

## Review Article

# Bone Disease in Primary Hyperparathyroidism

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## Abstract

Primary Hyperparathyroidism (PHPT) is a common endocrine disorder characterized by autonomous secretion of parathyroid hormone (PTH) leading to hypercalcemia. Whereas bone mineral density (BMD) is generally preserved at skeletal sites rich in trabecular bone, such as the lumbar spine (LS), studies, using peripheral quantitative computed tomography (pQCT) and high-resolution peripheral quantitative computed tomography (HR-pQCT), have revealed disruption of both cortical and trabecular bone microarchitecture, even in the contemporary 'asymptomatic' form of the disease, highlighting the catabolic effect of PHPT on bone. Moreover, epidemiological studies reported increased fracture risk in patients with PHPT, even in those with BMD T-score within normal or osteopenic range, suggesting that there is a discrepancy between BMD and fracture risk in patients with PHPT and that new diagnostic methods are needed for assessing bone fragility in this population. Surgery is the only definitive treatment for PHPT. Non-surgical treatment is recommended in patients who do not meet the criteria for surgical management, in patients who deny surgical treatment or are high-risk surgical patients. The most frequently used agents are bisphosphonates, denosumab, cinacalcet and vitamin D supplementation.

**Keywords:** Bone Disease, Fracture Risk, Primary Hyperparathyroidism

## Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by hypercalcemia accompanied by elevated or inappropriately normal parathyroid hormone (PTH) levels. 80% of PHPT cases are due to a sporadic, single parathyroid adenoma, 25% are due to hyperplasia of parathyroid glands, and less than 1% are due to parathyroid carcinoma<sup>1</sup>. The skeleton represents

one of the main systems affected in PHPT<sup>2</sup>. The effect of PTH on the skeleton results from its direct actions on bone cells and the kidneys. In particular, PTH increases bone remodeling and induces bone formation, due to its direct effect on osteoblasts and osteocytes. Simultaneously, PTH induces bone resorption through its indirect effect on osteoclasts<sup>3</sup>. The main determinants of the final effect of PTH on bone (anabolic or catabolic effect) are the duration and the periodicity of PTH action on bone. A characteristic example of the catabolic effect of the continuous secretion of PTH on bone is the case of PHPT. This review will focus on skeletal involvement in PHPT as well as treatment options.

## Methodology

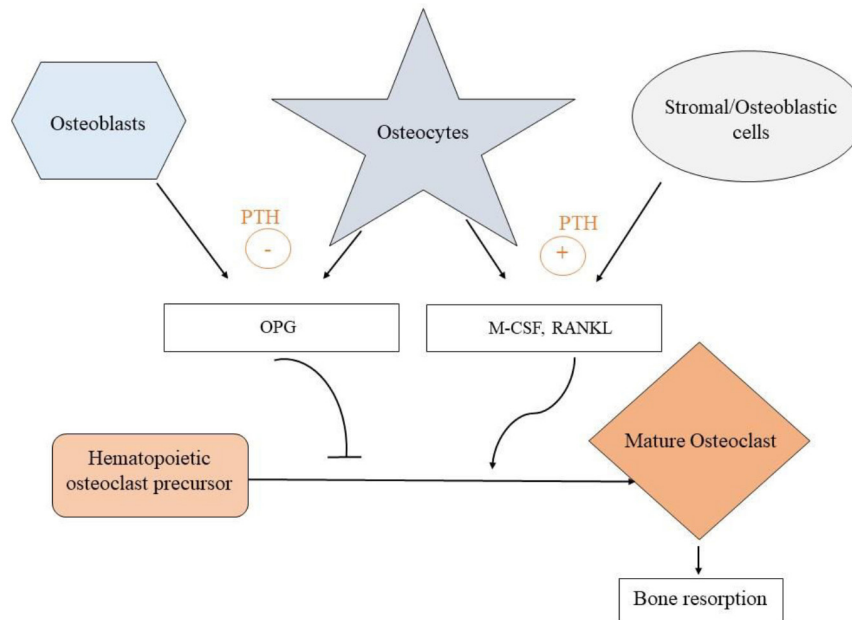
A literature search was performed and included articles available in PubMed, published between 1995 and 2025. The search string was: bone disease in primary hyperparathyroidism. The research lead to 1946 articles.

The authors have no conflict of interest.

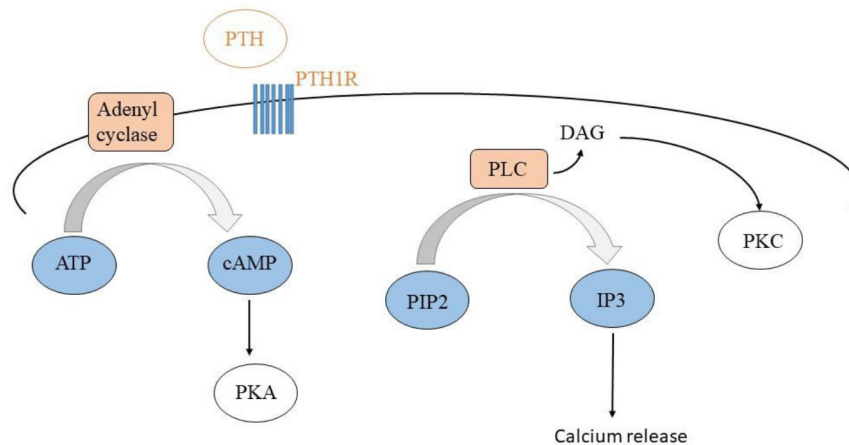
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**Figure 1.** PTH stimulates bone resorption by regulating the expression of pro- and anti-osteoclastogenic cytokines in cells of the osteoblastic lineage. *Osteoclast differentiation from hematopoietic precursors of osteoclasts is stimulated by RANKL and M-CSF and inhibited by OPG. PTH increases osteoclast production and bone resorption by increasing RANKL and inhibiting OPG. +: stimulation; -: inhibition.*



**Figure 2.** PTH's Signaling Pathways in Osteoblastic Cells. *PTH1R is a family B G-protein coupled receptor (GPCRs) which consists of an extracellular domain, seven transmembrane helices and a cytoplasmic tail. PTH binds to PTH1R and activates cellular signaling pathways which mediate PTH actions. In particular, Gs protein activates adenyl cyclase which catalyzes the reaction producing cyclic adenosine monophosphate (cAMP) from adenosine triphosphate (ATP). Consequently, cAMP activates protein kinase a (PKA) which phosphorylates serine and threonine amino acid residues, while Gq protein activates phospholipase C (PLC) which dissolves phosphatidylinositol 4,5-bisphosphate (PIP2), a cell membrane phospholipid, into diacylglycerol (DAG) and inositol 1,4,5-trisphosphate (IP3). Subsequently, IP3 activates calcium channels located in the endoplasmic reticulum and releases calcium into the cytoplasm. The increase of cytoplasmic calcium concentration activates protein kinase C which phosphorylates hydroxyl groups of serine and threonine amino acid residues.*

**Table 1.** Studies using DXA.

Author/Year	Study design	N (subjects)	Mean Age	Asymptomatic disease (N, subjects)	Results	Follow-up period
Silverberg S.J. et al, 1989 <sup>6</sup>	Cross-sectional study	52 (16 men, 36 women)	Men: 55±3, Women: 58 ±2	-	<u>DXA</u> : decreased BMD at the radius and hip, normal BMD at the lumbar spine in relation to the expected mean BMD for sex and age <u>Histomorphometric assessment of transiliac crest bone biopsies</u> : 84% had cortical width below the control mean, whereas cancellous bone volume was preserved	-
Silverberg S. J. et al, 1999 <sup>8</sup>	Prospective study	60 (14 men, 46 women)	58±2	52	<u>DXA</u> : 22 out of 60 had a decrease in BMD at any skeletal site (10% reduction)	10 years
Sudhaker D. et al, 2004 <sup>109</sup>	Prospective study	28 (7 men, 21 women)	63±7.21	28	<u>DXA</u> : Statistically significant BMD reduction at the hip	
Ambrogini E. et al, 2007 <sup>110</sup>	Prospective study	26 (2 men, 24 women)	65±6	26	<u>DXA</u> : Statistically significant BMD reduction at the hip	1 year
Bollerslev J. et al, 2007 <sup>111</sup>	Prospective study	95 (13 men, 82 women)	64.5±7.8	95	<u>DXA</u> : No statistically significant change of BMD at any skeletal site	2 years
Rubin M. R. et al, 2008 <sup>1</sup>	Prospective study	57 (12 men, 45 women)	57±2	49	<u>DXA</u> : 35% BMD reduction at the radius, 10% BMD reduction at the hip, stable BMD at the lumbar spine	15 years
Lundstam K. et al, 2017 <sup>7</sup>	Prospective study	73 (9 men, 64 women)	62.8±7.3	73	<u>DXA</u> : decreased BMD at the radius and hip, stable BMD at the lumbar spine	5 years

- Silverberg S.J. et al, 1989<sup>6</sup>. No definition for asymptomatic patients was mentioned
- Silverberg S. J. et al, 1999<sup>8</sup>. Asymptomatic patients were defined according to 1990 NIH criteria for asymptomatic PHPT<sup>9</sup>. The term “asymptomatic primary hyperparathyroidism” was used to describe the clinical profile of patients with documented primary hyperparathyroidism without symptoms or signs that are commonly attributable to the disease. In contrast, patients who present with important bone, renal, gastrointestinal, or neuromuscular symptoms that are typical of primary hyperparathyroidism were considered to be “symptomatic”
- Sudhaker D. et al, 2004<sup>109</sup>. Asymptomatic patients were not clearly defined (The patients in this study were asymptomatic, had milder disease, and were generally representative of the vast majority of patients with contemporary primary hyperparathyroidism, the inclusion criteria were age between 50 and 75 years old regardless of gender or ethnicity; albumin-adjusted serum calcium (Ca) levels between 10.1 and 11.5 mg/dl (2.52–2.87 mmol/liter); intact PTH level greater than 20 pg/ml (20 ng/liter); normal renal function, defined as serum creatinine (Cr) less than 1.5 mg/dl (133 mol/liter); forearm bone mineral density within 2 SD adjusted for age, sex, and race (Z-scores); absence of relevant symptoms and complications directly attributable to either hypercalcemia or excess PTH secretion;)
- Ambrogini E. et al, 2007<sup>110</sup> Asymptomatic patients were defined according to 1990 NIH criteria for asymptomatic PHPT, because this study began before the 2002 Workshop on Asymptomatic PHPT<sup>9</sup>
- Bollerslev J. et al, 2007<sup>111</sup>. Asymptomatic patients were defined according to 1990 NIH criteria for asymptomatic PHPT<sup>9</sup>
- Rubin M. R. et al, 2008<sup>1</sup>. Asymptomatic patients were defined according to 1990 NIH criteria for asymptomatic PHPT<sup>9</sup>
- Lundstam K. et al, 2017<sup>7</sup>. Asymptomatic patients were defined according to 1990 NIH criteria for asymptomatic PHPT<sup>9</sup>

The title and abstract of the articles retrieved were reviewed and evaluated for their relevance by two observers (EK, ST). 585 case reports were excluded, 112 articles referring to syndromic forms of PHPT, as well as genetics were also excluded, 72 articles referring to paediatric population and pregnancy were excluded, 240 articles referring to non-skeletal clinical manifestations of PHPT were excluded, 819 articles were excluded due to several other reasons (irrelevant information, no abstract available, no access

to the original article, other published language besides English, articles with repeated information and different publication year, from which the most recent published was included). Studies highlighting the effect of PHPT on bone tissue were eligible for further evaluation.

#### *Skeletal Manifestations of PHPT*

PTH can have both osteoanabolic and catabolic effect on the skeleton, depending on the amount, the duration and

most importantly on the periodicity of its action on bone cells (Figures 1, 2).

The skeleton is one of the main target organs in PHPT. Before the shift of PHPT presentation from symptomatic to asymptomatic or mildly symptomatic disease, the classical skeletal manifestation of PHPT was osteitis fibrosa cystica (OFC). This condition is characterized by bone pain and pathologic fractures as a result of the increased activation of osteoclasts leading to increased bone resorption, cortical bone destruction and formation of fibrous cysts. The most common histological finding of OFC is increased number of osteoclasts, with hemosiderin-laden macrophages and cyst formation, as well as bone marrow fibrosis<sup>4</sup>.

The classical radiologic feature of OFC is subperiosteal resorption of cortical bone, easily detected in x-rays images of the phalanges. Bone margins may be blurred by osteosclerotic or osteolytic lesions, usually found in the pelvis and long bones and, cortical bone may be extremely thin<sup>5</sup>. Bone cysts and brown tumors may also be present. X-ray images of the skull may show 'salt and pepper' appearance, due to multiple tiny well-defined lucencies in the calvaria caused by resorption of trabecular bone. Elevated alkaline phosphatase (ALP) is the most common laboratory finding.

Nowadays, OFC is extremely rare and bone disease in PHPT is usually subclinical.

#### BMD changes in PHPT

Studies with the use of dual X-ray absorptiometry (DXA), show that bone mineral density (BMD) is generally preserved at skeletal sites rich in trabecular bone, such as the lumbar spine (LS), whereas BMD is lower at skeletal sites that primarily consist of cortical bone such as the forearm. A cross-sectional study by Silverberg et al<sup>6</sup>, an RCT by Lundstam et al<sup>7</sup>, as well as long term observational studies have verified the above findings<sup>1,8</sup>. On the other hand, other RCT's showed no statistically significant change at any skeletal site or have revealed statistically significant BMD reduction only at the hip, probably due to the short-term of follow-up (1-3.5 years of follow-up) (Table 1). As shown in Table 1, these were studies that didn't clearly define asymptomatic patients, or they defined them, according to 1990 NIH criteria for asymptomatic PHPT<sup>9</sup>. In particular, the term "asymptomatic primary hyperparathyroidism" was used to describe the clinical profile of patients with documented primary hyperparathyroidism without symptoms or signs that are commonly attributable to the disease. In contrast, patients who present with important bone, renal, gastrointestinal, or neuromuscular symptoms that are typical of primary hyperparathyroidism were considered "symptomatic".

The relative preservation of trabecular bone in patients with PHPT can be explained by the longer active formation period that characterizes bone turnover in patients with PHPT. This is a result of the increased lifetime of osteoblasts due to the continuous effect of PTH<sup>10</sup>.

However, the elevated vertebral fracture risk in patients with PHPT is in contradiction with the preservation of trabecular bone<sup>11-16</sup>.

Since DXA measurements are 2-dimensional, they can be affected by bone size. The increase of bone cross-sectional area in patients with PHPT may be the cause that leads to the observed 'preservation' of BMD at the LS. Another reason for the above inconsistency, might be the so called 'trabecularization' of cortical bone. PHPT is characterized by increased bone turnover which leads to increased cortical porosity. The 'trabecularized' cortical bone can be perceived as trabecular bone, and be used for the estimation of trabecular bone density<sup>17</sup>.

#### Changes in histomorphometric parameters of transiliac crest bone biopsies

The preferential negative effect of PHPT on cortical bone with the apparent preservation of cancellous bone has been confirmed by studies with histomorphometric assessment of transiliac crest bone biopsies. These studies have shown low cortical thickness and increased cortical porosity, whereas trabecular number and connectivity were preserved<sup>10,18-22</sup> (Table 2). Those are cross-sectional studies, primarily analyzing postmenopausal women with mild PHPT (in some studies mild PHPT is not defined, whereas in others it is defined according to 1990 NIH criteria for asymptomatic PHPT). Also, it should be mentioned that since the iliac crest is not a weight-bearing bone, it is probably not a representative skeletal site for the assessment of bone disease in PHPT. Cohen et al found no association between parameters of bone microarchitecture as measured by HR-pQCT at the radius and tibia and histomorphometric parameters of transiliac crest bone biopsies, strengthening the argument that transiliac crest bone biopsies might not be suitable for the assessment of bone disease in PHPT<sup>23</sup>.

#### Bone microarchitecture parameters assessed by pQCT and HR-pQCT

Since bone strength is determined by other parameters besides BMD, such as cortical thickness, trabecular number and connectivity, it is possible that the disruption of these indices of microarchitecture might be responsible for the increased fracture risk in patients with PHPT. These properties can be assessed by pQCT and HR-pQCT, that can separately assess cortical and trabecular bone microarchitecture and bone geometry<sup>24-26</sup>. Studies with these techniques have revealed disruption of cortical and trabecular bone microarchitecture. In particular, cortical and trabecular volumetric bone mineral density (vBMD), cortical thickness, connectivity and number of trabeculae were reduced and cortical porosity was increased, both at the radius and tibia, highlighting the catabolic effect of PHPT on cortical and trabecular bone<sup>17,27-30</sup>. Also, endocortical circumference increased due to increased bone resorption, leading to enlargement of the medullary cavity, while bone cortex was thinning<sup>31,32</sup> (Table 3). The above studies

**Table 2.** Studies using histomorphometric assessment of transiliac crest bone biopsies.

Author/Year	Study design	N (subjects)	Age	Asymptomatic disease (N, %)	Histomorphometric assessment of transiliac crest bone biopsies
Parisien M. et al, 1990 <sup>21</sup>	Cross-sectional study	27 (10 men, 17 women)	Men: 28-68, Women: 26-72	-	Increased bone remodeling, lower cortical thickness and increased trabecular bone volume
Christiansen P. et al, 1992 <sup>22</sup>	Cross-sectional study	69 (21 men, 48 women)	Median: 58	9%	Increased bone remodeling, slight thinning of trabeculae
Parisien M. et al, 1992 <sup>18</sup>	Cross-sectional study	37 (14 men, 23 women)	Men: 49±11 Women: 53±11	82%	Increased trabecular bone volume and connectivity
Brockstedt H. et al, 1995 <sup>20</sup>	Cross-sectional study	39 (16 men, 23 women)	Men: 52, Women: 60	41%	Increased cortical porosity, no change in trabeculae
Dempster D.W. et al, 1999 <sup>10</sup>	Cross-sectional study	19 (19 women)	-	-	Increased trabecular bone volume
Dempster D.W. et al, 2007 <sup>19</sup>	Cross-sectional study	44 (15 men, 29 women)	-	-	No change in trabeculae

• Parisien M. et al, 1990<sup>21</sup>. No definition for asymptomatic patients was mentioned  
 • Christiansen P. et al, 1992<sup>22</sup>. No definition for asymptomatic patients was mentioned  
 • Parisien M. et al, 1992<sup>18</sup>. No definition for asymptomatic patients was mentioned  
 • Brockstedt H. et al, 1995<sup>20</sup>. Asymptomatic patients were defined according to 1990 NIH criteria for asymptomatic PHPT<sup>9</sup>  
 • Dempster D.W. et al, 1999<sup>10</sup>. Asymptomatic patients were defined according to 1990 NIH criteria for asymptomatic PHPT<sup>9</sup>  
 • Dempster D.W. et al, 2007<sup>19</sup>. Asymptomatic patients were defined according to 1990 NIH criteria for asymptomatic PHPT<sup>9</sup>

**Table 3.** Studies using pQCT and HR-pQCT.

Author/Year	Study design	N (subjects)	Age	Bone assessment technique/ Skeletal site	Results
Chen Q. et al, 2003 <sup>28</sup>	Cross-sectional study	36 (women)	Mean age: 60.5±10.8	pQCT/ radius	Decreased trabecular and cortical vBMD, decreased cortical thickness, increased endosteal and periosteal circumference
Charopoulos I. et al, 2006 <sup>29</sup>	Cross-sectional study	52 (women)	Mean age: 59.26±8.5	pQCT/ tibia	Decreased trabecular and cortical vBMD and BMC
Hansen S. et al, 2010 <sup>27</sup>	Cross-sectional study	27 (women)	Median: 60	HR-pQCT/ radius, tibia	<u>DXA</u> : reduced BMD at the radius, hip and lumbar spine <u>HR-pQCT</u> : reduced trabecular and cortical vBMD, reduced cortical thickness at the radius. No difference in HR-pQCT parameters were found at the tibia
Stein M. et al, 2013 <sup>31</sup>	Cross-sectional study	51 (women)	Mean age: 70±1	HR-pQCT/ radius, tibia	<u>DXA</u> : reduced BMD at the radius and the hip but not at the lumbar spine <u>HR-pQCT</u> : reduced cortical and trabecular vBMD, reduced cortical thickness at both skeletal sites
Thuy D.T. et al, 2013 <sup>17</sup>	Cross-sectional study	43 (12 men, 31 women)	Mean age: 62.9±13.8	HR-pQCT/ radius, tibia	Reduced cortical and trabecular vBMD, reduced cortical thickness and increased cortical porosity at both skeletal sites
Wang W. et al, 2019 <sup>30</sup>	Cross-sectional study	58 (17 men, 41 women), Chinese population	Mean age: 49.9±15.1	HR-pQCT/ radius, tibia	Reduced cortical and trabecular vBMD, reduced cortical thickness and widely spaced trabeculae at both skeletal sites
Karlafti E. et al, 2024 <sup>32</sup>	Cross-sectional study	41 (women)	Mean age: 60.1±8.4	pQCT/ radius, tibia	<u>DXA</u> : reduced BMD at the lumbar spine and the hip <u>pQCT</u> : reduced cortical and trabecular vBMD, reduced cortical thickness at both skeletal sites

included primarily postmenopausal women, limiting the ability to draw conclusions about males and premenopausal women with PHPT. However, we should bear in mind that PHPT primarily manifests in this population.

#### TBS and BSI for assessment of bone disease in PHPT

Given that the above techniques are currently employed in the research setting, assessment of bone microarchitecture by other methods that could easily be used in everyday practice, is more useful<sup>33</sup>. Trabecular bone score (TBS) and bone strain index (BSI) are tools that can be used to assess bone microarchitecture and bone strength indirectly. There are studies that have showed that TBS is related with parameters of bone microarchitecture such as the number and connectivity of trabeculae. High TBS values are related to preserved bone microarchitecture with high connectivity and number of trabeculae. On the other hand, low TBS values are related to disrupted bone microarchitecture and bone prone to fractures<sup>34,35</sup>. Moreover, TBS has been used for the estimation of fracture risk<sup>36</sup>. TBS values are reduced in postmenopausal women with a history of osteoporotic fracture compared to women matched for age and BMD, but with no such history<sup>37-39</sup>. TBS is also useful for the estimation of fracture risk in patients with secondary causes of osteoporosis, as well as in patients with PHPT<sup>40</sup>. Studies have shown that TBS is significantly lower in patients with PHPT, even if DXA measurements at the LS are within normal limits<sup>41-43</sup>. Indeed, Eller-Vainicher et al, found a significant decrease of TBS in patients with PHPT who had a vertebral fracture, compared to those without, with no statistical differences in BMD measurements, while TBS values <2.0 were associated with the presence of VFs<sup>41</sup>. Finally, BSI has been found to be an independent predictor for vertebral fractures (VFs) in patients with PHPT. Tabacco et al found that BSI was impaired, in 50 PHPT patients when compared to 100 age and sex-matched controls<sup>44</sup>.

The clinical utility of the above tools and their predictive value has not being fully assessed, that is why they are not recommended for systemically use for skeletal evaluation of patients with PHPT<sup>45</sup>. Future research will elucidate their clinical value.

#### Fracture risk

Fracture risk is increased in patients with PHPT<sup>13-15</sup>. The prevalence of VFs in patients with PHPT ranges from 5% to 35%<sup>15,46</sup>. The wide range of the reported prevalence might be related to the inconsistency in fracture definition (whether they came to clinical attention or they were asymptomatic) and to selection bias that could affect the results since some patients had primary hyperparathyroidism diagnosed while being examined and treated for a fracture. Also, the diagnosis of primary hyperparathyroidism might be related to an increased awareness for skeletal assessment and detection of otherwise asymptomatic VFs.

In 1975, Dauphine et al were the first to suggest that VFs might be clinical manifestations of both mild and severe PHPT<sup>47</sup>. In cohort studies, where patients with different disease severity were included, increased fracture risk was found at the forearm and the spine, while fracture risk at the hip was marginally increased<sup>11-13</sup>.

A prospective study by Cipriani et al and a case-control study by De Geronimo et al, showed that vertebral fractures can develop even in asymptomatic or mild PHPT, despite normal DXA measurements<sup>15,46</sup>. Cipriani et al, defined "asymptomatic" patients based on the absence of the following criteria: 1) symptomatic hypercalcemia, based on the patient's history and the presence of any of the following symptoms not ascribed to other concomitant conditions: polyuria, dehydration, nausea, vomiting, constipation, anorexia, fatigue, and neuromuscular symptoms (myopathy, depression, cognitive dysfunction, lethargy, coma), 2) history of fragility fractures in any of the following sites: vertebra, hip, distal radius, proximal humerus, and pelvis, and 3) history of nephrolithiasis or nephrocalcinosis (at least one episode of renal colic in the last 5 years and/or positive kidney imaging), while De Geronimo et al, defined mild PHPT according to the criteria established by the Consensus Development Conference on the Management of Asymptomatic Primary Hyperparathyroidism, recently reviewed by Bilezikian et al. as follows: 1) serum calcium greater than 1 mg/dl above the upper limit of normal, 2) 24-h total urine calcium excretion of more than 400 mg, 3) creatinine clearance reduced by more than 30% compared to age-matched persons, 4) bone density at the lumbar spine (LS), hip or distal radius that is more than 2.5 S.D. below peak bone mass, and 5) patients under 50 years of age.

Khosla et al found that fracture risk at the spine, forearm and pelvis was increased in patients with PHPT, whereas at the hip it was moderately increased, within the first five years of the disease<sup>48</sup>. A recent register-based survey of patients with PHPT and matched controls in Denmark, showed that fracture risk was increased in patients with PHPT irrespective of the disease severity, defined by serum calcium and PTH levels, as well as BMD measurements<sup>49</sup>.

In an attempt to elucidate fracture risk in PHPT two recent meta-analyses were published. The first meta-analysis reported a significantly increased risk of VFs in PHPT (OR 3.00). Moreover, the risk of VFs was increased if analyses were restricted to studies reporting on patients with mild PHPT (OR 4.22). Also, an increased risk of fracture at the forearm (OR 2.36) was reported while the risk estimate for hip fractures was non-significantly increased (OR 1.27). Finally, the risk of any fracture was increased in PHPT patients compared with controls (OR 2.01)<sup>50</sup>. It should be mentioned that the definition of mild PHPT, was determined by the authors of each study individually, increasing the heterogeneity of the analyzed studies. Moreover, most of the participants were postmenopausal women, so the findings can't be generalized in men and younger adults with PHPT.

The Fourth International Workshop for management of asymptomatic PHPT, recommended surgery in patients with VFs or a T-score less than or equal to -2.5 at the lumbar spine, total hip, femoral neck or distal 1/3 radius as assessed by DXA<sup>51</sup>. However, the above meta-analysis showed an increased risk of VFs even in patients with mild disease, who do not fulfill the above criteria, despite the fact that the risk of other types of fractures was undefined. Future studies exploring the risk of different fracture types in patients with mild PHPT are needed.

Another meta-analysis reported that the risk of VFs and total fracture risk was significantly higher among patients with PHPT compared with the control population (RR, 2.57, RR, 1.71), while there was no difference in hip fracture risk (RR, 1.45)<sup>52</sup>. As hip is rich in cortical bone, which is negatively affected in PHPT, an increased risk of hip fracture would have been expected. Cortical thinning through PTH-mediated endosteal resorption is compensated for by PTH-mediated periosteal apposition, leading to bone with increased cross-sectional diameter. This increase in bone size seems to provide biomechanical protection for the skeleton and may explain the absence of increased risk of hip fracture in patients with PHPT.

Finally, FRAX tool is a fracture risk calculator used for the assessment of fracture risk in general population, based on clinical risk factors and BMD measurements. It calculates the 10-year probability of a major osteoporotic fracture and a hip fracture. However, its credibility in fracture risk assessment in patients with PHPT has not been yet evaluated<sup>45,53</sup>.

In clinical practice, since up to 25% of patients with PHPT develop asymptomatic vertebral fractures<sup>16</sup>, the Fifth International Workshop on evaluation and management of PHPT, recommends routine vertebral imaging in the initial evaluation of all patients with PHPT [vertebral fracture assessment (VFA) or vertebral X-rays]<sup>45</sup>.

The discrepancy between low BMD and fracture risk in patients with PHPT, suggest that new diagnostic procedures, besides three-site DXA BMD measurements (lumbar spine, hip, distal 1/3 radius), are needed, to detect bone fragility in this population. Since no specific guidelines have developed for the assessment of fracture risk in patients with PHPT and DXA with T-scores >-2.5, the Fifth International Workshop on evaluation and management of PHPT suggests that, TBS, if available, can be used as a semi-quantitative measure of bone quality in PHPT. However, the uncertainty surrounding its utility mitigated against its inclusion as a stand-alone guideline for surgery<sup>45</sup>. Also, FRAX tool would help to estimate fracture risk in patients with PHPT. It is likely that the factors identified by FRAX are as important in PHPT as they are in subjects without PHPT, but at this point, disease-specific data in PHPT are not available. Also, FRAX score adjusted by TBS could be more reliable, for predicting the risk of osteoporotic fracture in patients with PHPT<sup>54</sup>.

#### *Risk factors for the development of vertebral fractures in patients with PHPT*

A retrospective cross-sectional study assessed the possible risk factors related to the occurrence of VFs in patients with PHPT. The rate of VFs assessed by vertebral fracture assessment (VFA) reached 12.8%. PTH, calcium levels and TBS were not associated with VFs. In addition, race, gender, body mass index (BMI), phosphorus, 25(OH)D levels, PHPT duration, calcium and vitamin D supplementation, the use of steroids and comorbidities such as diabetes mellitus and rheumatoid arthritis were also not related with the presence of VFs. On the other hand, patients with VFs were older, had worse renal function, osteoporosis at the hip and a history of osteoporotic fracture and also, most of them had taken anti-osteoporotic medication at least once<sup>55</sup>. Moreover, TBS was a poor prognostic factor for VFs<sup>56</sup>.

On the other hand, other studies have found that TBS was related to increased vertebral fracture risk<sup>41,42</sup>. In particular, TBS was significantly lower in patients with major osteoporotic fractures<sup>43,54</sup> even after adjustment for age, sex, BMI and years since menopause<sup>54</sup>. The discrepancy between studies might be due to the sample (different age of the participants, presence of other factors related to fracture risk) and different method for assessing VFs.

Another study has also showed that patients with VFs were older, shorter and had worse renal function, whereas there was no difference as far as PTH, calcium levels and BMI was concerned<sup>57</sup>. Also, BMD at the LS was an independent risk factor for VFs, while 16.1% of patients with PHPT and VFs had T-score at the LS > -2.5, suggesting that there is discrepancy between aBMD and fracture risk in patients with PHPT<sup>16</sup>.

Also, Cristina Eller-Vainicher et al found that A986S single-nucleotide polymorphism (SNP; AS/SS) in CaSR gene is often detected in patients with PHPT and VFs. AS/SS genotype is related with increased osteoclastogenesis and osteoclastic activity, low bone quality and increased prevalence of fractures<sup>58</sup>.

Finally, another study showed that low LDL cholesterol is related to increased risk for VFs in women with PHPT independently of renal function, age, body size index, BMD, bone turnover and serum levels of Ca, PTH and albumin<sup>59</sup>. The underlying mechanism is unknown. Also, Delfini et al found increased leptin levels and low levels of adiponectin, as well as increased total cholesterol, LDL cholesterol, triglycerides and low HDL cholesterol in patients with PHPT<sup>59,60</sup>. These cytokines can affect lipid metabolism and bone fragility in patients with PHPT.

However, due to low sensitivity of the above findings and the increased prevalence of VFs in patients with PHPT, these risk factors can't be used as criteria for the selection of patients with PHPT who are to be screened for VFs. Indeed, in the recent guidelines, it is suggested that all patients with PHPT, should be screened for the presence of VFs by -ray or VFA.

### *PHPT severity and bone disease*

The association between PHPT disease severity and fracture risk can be assessed by the severity of biochemical abnormalities of PHPT (e.g. hypercalcemia, hypophosphatemia, hypercalciuria, levels of PTH).

#### Normocalcemic primary hyperparathyroidism (NPHPT)

Normocalcemic primary hyperparathyroidism (NPHPT) is characterized by normal ionized and total calcium levels with increased levels of PTH on at least 2 measurements over a 3- to 6-month period. Many studies support that NPHPT is an earlier stage of PHPT that gradually evolves to hypercalcemia, since NPHPT seems to represent a biochemical phenotype in between hypercalcemic PHPT and normal healthy population<sup>61,62</sup>. Palermo et al. showed that patients with NPHPT had similar radial BMD to controls, whereas radial BMD was reduced in patients with hypercalcemic PHPT. On the other hand, patients with NPHPT, PHPT and controls had similar BMD at the LS and hip. Moreover, patients with NPHPT had similar prevalence of VFs to controls, whereas VFs were increased in patients with hypercalcemic PHPT. The above findings highlight that milder PHPT is related to less severe bone disease<sup>63</sup>. Also, serum phosphate is inversely related to PHPT severity, as defined by calcium and PTH levels and BMD impairment at the radius<sup>64</sup>. As far as TBS is concerned, in NPHPT TBS is not reduced<sup>65</sup>.

On the other hand, other studies concluded that the skeleton is similarly affected in normocalcemic and hypercalcemic hyperparathyroidism since no statistically significant difference in BMD was found between these patients and no association between the disease severity as defined by calcium levels and fracture risk in patients with PHPT was observed<sup>11,12,66</sup>. Patients with NPHPT had similar rates of osteopenia and osteoporosis and similar fracture rates compared to patients with symptomatic PHPT<sup>67</sup>. The basic limitation of the above studies is the small sample size as well as selection bias, since NPHPT was often diagnosed during the evaluation of a fracture. Conducting further studies focusing on NPHPT, will elucidate the bone parameters that are affected and give information about the natural history of this entity.

As far as fracture risk in NPHPT is concerned, in the MONICA study on a randomly selected Swedish cohort from the general population, there was no increase in fractures in normocalcemic PHPT patients over a 17-year period of follow-up<sup>68</sup>.

#### Asymptomatic primary hyperparathyroidism

Primary hyperparathyroidism is defined as asymptomatic when there is lack of symptoms or signs that are traditionally attributed to hypercalcemia or elevated parathyroid hormone (PTH)<sup>51</sup>. Silverberg et al, after a 10-year follow-up of asymptomatic patients with PHPT (without osteitis fibrosa cystica, nephrolithiasis, classic neuromuscular

symptoms, or hyperparathyroid crisis) reported a progression of disease, defined as the development of at least one new indication for parathyroidectomy in 25% percent of the patients<sup>8</sup>. A study on fracture risk in patients with hypercalcemic PHPT revealed increased fracture risk at the radius and the spine, even in milder forms of the disease (asymptomatic patients with mean calcium levels at  $10.9 \pm 0.6$  mg/dl), and moderately increased fracture risk at the hip<sup>13</sup>.

A recent meta-analysis has revealed that the increased vertebral fracture risk is present even in mild disease as defined by the absence of complications (impaired renal function or nephrolithiasis, BMD T-score  $< -2.5$ , radiological findings of OFC or a history of low-energy fractures) and calcium levels below 11.6 mg/dl, meaning serum calcium  $> 1$  mg/dL (0.25 mmol/L) above the upper limit of normal (one of the criteria used for surgical treatment of asymptomatic PHPT)<sup>50</sup>.

Also, another study has showed that VFs are increased in patients with clinically significant disease whether it is symptomatic (nephrolithiasis, symptomatic bone disease, neuromuscular symptoms) or asymptomatic but meet the criteria for parathyroidectomy, whereas vertebral fracture risk is not increased in asymptomatic patients who do not meet these criteria<sup>16</sup>. Patients were classified as asymptomatic if they didn't have symptoms of hypercalcemia, nephrolithiasis, OFC and low energy fractures, whereas the surgical criteria used were the ones that were established by the 2002 Workshop on asymptomatic PHPT<sup>69</sup>.

De Geronimo et al, also tried to assess fracture risk in PHPT in relation to the disease severity<sup>15</sup>. Fracture prevalence was increased in patients with PHPT as compared to controls, but no statistically significant difference was observed between mild and severe disease. Also, PTH levels were inversely associated with BMD. Since VFs prevalence wasn't different between mild and severe type of the disease, while BMD was, it seems that BMD is not the only parameter responsible for fracture risk in patients with PHPT.

Finally, another study showed that asymptomatic PHPT as defined by the absence of nephrolithiasis, radiological findings of OFC, T-score  $< 2.5$ , calcium levels less than 3.00 mmol/L, creatinine levels less than 133 mmol/L, is not characterized by increased vertebral fracture risk<sup>70</sup>.

In conclusion, the discrepancy between studies on fracture risk and PHPT disease severity highlights the need for conducting further studies with less heterogeneity, that could lead to safer conclusions on PHPT and bone disease.

#### *Management*

PHPT management includes surgical and medical therapy. Surgical treatment refers to parathyroidectomy (PTx). Medical therapy includes anti-resorptive agents such as bisphosphonates (mainly alendronate) and denosumab, calcimimetics, combination of calcimimetics and denosumab

or alendronate, hormone replacement therapy / SERMs (selective estrogen receptor modulators) and calcium and vitamin D supplementation.

### Surgical Management

Surgery is the only definitive treatment for PHPT, with a success rate of up to 95% and with low risk of postoperative complications. Surgical treatment is recommended to every symptomatic patient with PHPT, according to the recent international guidelines<sup>45</sup>. Symptomatic PHPT is associated with overt skeletal and renal complications that may include osteitis fibrosa cystica and/or fractures, chronic kidney disease, nephrolithiasis and/or nephrocalcinosis. In case of asymptomatic PHPT, surgical treatment is recommended in cases fulfilling at least one of the following criteria: 1. calcium levels 1 mg/dl above the upper limit of normal, 2. BMD by T-score below  $\leq -2.5$ , 3. Presence of vertebral fractures, 4. renal impairment (estimated glomerular filtration rate below 60 ml/min), 5. severe hypercalciuria (24h urinary calcium excretion >250 and 300 mg/d in women and men respectively), 6. nephrolithiasis or nephrocalcinosis and 7. age under 50. In case of absence of the above criteria, surgical management is still a therapeutic option, as long as there is a patient-physician agreement and there are no contraindications.

Parathyroidectomy (PTx) is a safe procedure in the hands of an experienced surgeon. An experienced surgeon is considered someone who performs at least 50 parathyroidectomies per year<sup>71</sup>.

Surgical management improves BMD, especially in patients with severe disease, younger age and better renal function<sup>72,73</sup>, as well as in patients with NPHPT, as reported by several studies<sup>74,75</sup>.

BMD is increased within the first year postoperatively and PTH levels normalize. BMD increase can reach 12% at the LS as well as at the femoral neck (FN) and this increase can be sustained for 15 years both at cortical and trabecular bone. Higher BMD increase is observed at LS (up to 8% within the first year), while BMD at the FN is increased more progressively, about 5% within the first year and reaches 10%, within the first 5 years<sup>1</sup>. Moreover, cancellous architecture evaluated by TBS has shown improvements 2 years after PTx<sup>41</sup>. Despite the fact that PTx increases BMD at the LS, a 10-year cohort study revealed that no statistically significant difference was found in fracture incidence in patients who underwent PTx<sup>76</sup>.

In a retrospective cohort study which included 16374 patients with PHPT, PTx was found to reduce the risk for any fracture, including hip fractures, as well as cardiovascular events and death<sup>77</sup>. Another observational study including 210206 patients with PHPT found that PTx reduced the risk of any fracture by 1.2%, 2.8% and 5.1%, at 2, 5 and 10 years postoperatively, respectively<sup>78</sup>. Also, a recent meta-analysis reported that PTx significantly reduced overall fracture risk, as well as risk of hip fracture<sup>79</sup>.

Another meta-analysis on the effect of PTx on skeletal

outcomes, risk of nephrolithiasis and quality of life in mild asymptomatic PHPT (not fulfilling the criteria for surgery) revealed that PTx significantly increases BMD at the LS and total hip (TH), but not in the FN and forearm and decreases calcium concentrations. No statistically significant effect was observed regarding nephrolithiasis and quality of life<sup>80</sup>.

On the other hand, a recent Cochrane review on the effect of PTx on asymptomatic PHPT reported that it has little or no effect on BMD at the LS and FN, as well as on serious adverse events and hospitalization for hypercalcemia, all-cause mortality and quality of life, although it increases the cure rates of PHPT<sup>81</sup>.

### Medical treatment

Medical treatment is recommended in patients who do not meet the criteria for surgical management, in patients who deny surgical treatment or are high-risk surgical patients. In those patients who do not undergo PTx, it is recommended that they have an annual measurement of calcium levels, 25(OH)D, PTH levels and assessment of renal function. An annual BMD measurement at three sites (lumbar spine, femur, radius) should be performed. Several studies reveal that after 10 years of follow-up, a significant reduction in BMD will develop in about 40% of these patients. An ideal medical treatment would be the one that could normalize calcium and PTH levels, reduce renal calcium excretion to normal and the risk of nephrolithiasis, increase BMD and reduce fracture risk.

Several agents have been used in patients with PHPT and have met some of the above goals. Most often used drugs are anti-resorptive agents such as bisphosphonates (mainly alendronate), denosumab, calcimimetics, the combination of calcimimetics and denosumab or alendronate, hormone replacement therapy / SERMs (selective estrogen receptor modulators) and calcium and vitamin D supplementation.

### Bisphosphonates

Studies have shown that bisphosphonates could be used for PHPT bone disease. Bisphosphonates inhibit osteoclastic activity and decrease the rate of bone turnover in patients with PHPT. This reduction in bone turnover is associated with increased BMD<sup>82</sup>. Several bisphosphonates have been studied for their efficacy.

Alendronate is the most broadly used bisphosphonate in PHPT bone disease<sup>83</sup>. Studies have shown a significant increase of BMD at the LS and FN, by 4.92% and 2.12% respectively, after 12 months, as well as in patients with NPHPT<sup>84-86</sup>. BMD changes are more apparent at skeletal sites rich in trabecular bone, such as the LS, whereas BMD changes are less obvious at skeletal sites rich in cortical bone, such as the distal radius. Moreover, alendronate seems to have small effect on calcium levels since the reduction is transient and it lasts for about 6 months<sup>87</sup>. Finally, some studies have used risedronate in PHPT but with no significant BMD change or change in pQCT variables<sup>88</sup>, while other studies revealed that surgical

treatment outweighs risedronate in improving trabecular bone mineralization and BMD at the tibia, whereas it has milder effect on cortical bone<sup>89</sup>.

In conclusion, bisphosphonates are used in patients with PHPT and low BMD who deny surgical treatment or are high-risk surgical patients due to comorbidities. Alendronate is the most studied bisphosphonate for PHPT bone disease and is recommended for those patients who do not undergo surgical therapy.

#### Denosumab

Studies have shown that denosumab increases BMD in patients with PHPT by 11.2% at the LS and by 7.9% at the FN. However, calcium levels remain stable while PTH increases in 28% of the patients<sup>90</sup>. Osteonecrosis of the jaw and atypical femoral fracture are rare adverse events. The incidence of osteonecrosis of the jaw is 0.04% after 2 years of denosumab administration and 0.5% after 7 years<sup>91</sup>. As far as the atypical femoral fracture is concerned, only 2 cases in 4550 patients that received denosumab for 10 years occurred, verifying its rarity. Finally, no risk for delayed fracture healing is observed<sup>92</sup>. Discontinuation of long-term denosumab (>2-3 years) is associated with increased risk for multiple vertebral fractures in up to 7-10% of patients. If denosumab discontinuation is considered in a patient with PHPT, prompt administration of bisphosphonates, mainly zoledronate, probably every 6-12 months with close monitoring of bone turnover markers is mandatory<sup>93</sup>.

#### Calcimimetics

Cinacalcet is a calcimimetic compound which activates CaSR of the parathyroid cell and inhibits parathyroid hormone secretion<sup>94</sup>. Studies have revealed that cinacalcet normalizes serum calcium and reduces PTH levels<sup>95</sup>. However, no significant change in BMD is observed<sup>96,97</sup>.

#### Combination of calcimimetics and denosumab or alendronate

Since cinacalcet and bisphosphonates differ in their mechanism of action, their combined administration could be useful for the reduction of calcium levels as well as for BMD increase<sup>83</sup>. Alendronate combined with cinacalcet, increased BMD at the LS and FN in 12 months, whereas no significant change was observed with cinacalcet alone<sup>98</sup>. Denosumab combined with cinacalcet, increased BMD at the LS and FN in 50 weeks, by 5.4% and 4.5% respectively, and normalized calcium levels in 64%<sup>99</sup>.

#### Other

Estrogens can be administered as monotherapy or combined with progesterone. Hormone replacement therapy (HRT) can be administered in women with perimenopausal symptoms who do intend to undergo surgical treatment for concomitant PHPT<sup>100</sup>. Studies have revealed

that HRT decreases bone turnover and increases BMD at the LS and FN, with no effect on fracture risk in patients with PHPT<sup>101</sup>. However, due to related increased risk for breast cancer and thromboembolic events, hormone replacement therapy is not broadly used for PHPT bone disease. Similarly, SERMs (selective estrogen receptor modulators) such as raloxifene, can be administered for PHPT bone disease, since studies have shown that it decreases bone loss in postmenopausal women with PHPT<sup>102,103</sup>. However, due to increased risk for thromboembolic events, SERMs are not broadly used for PHPT bone disease<sup>104</sup>.

#### Calcium and Vitamin D supplementation

It is known that dietary calcium restriction can induce PTH secretion in patients with PHPT leading to bone demineralization, while low vitamin D levels are related to high bone turnover, low BMD and more severe PHPT bone disease<sup>105</sup>. Calcium supplementation can be useful in asymptomatic PHPT patients with low dietary calcium intake. 800 mg/d of calcium intake is recommended in women under the age of 50 and in men under 70 years old, and 1000 mg/d of calcium intake is recommended in women above the age of 50 and in men above 70 years old. Calcium supplementation decreases PTH levels and increases BMD at the FN in asymptomatic patients with PHPT and low dietary calcium intake<sup>106</sup>. Also, vitamin D supplementation is recommended for patients with PHPT, who have serum 25(OH) vitamin levels below 30 ng/ml<sup>107</sup>. Administration of 2800 IU vitamin D in patients with PHPT has led to BMD increase at the LS by 2.5% and PTH reduction by 17%<sup>108</sup>.

In conclusion, medical, non-surgical treatment is recommended in patients who do not meet the criteria for surgical management, in patients who deny surgical treatment or are high-risk surgical patients. Bisphosphonates and denosumab are recommended in PHPT patients with low BMD, cinacalcet is recommended in patients with serum calcium levels above 11 mg/dl and vitamin D supplementation is recommended in patients with low 25 (OH) vitamin D levels (<30 ng/ml). However, no data is available on fracture risk reduction in patients under medical, non-surgical treatment.

#### Unmet needs and future research

There are still several aspects of bone disease in PHPT that need further research. First, assessment of bone quality by indirect, but easily available measures, like TBS, and their significance in fracture risk prediction. Second, evaluation of the credibility of the FRAX tool in fracture risk assessment, especially in young patients and patients with 'osteopenia' and PHPT. Finally, how surgical or pharmacological intervention influences fracture risk is another area in need of more research.

## Conclusion

PHPT is characterized by disruption of both cortical and trabecular bone microarchitecture, even in the contemporary 'asymptomatic' form of the disease. Increased fracture risk is apparent in patients with PHPT, even in those with BMD within normal or osteopenic range, suggesting that there is a discrepancy between BMD and fracture risk in patients with PHPT and that new diagnostic methods are needed for assessing bone fragility in this population.

### Authors' contributions

*Symeon Tournis contributed to the design, acquisition and writing of the manuscript. Efthymia Karlafti contributed to acquisition, data interpretation and writing of the manuscript. Irene Lambrinouadaki, Ioannis Vlamis, Efsthios Chronopoulos, Eva Kassi and Ismene Dontas revised the manuscript for important intellectual content. All authors read and approved the final version of the manuscript.*

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