Bone disease in primary hyperparathyroidism

Doença óssea no hiperparatiroidismo primário

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ABSTRACT
Bone disease in severe primary hyperparathyroidism (PHPT) is described classically as osteitis fibrosa cystica (OFC). Bone pain, skeletal deformities and pathological fractures are features of OFC. Bone mineral density is usually extremely low in OFC, but it is reversible after surgical cure. The signs and symptoms of severe bone disease include bone pain, pathologic fractures, proximal muscle weakness with hyperreflexia. Bone involvement is typically characterized as salt-and-pepper appearance in the skull, bone erosions and bone resorption of the phalanges, brown tumors and cysts. In the radiography, diffuse demineralization is observed, along with pathological fractures, particularly in the long bones of the extremities. In severe, symptomatic PHPT, marked elevation of the serum calcium and PTH concentrations are seen and renal involvement is manifested by nephrolithiasis and nephrocalcinosis. A new technology, recently approved for clinical use in the United States and Europe, is likely to become more widely available because it is an adaptation of the lumbar spine DXA image. Trabecular bone score (TBS) is a gray-level textural analysis that provides an indirect index of trabecular microarchitecture. Newer technologies, such as high-resolution peripheral quantitative computed tomography (HR-pQCT), have provided further understanding of the microstructural skeletal features in PHPT. Arq Bras Endocrinol Metab. 2014;58(5):553-61

Keywords
Hyperparathyroidism; osteitis fibrosa cystica; nephrocalcinosis

RESUMO
A doença óssea no hiperparatiroidismo primário grave é representada pela osteite fibrosa cystica (OFC). Dor óssea, deformidades esqueléticas e fraturas patológicas são achados comuns na OFC. A densidade mineral óssea está, usualmente, extremamente diminuída na OFC, mas é reversível após a cura cirúrgica. Os sinais e sintomas da doença óssea grave incluem dor óssea, fraturas patológicas e fraqueza muscular proximal com hiper-reflexia. O comprometimento ósseo é tipicamente caracterizado pela aparência em “sal-e-pimenta” nos ossos do crânio, erosões ósseas e reabsorção das falanges, tumores marrons e cistos. Na radiografia, observam-se desmineralização difusa e fraturas patológicas especialmente nos ossos longos das extremidades. No hiperparatiroidismo primário (HPTP) sintomático grave, as concentrações séricas de cálcio e PTH estão usualmente bem elevadas e o comprometimento renal se caracteriza pela presença de urolitíase e nefrocalcinose. Uma nova tecnologia, recentemente aprovada para uso clínico nos Estados Unidos e na Europa, torna-se provável se difundir rapidamente, pois utiliza as imagens geradas pela densitometria DXA. O escore trabecular ósseo (TBS), obtido por meio da análise do nível da textura cinza das imagens dos corpos vertebrais, fornece informações indiretas sobre a microarquitetura trabecular. Novos métodos, como a tomografia de alta resolução quantitativa periférica computadorizada (HRpQCT), têm proporcionado conhecimentos adicionais sobre os achados da microarquitetura esquelética no HPTP. Arq Bras Endocrinol Metab. 2014;58(5):553-61

Descritores
Hiperparatiroidismo; osteite fibrosa cystica; nefrocalcinose
SKELETAL DISEASE IN SEVERE PRIMARY HYPERPARATHYROIDISM

Bone disease in severe primary hyperparathyroidism (PHPT) is described classically as osteitis fibrosa cystica (OFC). Bone pain, skeletal deformities and pathological fractures are features of OFC (1). Bone mineral density is usually extremely low in OFC, but it is reversible after surgical cure (2).

The clinical presentation of PHPT has changed globally, with the first reports in the 1970s coming from the United States and Europe where the multichannel screening test was introduced. Most patients whose PHPT is discovered in this manner do not show overt skeletal or renal complications. In Latin America, at a time when the United States and European centers were describing a change in this clinical phenotype, most studies continued to see a very symptomatic disease. With time, however, countries such as Brazil have also seen a change in the presentation of PHPT toward the asymptomatic form (3). This change has also been reported recently in China (4). However, other Asian countries like India, Iran, Saudi Arabia and Thailand reported widespread prevalence of symptomatic disease with skeletal manifestations (3).

In a series of 124 patients from Recife, about ten years ago, 25% of patients had severe skeletal involvement and OFC (1). Similar data were found in the city of São Paulo (5). More recently, however, in a recent epidemiological study from the same institution with 4207 patients evaluated, only 6.1% had OFC (6).

The aim of this work is to review current more relevant data on bone involvement in the various forms of primary hyperparathyroidism.

Clinical manifestations

The signs and symptoms of severe bone disease include bone pain, pathologic fractures, proximal muscle weakness with hyperreflexia. Although these patients usually present with non-specific symptoms such as weakness, depression and constipation, the dominant picture occurs due to severe bone abnormalities (1). Bone involvement is typically characterized as salt-and-pepper appearance in the skull (Figure 1), bone erosions and bone resorption of the phalanges (Figure 2), brown tumors and cysts (1). The osteoclastomas are typical radiological changes of severe hyperparathyroidism, represented by OFC (7) (Figure 3).

Renal involvement is manifested by nephrolithiasis and nephrocalcinosis (3). The stones are usually small, comprised of calcium oxalate or calcium phosphate and are seen on abdominal radiographs or renal ultrasound. In the most severe cases, mineralization of renal tissue occurs (8).

Symptomatic patients may also present with neuropsychiatric symptoms, such as anxiety, depression, confusion, memory loss, irritability, difficulty in concentration, and sleep disorders (1). The prevalence of these symptoms is not known due to the lack of rigorous and systematic evaluation in most series (3).
Figure 3. Fifty-seven years old with female with osteitis fibrosa cystica showing huge osteoclastomas in the femurs bilaterally.

Diagnosis

Radiography

Diffuse demineralization is observed, along with pathological fractures, particularly in the long bones of the extremities along with a salt and pepper appearance of the skull (8).

Subperiosteal bone erosions in the distal phalanges and on the lateral aspects of the middle phalanges are also seen, appearing as sclerotic or lytic lesions with irregular margins. The pelvis, long bones and shoulders are common sites to see these manifestations. The cortex of the long bones is extremely thin and almost absent in some patients (9).

Ultrasound

Ultrasonography of the kidneys and urinary tract should be obtained if the clinical history suggests nephrolithiasis. It is reasonable to consider this even in the absence of symptoms of nephrocalcinosis or nephrolithiasis (8).

Bone mineral density

Bone mineral density of the lumbar spine, hip regions (total hip and femoral neck) and distal 1/3 radius should be measured in all patients. The distal 1/3 radius, a site of cortical bone, is particularly important to measure in PHPT because of the catabolic effects of PTH in cortical bone (10).

High-resolution peripheral computed tomography (HRpQCT) permits non-invasive assessment of cortical and trabecular microarchitecture of the distal radius and tibia. As noted below, HRpQCT has been applied recently to evaluate cortical and trabecular bone quality in PHPT (3).

Laboratory data

In severe, symptomatic PHPT, marked elevation of the serum calcium and PTH concentrations are common. The accurate measurement of the serum calcium should take into account the fact that 40% of circulating calcium is bound to albumin. If the serum albumin concentration is abnormal, the measured serum calcium concentration must be adjusted using the formula: \[ \text{corrected calcium} = \text{serum calcium concentration} \times 1000 \times [0.8 \times (\text{serum albumin})]. \] The direct measurement of ionized calcium can be useful in selected situations such as extreme hyper- and hypoalbuminemia, thrombocytosis, Waldenström’s macroglobulinemia and myeloma (8).

Biochemical markers of bone formation, such as osteocalcin, alkaline phosphatase (AP) or markers of bone resorption, such as deoxypyridinoline, N-telopeptide (NTX) and C-telopeptide (CTX) are typically markedly elevated in severe PHPT. Alkaline phosphatase is well above normal in virtually all patients with OFC (7).

Renal function and serum 25OHD, as well as 24-hour urine calcium must be evaluated. Low levels of 25(OH)D have been linked to the severity of the disease, increased bone turnover and low bone mineral density measurements (9). Table 1 shows the main differences between the various forms of hypercalcemic primary hyperparathyroidism.

Localization techniques

Among the several technologies that are useful in located the abnormal parathyroid gland, ultrasonography is inexpensive and noninvasive. Its disadvantage is in limited resolving power and in being operator dependent. Ultrasonography has a sensitivity of 88% and specificity of 94%, but when combined with Tc-99-sestamibi scintigraphy with SPECT-CT it can improve to 97 and 100% respectively (8,9,11).
Table 1. Clinical and laboratory data of 64 patients with primary hyperparathyroidism from one institution

<table>
<thead>
<tr>
<th>Baseline</th>
<th>Asymptomatic</th>
<th>Renal stone disease</th>
<th>Osteitis fibrosa cystica</th>
<th>P</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>66.75 ± 0.63</td>
<td>55.8 ± 5.09</td>
<td>38.7 ± 4.38</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Sex ratio (M:F)</td>
<td>1:4</td>
<td>2.7</td>
<td>11:10</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Serum calcium (mg/dL)</td>
<td>10.98 ± 0.02</td>
<td>11.32 ± 0.17</td>
<td>13.35 ± 0.35</td>
<td>&lt; 0.01</td>
<td>8.6–10.3</td>
</tr>
<tr>
<td>Serum phosphorus (mg/dL)</td>
<td>2.79 ± 0.29</td>
<td>2.56 ± 0.47</td>
<td>1.99 ± 0.29</td>
<td>&lt; 0.01</td>
<td>2.5–4.5</td>
</tr>
<tr>
<td>Serum PTH (pg/mL)</td>
<td>135.45 ± 13.50</td>
<td>165.85 ± 15.06</td>
<td>579.6 ± 628.4</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Serum 25-hydroxyvitamin D (ng/mL)</td>
<td>26.97 ± 4.13</td>
<td>20.02 ± 0.56</td>
<td>15.91 ± 1.11</td>
<td>&lt; 0.01</td>
<td>12–68</td>
</tr>
<tr>
<td>Urine NTx (nmol/mmol of creatinine)</td>
<td>51.3 ± 6.4</td>
<td>154.1 ± 62.9</td>
<td>501.5 ± 201</td>
<td>&lt; 0.05</td>
<td>50–60 (premenopausal) 15–120 (postmenopausal) 6–65 (men)</td>
</tr>
<tr>
<td>Serum CTx (pg/mL)</td>
<td>752.6 ± 496.3</td>
<td>727.3 ± 220.4</td>
<td>2,210.2 ± 375.4</td>
<td>&lt; 0.05</td>
<td>50–450 (premenopausal) 90–680 (postmenopausal) 70–480 (men)</td>
</tr>
<tr>
<td>BMD t score</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumbar spine</td>
<td>-2.02 ± 0.15</td>
<td>-1.83 ± 0.85</td>
<td>-4.25 ± 0.24</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Femoral neck</td>
<td>-2.03 ± 0.28</td>
<td>-1.81 ± 0.38</td>
<td>-5.44 ± 1.37</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
<tr>
<td>Distal radius</td>
<td>-2.23 ± 0.74</td>
<td>-1.79 ± 0.04</td>
<td>-5.33 ± 0.69</td>
<td>&lt; 0.01</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from: Bandeira and cols. (9).

The use of sestamibi scintigraphy in the preoperative localization of parathyroid lesions has improved the success of surgery, especially in patients who have had previous neck surgery. Success is dependent, in part, on successful localization of abnormal parathyroid tissue. This test can also be performed in suspected skeletal brown tumors and metastatic parathyroid cancer, which may be due to increased perfusion, metabolism and osteoclastic activity (9). In contrast to ultrasound and scintigraphy, 4D computed tomography can visualize, at times with greater accuracy, multiple gland involvement (8). Magnetic resonance imaging (MRI) may also be used especially to identify ectopic parathyroid tissue (11). Considering all options, SPECT-CT is often considered to be the first choice because of its better spatial resolution. The combination of two different methods can also be used to improve the localization of the parathyroid lesion (11).

The hungry bone syndrome

The “hungry bone disease” occurs in consequence of the rapid accrual of calcium from the intravascular compartment into the skeleton and under these conditions can result in severe hypocalcemia and the urgent need for intravenous calcium replacement (1,2,7,8).

As parathyroidectomy is the treatment of choice for all patients with symptomatic PHPT, various degrees of improvement have been shown following surgical cure.

In severe disease, these include regression of skeletal abnormalities with increased bone mineral density and in many cases shrinkage of osteoclastomas (1,8,12). In patients with OFC, the average gain in bone density after surgical cure was 40 ± 29% in lumbar spine, 86 ± 39% in femoral neck and 22 ± 11% in distal radial, only 1 year after surgery (7). The marked and rapid improvement in bone mineral density among subjects with OFC contrasts with the slower gains in those with asymptomatic PHPT (1,13).

In severe PHPT, markedly increase bone turnover results in the efflux of calcium from bone. After parathyroidectomy, rapid bone resorption ceases immediately, but bone formation continues (14-17).

Bisphosphonates, described in the table 2, have been used preoperatively in patients with severe PHPT in order to decrease bone turnover (bone resorption and bone formation) and to prevent, therefore, the development of postoperatively severe hypocalcemia and its complications such as seizures and coma (1,7,16).

A study that evaluated bisphosphonate use preoperatively in patients with OFC (7) showed that the speed and degree of postoperative hypocalcemia was significantly controlled preventing the occurrence of specific
signs and symptoms. Average serum calcium levels pre-operatively were 13.51 ± 0.87 mg/dL and PTH: 1389 ± 609 pg/mL. In the first week following surgical cure, serum calcium and PTH levels fell to 8.23 ± 0.46 mg/dL and 45.8 ± 72.9 respectively. Oral calcium carbonate and vitamin D3 were sufficient, without the need for intravenous calcium administration (7) (Figures 4 and 5). The preoperative use of bisphosphonates did not appear to compromise the recovery of bone density after parathyroidectomy. Mean increases after 1 year of 40 ± 29% in lumbar spine, 86 ± 39% in femoral neck and 22 ± 11% in distal radius were appreciated (7) (Figure 6).

### Table 2. Suggested bisphosphonate regimen for pre-operative use in patients with osteitis fibrosa cystica

<table>
<thead>
<tr>
<th>Compound</th>
<th>Route</th>
<th>Dose (mg)</th>
<th>Duration</th>
<th>Time before surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pamidronate</td>
<td>Intravenously</td>
<td>90</td>
<td>Single infusion</td>
<td>10 – 30 days</td>
</tr>
<tr>
<td>Zolendronic acid</td>
<td>Intravenously</td>
<td>5</td>
<td>Single infusion</td>
<td>10 – 30 days</td>
</tr>
</tbody>
</table>

Vitamin D deficiency is a risk factor for the development of hungry bone syndrome, and high-dose supplementation is recommended early postoperatively (14,17). Although most patients respond to high dose cholecalciferol, some patients will need active metabolites of vitamin D such as calcitriol (18).

In hungry bone syndrome, there is not a uniform standard therapeutic approach. Often, however, replacement amounts of calcium can be in the range of 6-12 g per day. The amount needed will vary according to the severity of hypocalcemia. Attention should be paid to the need for correction of hypomagnesemia also (15).

### SKELETAL DISEASE IN ASYMPTOMATIC AND IN NORMOCALCEMIC PRIMARY HYPERPARATHYROIDISM

The preceding section reviews aspects of symptomatic primary hyperparathyroidism, a classical presentation that has become more and more uncommon. Over the past 40 years, with the widespread use of the multichannel autoanalyzer in the United States and elsewhere in the world, the presentation of PHPT has shifted to a predominantly asymptomatic one (19). Overt skeletal disease, detected radiologically, occurs in a vanishingly small percentage of patients. The early clinical presentation of PHPT undoubtedly accounts, at least in part, for the observation that overt skeletal disease has become unusual. Despite the fact that most patients do
not show classical radiological findings of PHPT, bone involvement is readily detected in most patients by dual energy X-ray absorptiometry (DXA). By DXA, bone mineral density is typically reduced. More recently, application of newer imaging modalities such as the trabecular bone score (TBS) and high resolution peripheral quantitative computed tomography (HRpQCT), have demonstrated abnormalities in trabecular microarchitecture that are readily seen in the mild asymptomatic PHPT seen today in many parts of the world.

More recently, a newer presentation of PHPT has emerged, in which patients present with elevated PTH levels and consistently normal serum calcium. Patients with this phenotypical presentation, normocalcemic PHPT, are usually discovered during the evaluation for a metabolic bone disease. In this section we review the assessment of bone disease in mild asymptomatic and normocalcemic PHPT.

**Skeletal abnormalities in asymptomatic PHPT**

Most patients with PHPT in the developed, and now also in the developing world, are discovered to have hypercalcemia incidentally on routine blood tests. While X-rays rarely show classical findings of PHPT (see prior section), bone mass is typically reduced when it is measured by DXA. For many years, it was believed that the negative effects of PHPT on the skeleton were restricted to cortical bone. The densitometric profile of PHPT shows bone mineral density (BMD) reductions at the distal 1/3 forearm, a site composed primarily of cortical bone, with relative preservation of the lumbar spine, a predominantly trabecular site (13,19,20). Histomorphometric and micro-computed tomography analyses of bone biopsy specimens confirmed reductions in cortical bone, demonstrating that cortical thickness was significantly lower in patients with PHPT compared to controls, with relative preservation of trabecular parameters (20-22).

While the densitometric and histomorphometric findings are generally in agreement, they are inconsistent with numerous epidemiological reports demonstrating increased fracture risk at both vertebral and non-vertebral sites in patients with PHPT (23-27). Newer technologies, such as HRpQCT, have provided further understanding of the microstructural skeletal features in PHPT. Data from these newer technologies are more consistent with epidemiological fracture data in PHPT. HRpQCT measures volumetric bone density, bone geometry, skeletal microarchitecture, and bone strength in the cortical and trabecular compartments. By HRpQCT, both the cortical and trabecular compartments are affected adversely in PHPT, with reduced volumetric densities at cortical and trabecular compartments, thinner cortices, and more widely spaced and heterogeneously distributed trabeculae (28-30). These studies have also shown that the adverse effects of PHPT are likely to be mitigated by weight-bearing, since the radius, a non weight-bearing site, is generally more affected than the tibia, a weight-bearing site. Stein and cols. (29) have provided additional insight into trabecular microstructure by using individual trabecula segmentation analysis of the HRpQCT images, a technique to segment the trabecular network into individual plates and rods. By this analysis in postmenopausal women with PHPT, the trabecular network is topologically configured with relatively fewer plate-like than rod-like trabeculae, reduced connectivity, and a less well axially aligned trabecular network. This analysis is consistent with the expectation that trabecular bone strength is reduced in PHPT.

Although HRpQCT remains a research tool, a new technology, recently approved for clinical use in the United States and Europe, is likely to become more widely available because it is an adaptation of the lumbar spine DXA image. Trabecular bone score (TBS) is a gray-level textural analysis that provides an indirect index of trabecular microarchitecture. TBS is obtained from the DXA image through the application of TBS software (31-33). A high TBS value is associated with a dense trabecular network and greater bone strength, whereas a low TBS value is associated with qualitatively worse bone microarchitecture (32,33). Prospective studies in postmenopausal women have demonstrated that TBS predicts vertebral, hip and other major osteoporotic fractures (34-37). In PHPT, TBS shows a partially degraded microarchitecture (38-40) including cohorts that are predominantly asymptomatic with mild disease. In a predominantly asymptomatic cohort, Silva and cols. (38) demonstrated that while over half of the subjects presented with normal lumbar spine T-scores by DXA, only 27% of subjects had normal TBS values. TBS has also been found to be associated with vertebral fracture in subjects with PHPT (39,40).

**Natural history of bone loss in asymptomatic PHPT**

The natural history of asymptomatic PHPT was defined by two large prospective cohorts. Rao and cols.
(41,42) monitored 80 asymptomatic patients for up to 11 years, during which time there was no worsening of biochemical or densitometric indices. Silverberg and cols. (19) published their cohort of 101 asymptomatic patients followed for up to 10 years. Approximately 25% of these patients showed disease progression. Age was the only predictor of progression, with patients younger than 50 years of age three times more likely to show progression. Rubin and cols. (13) reported the 15-year follow-up study of these patients, finding that disease progression over that longer time period amounted to 37% of the cohort. Of particular interest was accelerated bone loss at the distal 1/3 radius and femoral neck between years 10 and 15. There are limited data on the natural history of PHPT using the new technologies described above. In a small cohort study by Eller-Vainicher and cols. (40) TBS remained stable in a non-operative cohort followed over 2 years. There are no published longitudinal HRPQCT data in subjects with PHPT not undergoing parathyroidectomy.

**Reversal of abnormalities post-parathyroidectomy**

In the cohort studied by the group at Columbia University Medical Center (13), patients who underwent successful parathyroid surgery experienced gains in bone density by DXA at 5, 10, and 15 years, respectively, of 9, 6, and 12% at the lumbar spine; 1, 7 and 10% at the femoral neck; and 4, 8, and 7% at the distal radius. The findings have been confirmed by randomized control trials of surgery versus observation (42-44) also demonstrating increased bone density at the hip and/or lumbar spine.

In the study of Eller-Vainicher and cols. (40) TBS was compared in a small cohort of subjects with PHPT undergoing parathyroidectomy to a non-operative cohort. While TBS remained stable in the non-operative group, it improved in surgically-treated patients at month 24. While similar data were observed for BMD at lumbar spine and hip sites, the mean Z-score increase for TBS was greater than for BMD at the lumbar spine or hip sites.

Hansen and cols. (45) prospectively followed women with PHPT before and 1 year post-parathyroidectomy using DXA and HRPQCT. By DXA, post-operative improvements in BMD were noted at the lumbar spine and total hip. By HRPQCT, at both the radius and tibia, there were significant improvements in various cortical and trabecular parameters, associated with significant changes in bone biomechanical properties. These changes were associated with an improvement in failure load.

**Normocalcemic PHPT**

Over the past decade, a newer clinical description of PHPT has emerged, characterized by consistently normal total and ionized serum calcium concentrations with elevated PTH levels, in the absence of obvious causes for secondary hyperparathyroidism (41,46-48). Individuals with this new phenotype, normocalcemic PHPT, are increasingly being discovered as many physicians are now requesting PTH levels in patients with, or suspected of, an underlying metabolic bone disease despite a normal serum calcium concentration (46-48). As a consequence, normocalcemic PHPT has primarily been diagnosed in populations referred to metabolic bone diseases units. One might expect, therefore, that these subjects are not truly asymptomatic because they constitute a referral population. For example, in a cohort described by Lowe and cols. (49) at the time of diagnosis, 57% had osteoporosis, 11% had documented fragility fractures, and 14% had nephrolithiasis. Other normocalcemic cohorts have been published (50-54), also describing patients from referral populations. While bone disease in these normocalcemic subjects has been noted, in some studies but not in others (51), to be more severe, as determined by DXA, than in subjects with asymptomatic hypercalcemic PHPT, this is likely to be a function of selection bias.

Charopoulos and cols. (55) utilized peripheral quantitative computed tomography to assess the skeleton in subjects with normocalcemic PHPT in comparison to those with hypercalcemic disease. The investigators found catabolic effects in both groups that were more pronounced in hypercalcemic subjects. However, while cortical geometric properties were also adversely affected in subjects with normocalcemic PHPT, trabecular properties were preserved.

The natural history of skeletal disease in normocalcemic PHPT is not well defined, nor is the response to parathyroidectomy. In the cohort described by Lowe and cols. (49) during a mean follow-up period of 3.1 years, 43% of patients had a decline in bone density of at least 5% by DXA, with similar reductions at all sites. In a cohort described by Koumakis and cols. (54), subjects with normal total and ionized calcium levels pre-operatively demonstrated a densitometric gain of 4.1% at the femoral neck at 1 year after parathyroid surgery (p = 0.044), without significant change at the spine or radius.
CONCLUSIONS

The classical descriptions of PHPT are of a highly symptomatic disease with overt skeletal manifestations, including osteitis fibrosa cystica. While uncommon, patients still present with this severe form of PHPT even in countries where multichannel screening is routine. In countries where screening tests are not routine, overt skeletal disease is more common. While the presentation of PHPT has shifted to an asymptomatic one, new technologies such as TBS and HRpQCT have documented more extensive skeletal involvement in asymptomatic PHPT than previously appreciated. Further studies are needed to delineate the skeletal involvement in normocalcemic PHPT. In addition, the extent to which subjects show improvement after successful parathyroid surgery, as determined by these more sensitive approaches to skeletal assessment, is needed.

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