought. The finding of normal levels for calcium corrected by albumin and associated with high serum PTH in the absence of other causes is compatible with normocalcemic PHPT.

Serum PTH and the biochemical markers of the bone remodeling are significantly higher in patients with severe disease. These patients frequently have vitamin D deficiency and easier localization of the parathyroid lesion than asymptomatic patients [3].

The levels of serum phosphorus are usually found to be in the lower normal range. Specific markers of bone modeling (osteocalcin and alkaline phosphatase osteo-specific) or markers of bone resorption (deoxypyridinoline, N-telopeptide, and C-telopeptide) seem to remain either in the high-normal range or slightly above reference values. Hypercalciuria is found in around 30% of asymptomatic patients, in 50% of patients with active urolithiasis, and in 40% with osteitis fibrosa cystica [3, 14]. Patients with severe PHPT have moderate levels of serum calcium and lower levels of serum phosphorus as compared to asymptomatic subjects (14.0 ± 0.7 vs. 10.9 ± 0.4 mg/dL; $p < 0.001$ and 2.0 ± 05 vs. 296 ± 0.2 mg/dL; $p < 0.01$, respectively). In the serum levels of intact PTH, there are greater differences: 1820 ± 349 vs. 133 ± 29 pg/mL; $p < 0.001$ [20].

Serum PTH and the biochemical biomarkers of the bone remodeling are significantly higher in the patients with

Table 22.2 Differential diagnosis of hypercalcemia

1. Malignancies	Solid tumors	Solid tumors	Hematologic malignancies (lymphoma, leukemia, multiple myeloma)	Ectopic production of PTH (thyroid carcinoma, ovarian, lung oat cells)
	Humoral hypercalcemia (carcinomas)	Osteolytic hypercalcemia (breast, lung)		
	Squamous lung, esophagus			
2. PTH-dependent	NEM	PHPT:	Familial hypercalciuric hypercalcemia (FHH)	Treatment with lithium
		(a) Adenoma		
		(b) Carcinoma		
		(c) Hyperplasia		
3. Related to vitamin D	Idiopathic familial hypercalcemia	Granulomatous diseases	Vitamin D intoxication	–
4. Other causes	Milk–alkali syndrome, aluminum intoxication	Endocrine diseases (hyperthyroidism, pheochromocytoma, adrenal insufficiency)	Advanced chronic disease of the liver/kidney	Drugs:
				Thiazide
				Theophylline
				Beryllium

Adapted from Refs. [21, 22]

severe disease, who frequently present vitamin D deficiency and easier localization of the parathyroid lesion than asymptomatic patients [21].

Differential Diagnosis

PHPT needs to be differentiated from other causes of hypercalcemia (Table 22.2), as well as from diseases that can cause osteoporosis, nephrolithiasis, nefrocalcinosis, and hypophosphatemia. PHPT and neoplasia correspond to 90% of hypercalcemia cases. Data from the literature shows that 50–60% of outpatients with hypercalcemia are carriers of the PHPT and about 31% present neoplasia [22].

Hypercalcemia with very low or undetectable PTH plasma levels can be found when the disease is malignant, and, in this case, the PTHrp is responsible for the increase in calcium [12]. Several laboratory characteristics associated with malignity are similar to those of PHPT, such as hypercalcemia, hypophosphatemia, hypercalciuria, and hyperphosphaturia and an increase in the nephrogenic cyclic AMP [23]. However, the difference between primary HPT and the malignant disease with hypercalcemia can be identified without difficulty, based on the clinical history of the patient. The hypercalcemia symptoms of PHPT are manifested over months or years, while in malignancy these symptoms are manifested within weeks and are secondary to the underlying malignant disease. Thus, hypercalcemia in malignant disease is readily revealed and is frequently associated with a survival of about 6 months. Other related symptoms are anemia and weight loss. In general, when hypercalcemia is found, malignancy is clinically revealed by imaging techniques or bone metastasis presented by the patient. In addition to these parameters, persistent hypercalcemia of early onset suggests malignancy, while a mild hypercalcemia lasting for more than 6 months is more likely to be caused by PHPT.

The definitive differential diagnosis is performed by means of serum PTH measurement. In PHPT, when PTH is increased or within normality, the condition may be regarded as PTH-dependent hypercalcemia but is frequently suppressed in malignant disease, which is independent of PTH [17]. In rare cases, PTH can be increased in malignancy due to ectopic production or when parathyroid carcinoma is the cause of the hypercalcemia [24].

Another differential diagnosis that should always be demanded is that of familial hypocalciuric hypercalcemia, which is characterized by a genetic defect in the calcium receptors in the parathyroid glands and kidneys, inherited as a dominant autosomal disorder [8]. The hypercalcemia is mild and followed by hyperphosphatemia, and levels of PTH are normal or slightly increased. The most pronounced laboratory finding is hypocalciuria, which suggests increased tubular resorption of calcium. This diagnosis is considered in young asymptomatic patients that present (1) levels of serum calcium with a slight-to-moderate increase, (2) hypocalciuria, (3) a familial history of hypercalcemia, and (4) a rate of calcium/creatinine clearance of less than 0.01 [2, 9].

Normocalcemic Primary Hyperparathyroidism

Patients that undergo routine evaluations during an investigation for bone loss may have increased levels of PTH, even without hypercalcemia [25].

The term normocalcemic primary hyperparathyroidism (NPHPT) was first used by Wills in 1960, who described a group of patients having characteristics different to those diagnosed with classic PHPT [26].

NPHPT is characterized by levels of serum calcium that remain normal, while PTH levels are high [27–29]. Since there is a greater availability and utilization of assays for the evaluation of this hormone, this condition has been frequently diagnosed. However, examining for other causes of secondary hyperparathyroidism, especially 25-hydroxyvitamin D deficiency, malabsorption syndromes, renal insufficiency, primary hypercalciuria, use of medications such as lithium, thiazide diuretics, and bisphosphonates, is necessary to confirm the diagnosis [13, 28].

Little is known about the epidemiology of NPHPT. In a village in southern Italy, the prevalence of NPHPT in the population above 18 years of age was 0.44% [30]. Another study with 156 female patients diagnosed with osteoporosis was observed in 14% of patients with normocalcemic primary hyperparathyroidism [28]. A pre In Sweden, Lundgren et al. studied 5202 postmenopausal women aged 55–75 years. In the 109 subjects studied, the researchers investigated two indices, observing whether the patients presented hypercalcemia associated with increased levels of PTH and higher levels of either hypercalcemia or PTH. Seventeen (16%) out of the 109 subjects studied had normal levels of serum calcium (<9.9 mg/dL) and increased PTH. This group of 17 subjects included people that had vitamin D deficiency as well as patients with NPHPT [31].

Some complications, such as nephrolithiasis, may be present in some frequency as hypercalcemic PHPT [28, 32, 33].

It remains debatable whether NPHPT incipiently represents classic PHPT or a different spectrum of this pathology [28]. Evidence suggests that patients without secondary causes of hyperparathyroidism may have early-stage PHPT since, if the disease is diagnosed early, it can progress with isolated increased serum PTH, which may or may not be followed by an increase in serum calcium. For these patients, serum calcium should be periodically evaluated during the development of the disease [29, 34].

Skeletal Manifestations

The skeletal complications of PHPT are well-known. Among the classic symptoms, these complications are considered the most familiar consequences of PHPT. The clinical presentation may include focal or widespread bone pain, localized bone edema (“brown tumors”), and fragility fractures [25].

Intense bone demineralization is seen in X-rays of patients with this severe disease. Pathological fractures are frequently seen, especially in the long bones of the lower extremity, and also loss of the lamina dura of the teeth and brain lesions in the salt-and-pepper pattern which refers to the speckled appearance of the tissue. Subperiosteal bone erosions in the distal phalanges and on the edges of the medial phalanges are usually seen as numerous lytic lesions with irregular sclerotic margins, which are more common in the pelvis, long bones, and shoulders. The cortical bone of the long bones is extremely thin and in some patients is almost absent [21].

Bone densitometry is a useful tool for investigating the classic effects of PTH, such as reduction in bone mineral density (BMD) in the distal radius, the site of the cortical bone. The catabolic ability of PTH on the cortical bone is the opposite of its anabolic effect on cancellous bone. In the lumbar spine, the site of cancellous bone, BMD seems to be normal. The hip contains a more uniform mix of cortical and cancellous bone elements, and the BMD is classified as being of an intermediate density between the distal radius and the lumbar spine. Although this classic densitometric profile is usually seen as a distinct pattern characterized by vertebral osteopenia, it can also be seen at the moment of diagnosis. In the more severe types of PHPT, there is an overall decrease in bone density [35].

The prevalence of PHPT and its impact on BMD were evaluated in 3014 men aged 69–81 years in a Swedish cohort, *MrOs*. Subjects with a low glomerular filtration rate (<21 mL/min/1.73 m^2) and vitamin D deficiency (<50 nmol/l) were excluded from the study. BMD was compared between patients with and without PHPT. The prevalence of PHPT was estimated to be 0.73%. BMD in the total hip and femur neck was lower among the PHPT group than in the control group. Subjects with high levels of intact PTH were compared with the other subjects from the cohort. For that subgroup, BMD was lower for the total hip and lumbar spine ($p < 0.05$) [36].

A controlled clinical trial compared two groups: (1) carriers of mild PHPT that were submitted to parathyroidectomy ($n = 25$) and (2) patients that had an intact parathyroid ($n = 28$). After 24 months, there was a significant increase in the BMD in the femur neck and total hip, but not in the lumbar spine or forearm of patients submitted to parathyroidectomy when compared with those that did not undergo a parathyroidectomy. There was also a decrease in the biochemical markers of bone remodeling after parathyroidectomy [37]. Another study with 11 patients, including a 5-year follow-up after parathyroidectomy, showed a significant BMD increase in the lumbar spine. However, neither the hip nor the distal radius showed any BMD increase when compared to baseline values. They also observed a reduction in the markers for bone remodeling [38].

Extraskeletal Manifestations

Neuropsychiatric Symptoms

In addition to skeletal manifestations, PHPT may be associated with alterations in other organ systems within the body. Neuropsychiatric symptoms can occur in about 23% of patients with PHPT, such as fatigue, difficulty concentrating, irritability, and mood and sleep disorders [39]. Since few studies have evaluated the prevalence of these manifestations, they remain uncertain [40]. A case–control study compared 39 postmenopausal patients with mild PHPT and 89 women without PHPT. This study revealed a higher prevalence of depression and anxiety and a higher performance on tests for verbal and nonverbal memory in the PHPT carriers. Also observed was the fact that depressive symptoms, nonverbal abstraction, and aspects of the verbal memory were significantly improved after parathyroidectomy [41]. Peripheral neurological alterations, especially sensory–motor polyneuropathy and PHPT, have been suggested by some authors [42, 43]. Recent data report clinical improvement after surgical treatment, which is recommended in patients that have neurological symptoms related to PHPT and do not present any contraindication for surgery [44].

Cardiovascular Symptoms

The literature shows a relationship between PHPT and abnormalities such as arterial hypertension, left ventricular hypertrophy, abnormal heart function, coronary artery disease, vascular abnormalities, conduction disorders, and valvular and myocardial calcification [45]. The mechanism for this aforementioned relationship remains uncertain, but it has been shown that morbidity and the risk of cardiovascular death are greater in PHPT carriers. This is mainly observed in patients with the mild to severe form of the disease [46]. On the other hand, parathyroidectomy decreases cardiovascular risk, as shown in a number of population studies, even with mild forms of the disease. Surgery is therefore indicated in all patients with PHPT and other factors of cardiovascular risk [47, 48].

Renal Manifestations

Nephrolithiasis and nefrocalcinosis are major complications of primary hyperparathyroidism. Hypercalcemia leads to increased filtered calcium load on the glomerulus, leading to hypercalciuria, increasing the risk kidney stones. Although high levels of parathyroid hormone stimulate renal resorption of calcium, renal excretion exceeds resorption. However, hypercalciuria may not be the only factor for the onset of nephrolithiasis. Studies have shown that PTHP patients may present polymorphisms in the gene that encodes the calcium-sensing receptor or CaSR, which is present in the parathyroid glands and in the kidney, modulating PTH actions. CaSR influences renal phosphate homeostasis, urinary acidification, and in urine concentration. This may explain the occurrence of nephrolithiasis in normocalcemic patients [49]. Nefrocalcinosis and nephrolithiasis are also clinical manifestations of asymptomatic and NPHPT. From the experience of our group, a recent study demonstrated an 18.2% rate of nephrolithiasis in NPHPT patients, as well as in the hypercalcemic modality (18.9%), may have shown a non-indolent presentation [50]. A recent study from our group found a prevalence of 20% for occult nephrolithiasis in NPHP patients [32].

Localization of Parathyroid Lesions

Imaging examinations are not indicated for the diagnosis of PHPT. The location of the affected parathyroid is an indication for surgery and can permit the use of less invasive techniques, which is associated with a lower morbidity rate [51]. Ultrasonography and Sestamibi scintigraphy are the most common techniques used for PHPT diagnosis (Figs. 22.1 and 22.2). Cervical ultrasonography is a low-cost examination, as well as noninvasive. When performed by an experienced examiner, it presents a sensitivity and specificity of 88% and 94%, respectively [52]. In cases of ectopic glands or an intrathyroid adenoma, identification and differentiation of thyroid nodules can be difficult. Thus, ultrasonography coupled with 99mTc-labeled Sestamibi scintigraphy increases the chance of identification to almost 100% of the lesions [53]. These two methods are complementary, since ultrasonography provides anatomic information, while the scintigraphy provides functionality data.

Scintigraphy is able to identify the topic and ectopic parathyroid tissues. A study with 64 PHPT patients presented positive scintigraphy in 64% of the patients that had asymptomatic PHPT and 83% of the group that carried nephrolithiasis without bone involvement. That same study showed that 100% of the subjects with the severe disease presented positive scintigraphy as well, but in this case it was characterized by osteitis fibrosa cystica. These results were found when the imaging was evaluated early, which occurred in 70% of the cases analyzed [53] (Fig. 22.3). A small number of patients may have negative imaging, which suggests multiglandular disease. In these cases, the use of the most advanced imaging techniques may be necessary to increase the chances of localizing the affected parathyroid and ectopic tumors and also assist in the decision to proceed with

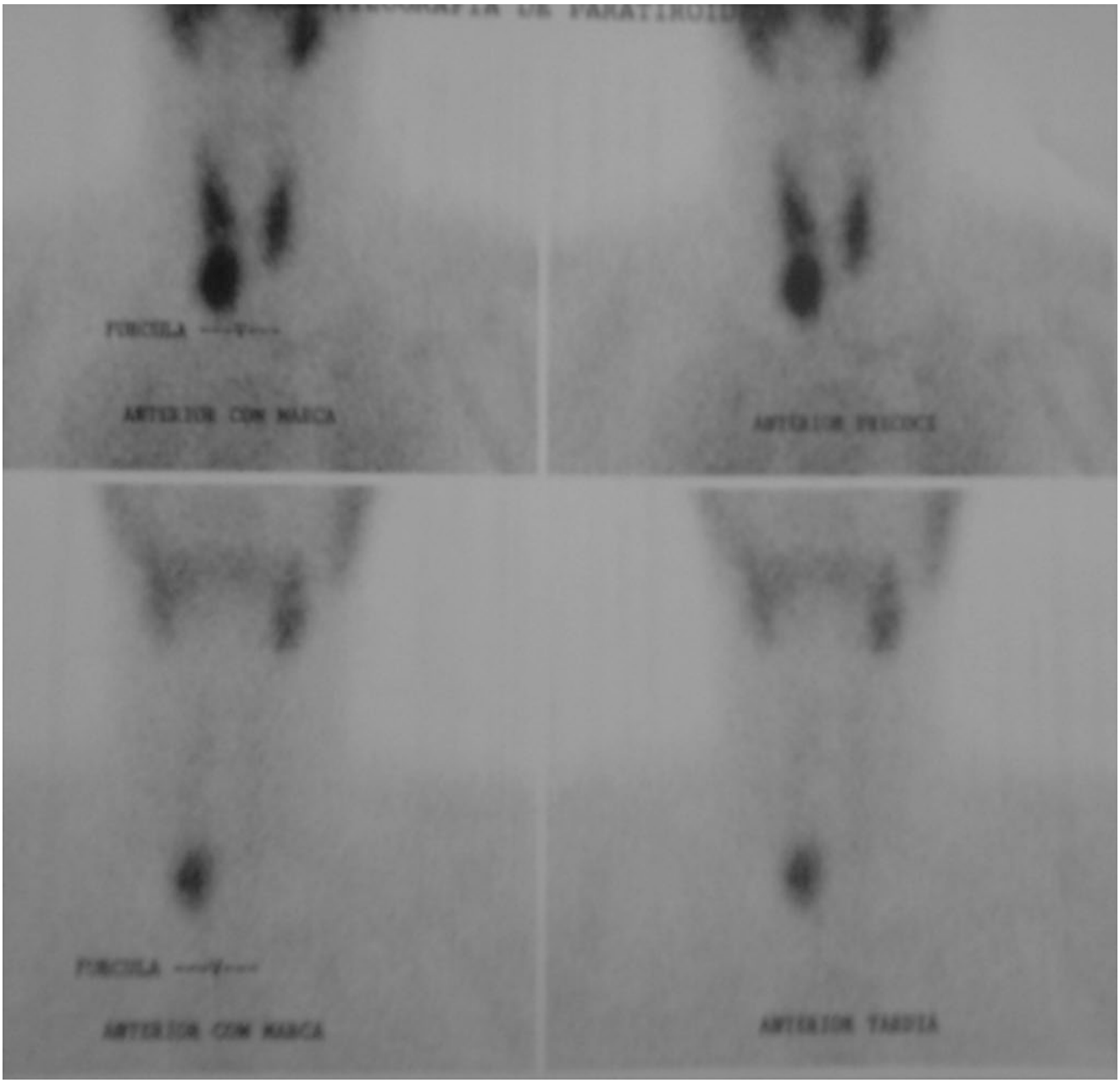

Fig. 22.1 Tc-99-Sestamibi scintigraphy showing a right inferior parathyroid lesion

surgery. Four-dimensional computed tomography was able to localize the adenoma with 82 and 92% sensitivity and specificity, respectively, in 34 PHPT patients [54]. A retrospective trial found almost 100% specificity in the diagnosis of multiglandular disease in 35 patients evaluated; however, the sensibility was much lower (42.9%). As regards the localization of only one lesion, they were able to identify 32 cases with a sensibility of 91% [55]. The preoperative localization of an adenoma allows the use of minimally invasive parathyroidectomy (MIP) with lower morbidity and can be done in an outpatient facility [55].

One of the main disadvantages of imaging examinations is the high incidence of false-positive results due to the size and localization of the parathyroid affected. As a result, fine-needle aspiration of the nodule that was identified by imaging for measurement of PTH in the aspirated material has become an auxiliary method for diagnosing lesions, as shown by a study performed by our group. A group of 15 women without PHPT, who had nodules identified by ultrasonography, showed very high PTH levels, presenting a mean of 4.919 ± 5.124 pg/mL, while the control group had a mean of 10.65 ± 3.49 pg/mL. This tech-

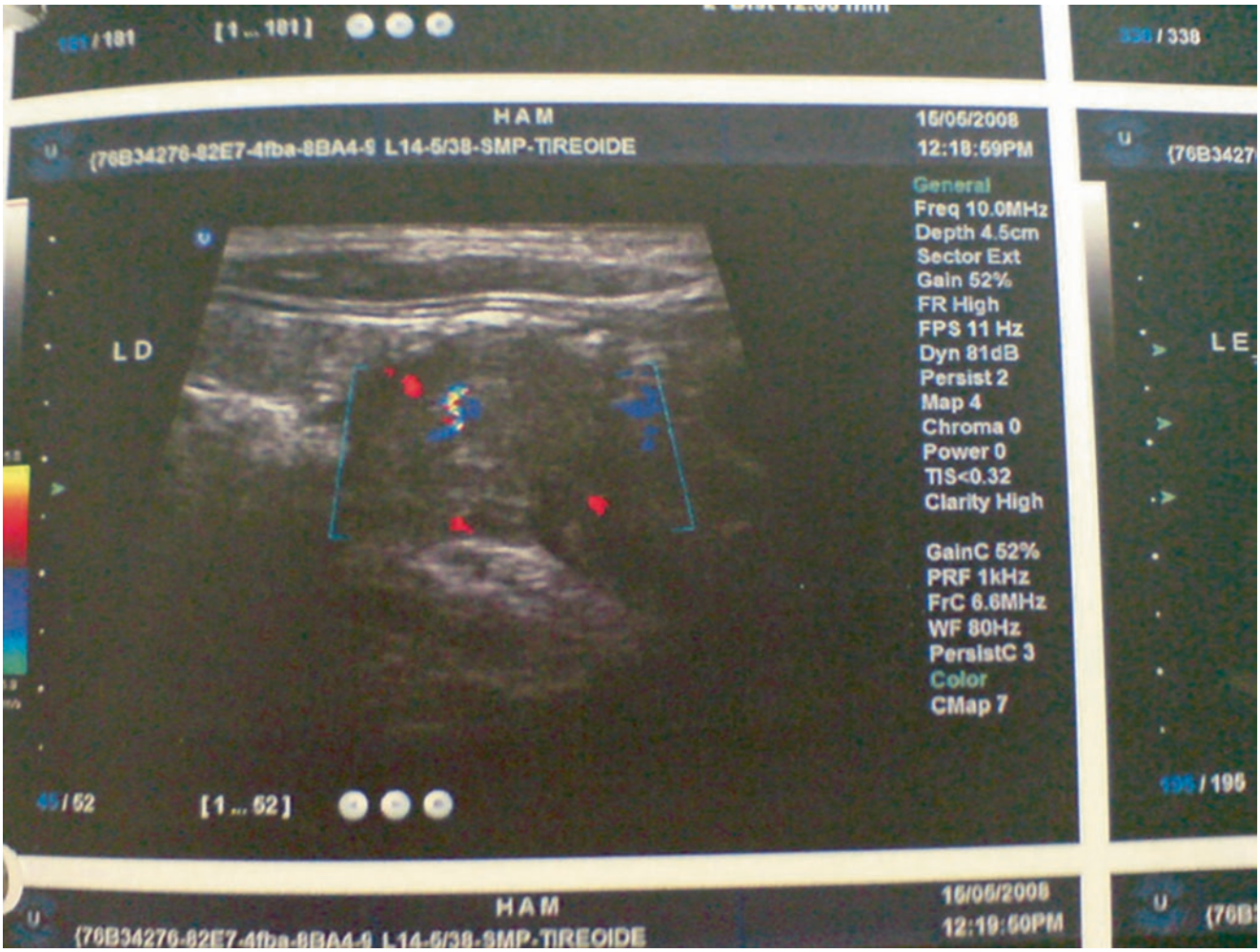

Fig. 22.2 Cervical ultrasound from the same patient in Fig. 23.1

nique showed a greater sensitivity in locating the affected gland than the use of imaging alone [56]. The main methods for locating parathyroid lesions are shown in Table 22.3.

Indications for Parathyroidectomy in PHPT

Parathyroidectomy is the treatment of choice for patients with PHPT, but indicating surgery for subjects in whom a parathyroid lesion was not found may need some criteria. The aim of surgery is to provide treatment by removal of the affected parathyroid. This occurs in 95–98% of the patients operated on by an experienced surgeon, with the number of complications being low. According to the Fourth International Workshop, surgery is indicated for asymptomatic patients if there is a greater benefit than with drug treatment [57, 58]. Table 22.4 lists the conditions in which surgery is particularly indicated.

For patients with normocalcemic primary hyperparathyroidism, surgery is indicated for those, who present with complications such as kidney stones and osteoporosis [58].

With regard to the minimal significant alterations in the bone loss rate during the natural disease progression, asymptomatic PHPT patients who do not meet the criteria for surgery or patients that have some contraindication should have their BMD monitored by biannual bone densitometry (dual-energy X-ray absorptiometry—DXA) [57]. The patients with a vitamin D deficiency (serum levels of 25-OHD below 20 ng/mL) should receive adequate replacement, in accordance with the recommendations for patients without PHPT [46].

Randomized studies [41, 59, 60] have demonstrated the benefits on the quality of life and on BMD of asymptomatic patients submitted to surgery. Even though these studies were randomized, they had a short follow-up period. Finally, another important point about MIP is that this procedure yields excellent t results, produces few complications, and decreases the cost of a surgical procedure [61].

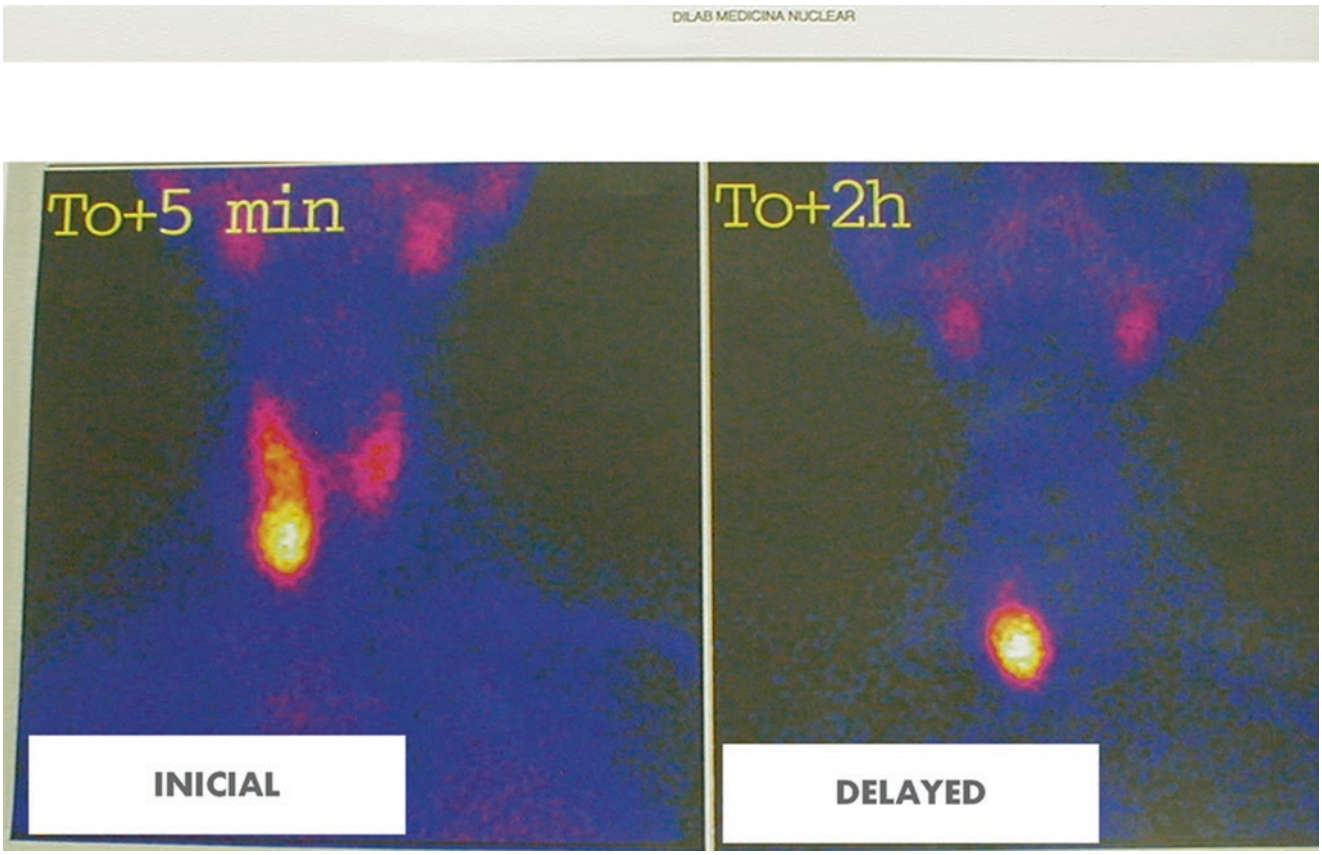

Fig. 22.3 99mTc-Sestamibi scintigraphy showing a large parathyroid adenoma

Table 22.3 Localization procedures for the identification of parathyroid adenoma

Methods	Sensitivity (%)	Specificity (%)
Cervical ultrasonography (US)/ Doppler US	88/97	94/100
Computed tomography fourth dimension	82	92 a 100[a]
Technetium-99 m Sestamibi scintigraphy	90[b]	100
PTH measurement in aspiration fluid (FNA[c])	100	100

Adapted from Refs. [51–54]
[a]The specificity for multiglandular disease is close to 100%
[b]The sensitivity increases in more serious cases being close to 100% in patients with osteitis fibrosa cystica. The accuracy is lower in multiglandular disease
[c]*FNA* fine-needle aspiration

Table 22.4 Surgical indications for asymptomatic primary hyperparathyroidism

Nephrolithiasis
Osteitis fibrosa cystica
Asymptomatic primary hyperparathyroidism associated with one or more of the following conditions:
Serum calcium >1 mg/dL above ULN[a]
Age < 50 years
T-score < −2.5 at the lumbar spine, hip, and/or distal radius
Vertebral fracture by X-ray, CT, MRI, or VFA or deteriorated Trabecular Bone Score
Estimated Glomerular Filtration Rate (Creatinine clearance) <60 mL/min/1,73 m^2
24-h urine for calcium>400 mg/d (>10 mmol/d)
Presence of nephrolithiasis or nefrocalcinosis by X-ray, ultrasound, or CT
Patients whose medical monitoring is not possible

Adapted from Refs. [57, 58]
[a]*ULN* upper limit of normality

Surgical Techniques

Bilateral cervical exploration is the traditional surgical technique and consists of the evaluation and removal of the affected parathyroid glands. However, the morbidity, surgical duration, and risks of complications are greater. The early localization of the lesion therefore allows the use of MIP as mentioned above [61].

A prospective, randomized, and blinded study compared MIP with conventional parathyroidectomy in 48 patients with PHPT. In the group submitted to MIP, there was a lower pain intensity in the postoperative period ($p < 0.001$), less use of analgesics ($p < 0.001$), a lower rate of anesthesia procedures ($p < 0.001$), a smaller scar ($p < 0.001$), and greater aesthetic satisfaction postoperatively at 2 days, 1 month ($p < 0.01$), and 6 months ($p < 0.05$); however, 1 year after surgery, aesthetic satisfaction was no longer significantly different in the two groups($p = 0.38$). On the other hand, there was a higher cost with MIP and no significant difference in the quality of life in either group 6 months after the surgical procedure [62].

Intraoperative PTH Monitoring

This procedure is used during MIP for the treatment of PHPT. As regards the time frame for intraoperative PTH monitoring, this is performed after the anesthesia, before the skin incision, and 10 minutes after removal of the enlarged gland [63]. One can observe a fall of less than 50% in the PTH levels, when compared with the baseline values. This fall of less than 50% shows the risk of persistent disease. Several studies have analyzed how useful the intraoperative PTH evaluation can be, and they suggest that this measurement should be indicated in cases (1) that present only an imaging study during preoperative care of positive MIP, (2) when the imaging studies for preoperative localization are discordant, and (3) of reoperation [63–66].

Medical Therapy

Drug therapy is indicated for patients contraindicated for surgical treatment, those with therapy failure, and patients that either do not want the surgical procedure or did not meet the current criteria. Among the options to replace a surgical procedure is cinacalcet, which acts as a calcimimetic and is able to decrease the PTH release. Other options are an antiresorptive agent which inhibits bone remodeling, for example, a bisphosphonate, hormone therapy, and selective modulators of estrogen receptors [46].

Calcimimetic Agents

Calcimimetic agents are drugs that can increase the sensitivity of the calcium-sensing receptor to extracellular calcium, which results in a reduction of PTH. The first calcimimetic developed was a derived phenylalkylamine (R-568); however, it had low availability and a high variability of response. As a result, cinacalcet hydrochloride, with higher availability and a lower pharmacologic variability, was developed [67]. Studies show that cinacalcet decreases PTH levels by up to 50% and is thus able to regulate serum calcium in approximately 80% of treated patients [67]. The recommended starting dose for PHPT is 30 mg once daily which may be adjusted up to 300 mg/day [67].

A multicenter, randomized, double-blind, placebo-controlled study evaluated 78 patients with PHPT to ascertain the long-term ability of cinacalcet to reduce serum calcium and PTH. The patients received a dose starting at 30 mg, twice a day; if there was a persistent hypercalcemia, the dose was increased to 40–50 mg during a 12-week period. The final dose was maintained for 12 weeks, and patients were followed for another 28 weeks. Two doses per day of cinacalcet decreased serum calcium by 0.5 mg/dL or more and normalized (calcium <10.3 mg/dL) in 73% patients treated during a maintenance phase and also decreased levels of PTH by 7.6% over the same period [68]. Serum calcium levels remained normal and PTH remained lowered for up to 52 weeks.

With regard to BMD measured by dual-energy X-ray densitometry (DEXA), no significant changes were found during the 52-week period or the following 5 years [69, 70]. Cinacalcet significantly increased some of the markers of bone remodeling (bone alkaline phosphatase and NTx), and the rate of NTX/urinary creatinine for 52 weeks, when compared with the placebo group, however, remained within the normal range [69].

The use of calcimimetics is indicated for those patients that have hypercalcemia related to renal insufficiency of the tertiary hyperparathyroidism, for those who are carriers of parathyroid carcinoma, or when there is a contraindication for surgery [67].

Hormone Replacement Therapy

The use of estrogens is a therapeutic option for postmenopausal women because it increases BMD in the femoral neck and lumbar spine. This protective effect from fractures was demonstrated in the WHI trial with the use of conjugated estrogens at a dose of 0.625 mg together with a daily 5 mg dose of medroxyprogesterone for 2 years [71]. Nevertheless, their long-term use is not indicated, since they

also increase the risk of cardiovascular and breast cancer. Thus one should analyze the risks and benefits before suggesting this therapy [71].

Furthermore, another randomized, double-blind, placebo-controlled study with 42 menopausal women with PHPT over 2 years evaluated the effects of conjugated estrogens at a dose of 0.625 mg, together with a daily 5 mg dose of medroxyprogesterone on BMD, biochemical parameters of bone remodeling, and calcium metabolism. In this study, there was a reduction in total serum calcium, but no changes in the ionized calcium and intact PTH. Regarding the markers of bone remodeling, there was a 22% decrease in alkaline phosphatase, and a 38% decrease in urinary hydroxyproline excretion was also observed. In addition, 60 and 33% reductions were found in N-telopeptide excretion and urinary calcium excretion, respectively [72]. This therapy showed positive effects on the total BMD of the body, lumbar spine, femur, and forearm over the 2 years. These positive effects remained for at least the 4 years of follow-up [73].

Estrogen therapy may thus be the treatment of choice for women that have bone loss and PHPT in the postmenopausal period. This therapy should be indicated if there is no contraindication for its use.

Selective Modulators of Estrogen Receptors (SERMs)

Nowadays, there is little evidence in the literature concerning the selective modulators of estrogen receptors (SERMs). A randomized, double-blind, placebo-controlled investigation, with 18 patients, demonstrated the efficacy of 60 mg/day raloxifene in reducing both serum calcium levels and markers of bone remodeling (serum NTx and osteocalcin) over an 8-week period. After 4 weeks of treatment with raloxifene, there were no alterations in the calcium and PTH levels. Moreover, during the same period, the markers of bone remodeling returned to baseline values [74].

Bisphosphonates

The bisphosphonates, administered to patients with PHPT, have proven their efficacy in the improvement of bone mass as compared to a placebo, which was measured by DEXA. The use of oral alendronate has been evaluated in 5 studies involving 119 postmenopausal women and 24 men treated for 2 years (Fig. 22.4). The results showed a significant increase in BMD at the lumbar spine and femoral neck, but no substantial change in density of the distal radius. There was also a decrease in the levels of calcium adjusted for albumin and a decrease in PTH and markers of bone turnover [75–79].

Another example [79] is a double-blind, controlled trial with 44 patients who did not undergo parathyroidectomy and used alendronate (10 mg/day) for 2 years. In this case, the study showed a gain in bone mass in the lumbar spine and femoral neck, but there were no changes in calcium or PTH levels. Markers of bone turnover had reduced levels without modifying the risk of fractures.

Jansson and Cols [80] evaluated 21 patients with PHPT who were given 30–40 mg of pamidronate before surgery. A temporary reduction in the levels of serum calcium was

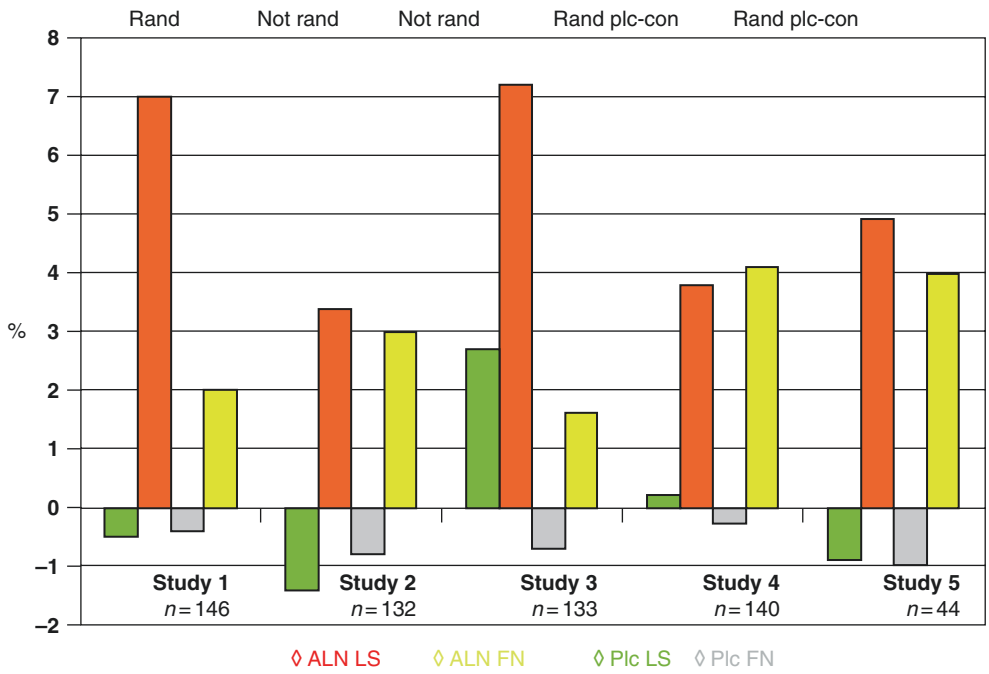

Fig. 22.4 Clinical trials on alendronate therapy for PHPT

observed with the nadir after 6–10 days of infusion, and a return to high levels after this period.

In conclusion, alendronate may represent a therapeutic option and the possibility of bone protection, albeit with no prospect of achieving long-term normocalcemia, and may be associated with increased levels of serum PTH.

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