REVIEW PAPERS

Bone disease in primary hyperparathyroidism

Zanik kostny w przebiegu pierwotnej nadczynności przytarczyc

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- primary hyperparathyroidism
- bone disease
- bisphosphonates
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- vitamin D3

ABSTRACT

Primary hyperparathyroidism (PHPT) is a disorder of calcium-phosphate homeostasis and bone metabolism, characterized by increased bone turnover, reduced bone mineral density (BMD) – especially in cortical bone – and an elevated risk of fractures. The introduction of automated methods for measuring serum calcium levels, along with the widespread use of reliable techniques for determining parathyroid hormone levels (PTH), has contributed to the earlier diagnosis of the disease. The classic form of the disease (osteitis fibrosa cystica), which requires differentiation from bone malignancies, is now seen much less frequently. Effective surgical treatment of primary hyperparathyroidism leads to skeletal recovery ("self-repair") and an increase in bone mineral density (BMD). With the growing number of patients presenting with subclinical primary hyperparathyroidism, there is an increasing need to explore alternative – pharmacological – treatment options. Anti-resorptive drugs, such as bisphosphonates and denosumab, have attracted particular interest in the context of managing bone loss in patients with PHPT.

This article aims to present the current state of knowledge regarding bone loss in primary hyperparathyroidism.

SŁOWA KLUCZOWE:

- pierwotna nadczynność przytarczyc
- zanik kostny
- bisfosfoniany
- denosumab
- witamina D.

STRESZCZENIE

Pierwotna nadczynność przytarczyc (PNP) jest to zespół zaburzeń gospodarki wapniowo-fosforanowej i metabolizmu kostnego charakteryzujący się zwiększonym obrotem kostnym, obniżeniem gęstości mineralnej kości (BMD), głównie w obrębie kości korowej i zwiększonym ryzykiem złamań. Wprowadzenie automatycznych metod oznaczania stężenia wapnia w surowicy oraz upowszechnienie metod wiarygodnego oznaczania stężenia parathormonu (PTH) przyczyniły się do rozpoznawania choroby na wcześniejszym etapie. Coraz rzadziej spotyka się klasyczną postać choroby (osteotitis fibrosa cystica), która wymaga różnicowania z procesami nowotworowymi kości. Skuteczne leczenie pierwotnej nadczynności przytarczyc owocuje odbudową („autonaprawą") szkieletu i wzrostem BMD. Wobec rosnącej liczby pacjentów z subklinicznym przebiegiem pierwotnej nadczynności przytarczyc rośnie potrzeba poszukiwania alternatywnych – farmakologicznych metod postępowania. Szczególnym zainteresowaniem w temacie leczenia zaniku kostnego u pacjentów z PNP cieszą się leki antyresopcyjne, do których należą bisfosoniany i denosumab.

Ten artykuł ma na celu przybliżyć aktualną wiedzę na temat zaniku kostnego w przebiegu pierwotnej nadczynności przytarczyc.

Introduction

Primary hyperparathyroidism (PHPT) is a disorder of calcium-phosphate homeostasis and bone metabolism caused by excessive and uncontrolled secretion of parathyroid hormone (PTH). It is characterized by a lack or dysfunction of the feedback mechanism between serum calcium levels and PTH secretion (1). The most common cause of PHPT

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is a single parathyroid adenoma (2). Other, less common causes of primary hyperparathyroidism (PHTP) include parathyroid hyperplasia, which is often observed in multiple endocrine neoplasia syndromes type 1 (MEN1) and type 2A (MEN2A), as well as inactivating heterozygous mutations of the CaSR gene, which are responsible for the majority of familial hypocalciuric hypercalcemia (FHH) cases (3).

Epidemiology

Historically, PHPT was described in its fully symptomatic form by Albright as osteitis fibrosa cystica with recurrent kidney stones, and for decades it was considered a rare disease (4).The introduction of automated serum calcium testing in the 1970s, along with the widespread availability of reliable PTH assays, significantly increased the detection rate of the condition. Today, PHPT is recognized as the third most common endocrine disorder (5). The prevalence of PHPT varies by geographic region. The highest detection rates are observed in North America and Western Europe, which is attributed to the greatest access to diagnostic testing in these parts of the world (3).

Clinical Presentation

In the 1970s, with widespread biochemical screening, asymptomatic PHPT emerged as the predominant clinical form of disease, limited to mild, often intermittent hypercalcemia, which is usually detected incidentally during routine blood tests (6). Nevertheless, patients with subclinical disease may still exhibit some clinical symptoms, such as subtle neuropsychiatric manifestations – including fatigue, memory problems, or emotional lability – or asymptomatic kidney stones identified through imaging studies (7). In fact, in a number of “asymptomatic” patients, a progressive bone loss is the most frequent clinical manifestation of PHPT.

Chronic, excessive stimulation of bone resorption by parathyroid hormone inevitably leads to gradual loss of bone mass and a significantly increased risk of fractures (8).

Low BMD, corresponding to a diagnosis of osteoporosis according to WHO criteria, is found in 50-65% of individuals with PHPT (9). At the same time, we have shown that in the broader population of people with reduced BMD, the prevalence of PHPT can reach as high as 10% (10).

The normocalcemic variant of primary hyperparathyroidism (NPHPT) was first described in the first decade of the 21st century (11). It was identified in patients evaluated for low bone mass or overt osteoporosis. Therefore, since its initial description, NPHPT should not be regarded as an asymptomatic condition, but rather as one associated with overt bone loss, warranting its consideration in the differential diagnosis of bone mass loss. There is ongoing debate as to whether NPHPT represents a very early stage in the natural history of the disease or whether it is rather a variant associated with an altered response at the receptor level.

The classic form of PHPT – characterized by pronounced hypercalcemia (11.5-16.8 mg/dL), symptomatic kidney involvement such as nephrolithiasis, hypercalciuria, renal impairment, and typical skeletal changes (osteitis fibrosa cystica) – is diagnosed much less frequently. Classic skeletal symptoms include bone pain and fractures. Imaging and diagnostic studies may also reveal complications such as brown tumors, osteoporosis, and chondrocalcinosis (12).

Changes in Bone Metabolism Due to PHPT

PTH is a polypeptide composed of 84 amino acids, synthesized and secreted by the parathyroid glands. Its primary function is to regulate calcium and phosphate metabolism in the body through direct effects on bones and kidneys, and indirect effects on the intestines (13).

The mechanism by which PTH regulates calcium-phosphate balance is closely linked to its unique influence on bone metabolism.

The action of PTH on bone is mediated by its receptors (PTH1R) located on osteoblasts (bone-forming cells) (14). Under normal physiological conditions, when PTH is secreted in a pulsatile and regulated manner, it stimulates bone formation, and its main role appears to be the maintenance of bone mass. However, in conditions of elevated PTH levels – particularly when its pulsatile secretion is lost, as in hyperparathyroidism – osteoblasts begin to produce increased amounts of pro-resorptive cytokines, primarily tumor necrosis factor-related cytokines and receptor activator of nuclear factor κB ligand (RANKL), while simultaneously reducing the synthesis of osteoprotegerin. This shift enhances osteoclastogenesis and increases osteoclast activity, ultimately leading to intensified bone resorption that exceeds bone formation (15).

It has been shown that in cortical (compact) bone, excess PTH primarily exerts catabolic effects, whereas in trabecular bone, it may also demonstrate anabolic activity (16).

The presence of areas of increased bone formation in trabecular bone distinguishes the bone changes seen in PHPT from the histomorphometric features of active osteoporosis, such as that observed in postmenopausal women (17).

However, other risk factors – such as disease duration, advanced age, and low estrogen levels after menopause – can lead to decreased bone density even in skeletal regions dominated by trabecular bone (11, 18).

Regardless of the specific mechanisms underlying bone metabolism disturbances in PHPT, a long-standing imbalance between bone formation and resorption inevitably results in significant bone loss.

Radiologically and densitometrically, this loss resembles classic osteoporosis, but more prominently affects the peripheral skeleton, where cortical bone predominates.

As a consequence of the metabolic and structural changes described above, the risk of fractures – especially in the vertebral bodies, tibia, and forearm – is nearly double (19).

In summary, chronic, continuous, and excessive secretion of parathyroid hormone leads to enhanced bone resorption, gradual loss of bone mass, and a significantly increased risk of fractures.

Classic Bone Changes in Primary Hyperparathyroidism

Osteitis fibrosa cystica is classified as a rare benign metabolic bone disorder. Triggered by elevated PTH levels, it leads to excessive osteoclast activation and the formation of osteolytic lesions visible on imaging studies.

Clinically, it presents with bone pain. Radiologically, it is characterized by subperiosteal bone resorption (Figure 1.), distal clavicular osteolysis, a “salt and pepper” appearance of the skull, bone cysts, and brown tumors (Figure 2.) (20).

Brown tumors represent the end-stage manifestation of PTH-dependent bone pathology. They may cause

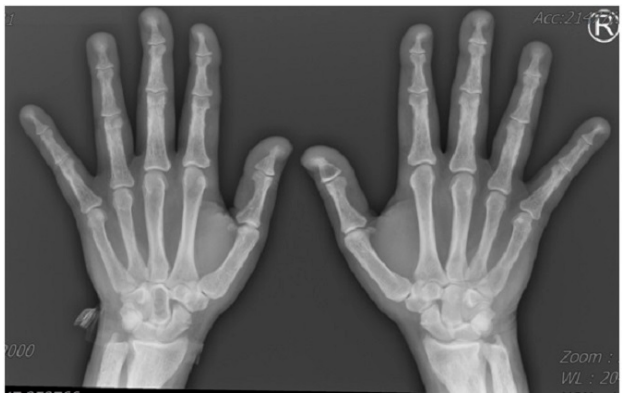

Figure1. Subperiosteal bone resorption.
Source: own elaboration.

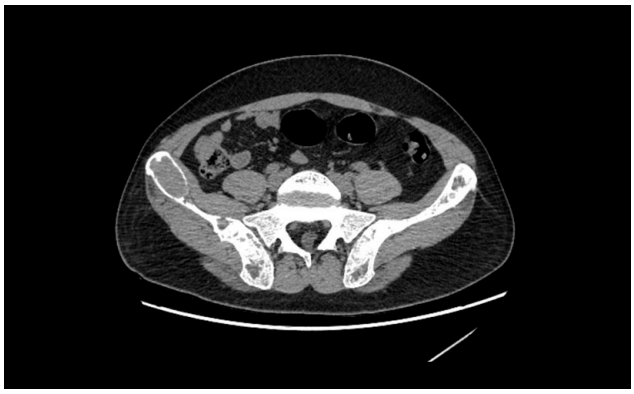

Figure 2. Brown tumor.
Source: own elaboration.

swelling, pathological fractures, and bone pain. These lesions may be solitary or multifocal and tend to occur in areas with particularly rapid bone turnover, including the jaw, skull, pelvis, clavicles, ribs, femurs, and spine (21, 22).

On imaging – particularly CT scans – such lesions may be misdiagnosed as primary bone tumors (e.g., bone cysts, osteosarcoma, or most notably, giant cell tumors) or as metastatic bone disease (21, 23).

Histological examination may also be inconclusive, as other lesions – such as giant cell tumors or giant cell granulomas – exhibit similar macro- and microscopic features. All of these lesions contain multinucleated giant cells (24).

Due to the overlap in radiologic and histologic features with other bone pathologies, diagnosis can be challenging and requires an individualized approach to differential diagnosis.

Bone Changes in Asymptomatic and Normocalcemic Hyperparathyroidism

The increasing frequency of routine serum calcium testing has led to more frequent diagnoses of the asymptomatic form of PHPT. In standard imaging studies, such as skeletal X-rays, classical bone changes are rarely observed in these patients. However, BMD is typically reduced on dual-energy X-ray absorptiometry (DXA) scans (25).

The preferential involvement of the distal one-third of the forearm in PHPT is consistent with that the catabolic effects of excessive PTH would be seen first at a cortical site (16). For this reason, although radial bone DXA is not part of the standard central DXA examination used in the diagnosis of osteoporosis, current recommendations for the management of primary hyperparathyroidism clearly indicate the need for DXA assessment in the diagnosis of this disease. The hip regions, consisting of a mixture of cortical and cancellous bone, usually exhibits intermediate densitometric values, between the relatively well-preserved lumbar spine and the affected distal one-third radius sites. The lumbar spine, a skeletal site in which trabecular bone predominates, usually displays the lowest degree of involvement.

In contrast, both the pattern of bone changes and the skeletal response to parathyroidectomy in normocalcemic PHPT remain not fully understood.

In a study by Lowe et al., during approximately three years of follow-up, 43% of patients experienced a ≥5% decline in BMD, with similar reductions across all measured sites (26). Conversely, in a study by Koumakis et al., a 4.1% increase in BMD at the femoral neck was observed one year after parathyroid surgery, with no significant changes seen in the lumbar spine or distal radius (27).

Surgical Treatment

The primary method for treating bone loss in PHPT is the surgical removal of the abnormal parathyroid gland. Successful parathyroidectomy leads to normalization of biochemical markers, improved BMD, reduced fracture risk, and decreased risk of other complications (18).

Additionally, the surgery restored balance in bone remodeling processes and promoted regeneration, particularly in damaged areas such as cysts or subperiosteal resorption sites (28, 29).

Despite the proven efficacy of surgical treatment, some patients – especially those for whom bone loss is the only clinical manifestation of PHPT – refuse consent to surgery. Moreover, in elderly individuals, particularly those with significant comorbidities, the benefits of surgery may not outweigh the risks.

This issue also affects patients in whom pathological parathyroid glands cannot be visualized using currently available imaging techniques.

Given the growing need for non-surgical treatment standards, it is necessary to explore alternative pharmacological options for managing bone loss in PHPT (30, 31).

Ongoing studies are evaluating the effects of various drug classes on improving bone density in patients with PHPT. Among these, denosumab and bisphosphonates have received particular attention in the literature. According to the 2022 guidelines, alendronate or denosumab may be used to increase bone density, provided there are no contraindications (19).

Calcium and Vitamin D3

Vitamin D3 deficiency may stimulate the parathyroid glands to produce excessive amounts of PTH. The issue of vitamin D supplementation in patients with PHPT has been the subject of extensive discussion and numerous publications. Ultimately, it has been demonstrated that vitamin D supplementation in PHPT patients with biochemically confirmed

deficiency is safe – it improves serum 25-hydroxyvitamin D [25(OH)D] levels, significantly reduces PTH and alkaline phosphatase (ALP) concentrations, and does not lead to hypercalcemia or hypercalciuria (32, 33). Supplementation is recommended to maintain levels above 30 ng/mL but below the upper limit of the laboratory's reference range (e.g., below 50 ng/mL) (19).

As in the general population, adequate dietary calcium intake is also recommended for patients with PHPT (34). The optimal daily intake from all sources is considered to be 1,000-1,200 mg (35), and reducing calcium intake may lead to compensatory increases in PTH secretion, potentially worsening the course of the disease (36).

Anti-resorptive Medications

Anti-resorptive agents – particularly bisphosphonates and denosumab – have drawn special interest in the treatment of bone loss in patients with PHPT.

Bisphosphonates

Introduced in the 1990s, bisphosphonates are now among the most commonly used medications for the treatment of osteoporosis. Their mechanism of action involves binding to hydroxyapatite in bone – particularly at sites of active remodeling – and inhibiting the activity of osteoclasts responsible for bone resorption. Numerous studies have confirmed the anti-fracture efficacy of alendronate, risedronate, and zoledronic acid in patients with osteoporosis. Several reports also indicate that in patients with PHPT, both alendronate and zoledronic acid reduce bone turnover and stabilize or even increase BMD, without affecting serum calcium levels (37, 38, 39). Recent reports show that bisphosphonates improve BMD in the lumbar spine, femoral neck, and total hip, and reduce bone turnover markers without affecting serum calcium levels. However, there is no data confirming a reduction in fracture risk (34) .

We have also conducted research on this topic in our clinic. In 2005, we published findings in Endokrynologia Polska from a prospective study in which patients with advanced bone loss due to PHPT were treated with alendronate at a dose of 10 mg daily. The study demonstrated that two years of alendronate therapy led to a significant increase in lumbar spine BMD compared to baseline, with no changes observed in serum calcium, phosphate, or PTH levels, nor in urinary calcium excretion (40).

In 2009, the Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism: Summary Statement from the Third International Workshop for the first time included a recommendation for the symptomatic use of alendronate to protect the skeletal system in patients with PHPT (30). These recommendations were reaffirmed in the 2022 reports (19).

Denosumab

Denosumab is a fully human monoclonal antibody (IgG2) that acts as an inhibitor of RANKL. By blocking the interaction between RANKL and its receptor activator of nuclear factor κB (RANK)on osteoclasts, it suppresses the proliferation and maturation of bone-resorbing cells and negatively affects their survival. As a result, denosumab reduces the loss of both cortical and trabecular bone (41).

In the treatment of osteoporosis, denosumab is administered subcutaneously every six months, with therapeutic effects observed as early as 12 months after initiation. Its anti-fracture efficacy has been confirmed at vertebral, hip, and non-vertebral sites. In a 10-year follow-up study, Bone et al. demonstrated sustained fracture protection and a favorable safety profile for the drug (42).

Unlike bisphosphonates, denosumab can be safely used in patients with impaired renal function. In this population, it is well tolerated, improves bone health, and reduces the risk of new fractures (43). Due to its molecular mechanism of action and its more potent anti-resorptive effect compared to bisphosphonates, denosumab may have particular utility in protecting the skeletal system in patients with PHPT. However, only limited data are currently available on its efficacy for bone loss treatment in the context of PHPT.

In a one-year retrospective study assessing the effects of either denosumab or parathyroidectomy (PTX) in 39 patients, increases in BMD were observed following both interventions, though the post-surgical gains were greater after one year. Notably, no changes in serum calcium levels were observed in the denosumab-treated group.

Another retrospective study in 50 elderly women with PHPT found that denosumab increased BMD over two years to a greater extent than in women with osteoporosis who did not have PHPT (44).

Summary

Bone loss is one of the most common manifestations of PHPT. The introduction of automated serum calcium testing and the widespread use of reliable assays for PTH have significantly altered the clinical presentation of PHPT. The classic form of the disease – osteitis fibrosa cystica – is now rarely encountered and requires careful differentiation from bone malignancies.

Nevertheless, a valid question remains: has the absolute incidence of severe PHPT with classic, overt skeletal involvement (e.g., OFC) truly declined, or are these cases being overlooked because the growing number of milder or asymptomatic cases dominates the clinical landscape? In other words, the true incidence of severe PHPT with OFC may be unchanged, but its apparent rarity could result from dilution within a much broader population of asymptomatic patients (45).

Surgical treatment – parathyroidectomy – is the only causal therapy for PHPT and effectively reverses the bone-related consequences of the disease. However, it remains the primary approach to managing skeletal complications. Given the increasing number of patients who are either ineligible for surgery or decline it, and the rising prevalence of subclinical disease, there is a clear need to establish standardized non-surgical treatment protocols.

Ongoing research is focused on evaluating the effectiveness of pharmacological strategies for managing bone loss in PHPT. According to the latest international recommendations, in patients who have not undergone parathyroidectomy, the use of anti-resorptive agents – such as bisphosphonates and denosumab – can be considered to improve BMD. However, further studies are necessary to confirm the efficacy of symptomatic pharmacological treatment for bone loss in the course of PHPT.

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