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PRIMARY HYPERPARATHYROIDISM: ETIOLOGY, DIAGNOSIS, AND SKELETAL COMPLICATIONS

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ABSTRACT

Primary hyperparathyroidism (PHPT) is one of the most common endocrine diseases and is often asymptomatic, making its timely diagnosis difficult. Despite its subtle clinical manifestations, PHPT is associated with increased bone remodeling, decreased bone mineral density, and an increased risk of fractures, primarily of the vertebrae and proximal femur. This article examines current understanding of the etiology, pathogenesis, and diagnosis of primary, secondary, and tertiary hyperparathyroidism, as well as their impact on the skeletal system. Particular attention is paid to the role of vitamin D deficiency as a disease-modifying factor affecting the severity of skeletal complications. Current treatment approaches, including parathyroidectomy and drug therapy, and their impact on bone parameters and fracture risk are analyzed.

Keywords

hyperparathyroidism, primary hyperparathyroidism, secondary hyperparathyroidism, parathyroid hormone, vitamin D, bone mineral density, fractures, parathyroidectomy.

ПЕРВИЧНЫЙ ГИПЕРПАРАТИРЕОЗ: ЭТИОЛОГИЯ, ДИАГНОСТИКА И СКЕЛЕТНЫЕ ОСЛОЖНЕНИЯ

АННОТАЦИЯ

Первичный гиперпаратиреоз (ПГПТ) является одним из наиболее распространённых эндокринных заболеваний и нередко протекает в бессимптомной

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форме, что затрудняет его своевременную диагностику. Несмотря на маловыраженную клиническую картину, ПГПТ ассоциирован с повышенным костным ремоделированием, снижением минеральной плотности костной ткани и увеличением риска переломов, преимущественно позвонков и проксимального отдела бедренной кости. В статье рассматриваются современные представления об этиологии, патогенезе и диагностике первичного, вторичного и третичного гиперпаратиреоза, а также их влияние на скелетную систему. Особое внимание уделено роли дефицита витамина D как фактора, модифицирующего течение заболевания и влияющего на выраженность костных осложнений. Проанализированы современные подходы к лечению, включая паратиреоидэктомию и медикаментозную терапию, и их влияние на показатели костной ткани и риск переломов.

Ключевые слова

гиперпаратиреоз, первичный гиперпаратиреоз, вторичный гиперпаратиреоз, паратиреоидный гормон, витамин D, минеральная плотность костной ткани, переломы, паратиреоидэктомия.

RELEVANCE: Hyperparathyroidism occurs due to overactivity of the parathyroid glands, caused either by intrinsic abnormalities affecting the secretion of parathyroid hormone (primary or tertiary hyperparathyroidism) or by extrinsic abnormalities affecting calcium homeostasis and stimulating parathyroid hormone production (secondary hyperparathyroidism).[1] Primary hyperparathyroidism is the third most common endocrine disorder, occurring most often in postmenopausal women.[1] The disease is often asymptomatic, and severe forms with kidney stones and metabolic bone disease are less common than they were 20 to 30 years ago.[1] Primary hyperparathyroidism can be cured by surgical removal of the adenoma, most commonly by minimally invasive parathyroidectomy.[1] In mild cases, drug therapy with bisphosphonates, hormone replacement therapy, and calcimimetics can be used.[1] Vitamin D deficiency is a common cause of secondary hyperparathyroidism, especially in the elderly. However, the biochemical definition of vitamin D deficiency and its treatment methods are highly controversial.[1] Secondary hyperparathyroidism resulting from chronic kidney disease plays an important role in the development of kidney stones.[1] Several new treatments may help achieve the goals of the Kidney Disease Quality Improvement Initiative.[1]

MATERIALS AND METHODS: This article was conducted as a narrative analytical review focusing on primary, secondary, and tertiary hyperparathyroidism, with particular emphasis on skeletal involvement, changes in bone mineral density (BMD), fracture risk, and the role of vitamin D deficiency in disease progression. Scientific publications including original clinical studies, randomized controlled trials, cohort and case–control studies, systematic reviews, and meta-analyses were analyzed.

A comprehensive literature search was performed using the PubMed, Scopus, and Web of Science databases, covering publications mainly from 1990 to 2023. Key search terms included “primary hyperparathyroidism,” “vitamin D deficiency,” “bone mineral density,” “fracture risk,” “parathyroid hormone,” and “calcium-sensing receptor.”

Inclusion criteria comprised studies evaluating biochemical parameters (serum calcium, parathyroid hormone, 25-hydroxyvitamin D), skeletal outcomes, and therapeutic interventions such as parathyroidectomy and pharmacological treatment. Data were critically analyzed with respect to study design, population characteristics, diagnostic methods, and bone assessment

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techniques including DXA, QCT, and pQCT. The findings were synthesized to provide an integrated overview of skeletal complications and management strategies in hyperparathyroidism.

RESULTS AND DISCUSSION: Etiology of Primary Hyperparathyroidism

PHPT occurs due to unregulated and excessive secretion of parathyroid hormone (PTH) by one or more parathyroid glands[2]. Solitary parathyroid adenomas account for 85% to 90% of cases of PHPT(1,2). Most other cases involve multiple parathyroid gland hyperfunction, including hyperplasia and multiple adenomas. Multiple thyroid disease is the most common disorder in individuals with familial hyperparathyroidism syndrome, accounting for approximately 10% of all cases[2]. Parathyroid carcinoma is rare, accounting for only 0.7% of all cases. PHPT is the most common endocrine disorder in this disorder, occurring in almost 100% of patients over 50 years of age and is the primary cause[2]. The prevalence of PHPT in males is lower than in females and accounts for 20-30% of cases. Hyperparathyroidism and jaw tumor syndrome is a rare disorder in which tumors of the jaw bone associated with PHPT are found.[2] Parathyroid cancer is diagnosed in more than 15% of cases. In isolated familial hyperparathyroidism, the diagnosis is made in close relatives in the absence of other endocrinopathies. Severe neonatal hyperparathyroidism is a rare disorder in which newborns have severe hypercalcemia associated with high PTH levels, muscle hypotonia, and respiratory failure. This is usually due to the presence of a homozygous inactivating mutation in the calcium-sensing receptor gene. Certain situations that may explain the occurrence of PHPT, such as radiation exposure or rare genetic abnormalities, may be identified in a small percentage of patients.[2] A cohort study of Chernobyl nuclear power plant workers in 1986 found that subsequent PHPT developed in 15 of 61 individuals (OR 63.4, 95% CI 35.7–112.5). The mean radiation dose received ranged from 0.3 to 8.7 Gy (13) (B-2B). Cases of PHPT have also been reported in patients receiving radiation therapy for benign conditions. A study of 2,555 patients receiving only 0.5 Gy before age 16 and followed for 50 years showed a dose-dependent increased risk of PHPT.[2] When patients with sporadic PHPT (389 patients) were compared in a retrospective study with those with a history of radiation (49 patients), no differences in clinical presentation, pathology, or recurrence were observed over a 6-year follow-up period [2]. However, patients exposed to radiation may have concomitant thyroid nodules, which may also be associated with intrathyroidal and parathyroid lesions. Regarding radioactive iodine therapy, in a prospective study of 125 patients with thyrotoxicosis treated with I131, the incidence of PHPT did not significantly increase after 21 years of follow-up [2].

Diagnosis of Primary Hyperparathyroidism

Hyperparathyroidism is diagnosed by the presence of hypercalcemia and elevated parathyroid hormone levels [2]. Inappropriately normal PTH levels are also consistent with the diagnosis. Malignancy, the other major cause of hypercalcemia, is easily distinguished from PHPT by the decreased PTH level.[2] Furthermore, both the clinical presentation and the biochemical profile of PHPT and hypercalcemia of malignancy help differentiate them. Patients with hypercalcemia of malignancy typically have severe and symptomatic hypercalcemia and clinically evident stages of advanced cancer.[2] On the other hand, with hyperparathyroidism, most patients are asymptomatic, and serum calcium levels are usually mildly elevated (within 1 mg/dL of the upper limit of normal).[2] Very rarely, patients with malignancy have elevated PTH levels caused by ectopic secretion of native PTH by the tumor itself. Much more commonly, malignancies are associated with the secretion of parathyroid hormone-related protein, a molecule that does not cross-react with intact PTH [2]. Finally, it is possible that malignancy is

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associated with the syndrome of excessive parathyroidism. If a person with malignancy has elevated parathyroid hormone levels, it is most likely not true ectopic syndrome of excessive parathyroidism [2].

Although 90% of patients with hypercalcemia have either renal cell carcinoma or malignancy, the differential diagnosis of hypercalcemia includes a number of other causes, such as vitamin D intoxication, granulomatosis, and others [2]. With the exception of lithium and thiazide diuretic use, and familial hypocalciuric hypercalcemia (FHCH), virtually all other causes of hypercalcemia are associated with decreased parathyroid hormone levels. If it is safe to discontinue.

If lithium and/or thiazide diuretics are used, elevated serum calcium and parathyroid hormone levels after 3–6 months will confirm the diagnosis of hereditary hypoparathyroidism. On the other hand, familial hypoparathyroidism differs from hereditary hypoparathyroidism by a family history, usually (but not always) low urinary calcium excretion and mutations in the calcium-sensing receptor (CASR) or in the recently linked genes GNA11 and AP2S1. Furthermore, near-complete genetic penetrance means that the disease typically presents clinically before the age of 30. It is extremely rare for FHG to present without a previous history after the age of 50 [2]. To distinguish PTH-mediated from non-PTH-mediated causes of hypercalcemia, PTH levels should be measured using an intact immunoradiometric assay (IRMA) or immunochemiluminometric assay (ICMA), which can readily differentiate PHPT from hypercalcemia of malignancy. In PHPT, PTH concentrations are typically markedly elevated, but most often within 2 times the upper limit of normal.[2] A minority may have PTH levels within the normal range, typically in the upper range of normal. With PTH, such values, although within the normal range, are clearly abnormal in hypercalcemia.[2] Several factors influence PTH levels in people with and without PHPT, including age, vitamin D status, and kidney function. Because PTH levels generally increase with age, the wide normal range (usually 10–65 pg/mL) reflects values for the general population. In younger individuals (under 45 years of age), a narrower and lower reference range (10–45 pg/mL) is expected. Occasionally, measured PTH levels reach only 20–30 pg/mL. Such unusual cases require a more thorough investigation of other causes of hypercalcemia, but such patients are usually found to have vitamin D-deficiency hyperparathyroidism syndrome, since hypercalcemia unrelated to parathyroid hormone reduces parathyroid hormone concentrations to levels that are either undetectable or at the lower end of the reference range. Suberbielle et al. showed that the normal range depends on whether the reference population is vitamin D deficient. When patients with vitamin D deficiency are excluded, the upper limit of the parathyroid hormone reference interval is lowered. Patients with PHPT and vitamin D deficiency have “elevated” PTH levels compared to those with sufficient vitamin D[2]. On the other hand, impaired renal function tends to increase PTH levels through a number of mechanisms, including decreased clearance and degradation of PTH.[2] Indeed, patients with PHPT and severe renal dysfunction (GFR <30 mL/min) may also have higher PTH levels compared to patients with better renal function. Furthermore, “intact” IRMA for PTH overestimates the concentration of biologically active PTH, particularly in renal failure. In 1998, Lepage et al. demonstrated the presence of a large amino acid-free fragment of PTH that co-migrated with a large amino-terminally truncated fragment and exhibited significant cross-reactivity with commercially available IRMAs. This large inactive fragment accounted for up to 50% of the immunoreactivity of IRMAs to PTH in people with chronic renal failure.[2] Recognition of this molecule led to the development of a new IRMA using affinity-purified polyclonal antibodies to PTH and to the extreme N-terminal amino acid regions, PTH. This “total PTH” or third-generation assay detects only the full-length PTH molecule. This assay has

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obvious value in patients with uremia, but in primary hyperparathyroidism, both assays are equally useful.[2] The third-generation PTH assay identified a second molecular form of PTH that is immunologically intact at both ends. This molecule reacts poorly to second-generation PTH assays. It accounts for less than 10% of immunoreactivity in healthy individuals and up to 15% in patients with renal failure. Overexpression of this gene may be observed in a limited number of patients with severe primary hyperparathyroidism or parathyroid cancer.[2] Primary hyperparathyroidism can be distinguished from secondary and tertiary hyperparathyroidism by its biochemical profile.[2] Secondary hyperparathyroidism is associated with a corresponding increase in parathyroid hormone levels in response to a hypocalcemic challenge and with frankly low or normal serum calcium levels.[2] Secondary hyperparathyroidism is often due to vitamin D deficiency. Other causes include malabsorption, kidney disease, or hypercalciuria.[2] Rarely, patients with secondary hyperparathyroidism may develop hypercalcemia and will eventually be diagnosed with primary hyperparathyroidism once the underlying condition (eg, vitamin D deficiency) is treated.

In such cases, hypercalcemia in primary hyperparathyroidism was "masked" by an underlying condition.[2] On the other hand, tertiary hyperparathyroidism is a condition in which long-standing and severe secondary hyperparathyroidism (e.g., in end-stage renal disease) progresses to a hypercalcemic state due to the development of autonomous function of one or more hyperplastic parathyroid glands.[2] This can be observed in patients on dialysis or after a kidney transplant. Tertiary hyperparathyroidism is usually diagnosed based on the patient's history.[2]

Normocalcemic primary hyperparathyroidism (NPHPT) describes a condition characterized by normal serum calcium levels corrected for albumin and ionized calcium values with elevated PTH levels. This condition can only be diagnosed when all known causes of secondary hyperparathyroidism have been excluded.[2] The diagnosis of NPHPT is typically made in patients who have PTH levels measured during the evaluation of low bone mass. NPHPT may represent the earliest manifestations of PHPT, a "disturbed form" of the disease. Several case reports have appeared describing such patients, some of whom developed overt hypercalcemia during follow-up.[2]

Although the term "normacalcemic PTH" has been used for several decades, its accuracy has been the subject of considerable controversy.[2] In many cases, elevated PTH levels have been attributed to limitations of available assay technologies. Using the older middle molecular weight radioimmunoassay method to measure PTH levels, fragments of the hormone were measured in addition to the intact molecule.[2] Falsely elevated PTH levels have been observed, particularly in patients with renal insufficiency, in whom clearance of the fragments of the hormone is impaired. Alternative causes of hyperparathyroidism in PHPT have been identified, including medications, hypercalciuria, renal failure, and some forms of liver and gastrointestinal disease.[2] In recent years, it has become clear that many patients with PHPT have vitamin D deficiency. Vitamin D deficiency in combination with PHPT can create the appearance of normal calcium levels, when in fact, hypercalcemic syndrome would be observed with normal vitamin D levels. Because non-Hodgkin lymphomas are thought to arise from vitamin D resistance, it is important to ensure adequate vitamin D levels. Although the Institute of Medicine states that the normal vitamin D level, measured with 25-hydroxyvitamin D, is 20 ng/mL, it did not address conditions with abnormal mineral metabolism such as PHPT. Specifically, in patients with PHPT, we and others recommend increasing 25-hydroxyvitamin D levels, if necessary, to >30 ng/mL for at least 3 months to exclude vitamin D deficiency in this population [2].

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Skeletal Manifestations of Primary Hyperparathyroidism

Since the 1970s, when routine use of serum calcium as part of biochemical screening became common practice, the diagnosis of PHPT on biochemical grounds has increased markedly without evidence of overt skeletal manifestations [2]. However, even at this early stage of the disease, asymptomatic PHPT can be associated with high bone mobility, decreased BMD, and an increased risk of fractures. After successful parathyroid surgery, increased bone remodeling decreases, BMD increases, and, according to limited data, the risk of fractures decreases [2]. Improvement in preoperative parameters after parathyroid surgery suggests that the hyperparathyroid state is directly responsible. The prevalence of PHPT and its effect on BMD were assessed in 3014 men aged 69 to 81 years in the Swedish MrOs study cohort.[2] Fifty-seven of 6 patients with low glomerular filtration rate (< 21 ml/min/1.73 m2) and vitamin D deficiency (< 50 nmol/L) were excluded from the study. BMD was compared in patients with and without PHPT. The prevalence of PHPT was 0.73%. BMD of the total hip and femoral neck was lower in the PHPT group than in the control group. Patients with inappropriately high unchanged PTH levels were compared with the rest of the cohort.[2] In this subgroup, BMD was lower at the hip and lumbar spine ($p < 0.05$). In another subgroup, Mr. The operating system yielded similar results (59). In a controlled clinical trial, patients with mild PHPT were randomized to parathyroidectomy (PTH) ($n = 25$) and without it ($n = 28$). After 24 months of follow-up, there was a significant increase in BMD at the femoral neck and hip as a whole, but not at the lumbar spine or forearm in patients who underwent PTH compared with patients who did not undergo PTH[2]. Also observed A decrease in bone-specific alkaline phosphatation activity was observed after PTH. Another study of patients followed for 5 years after PTH showed a significant increase in BMD of the lumbar spine, but not the hip or distal third of the radius, compared with baseline, and a decrease in bone turnover indices.[2] A case-control study assessed the incidence of vertebral fractures in 150 postmenopausal women with sporadic PHPT and 300 healthy controls. Vertebral fractures were found in 24.6% of patients with PHPT and 4.0% of controls ($P < 0.0001$). Most vertebral fractures were mild. To determine whether risk factors associated with vertebral fractures differed in patients with PHPT compared with controls, logistic regression analysis was performed with age, age at menopause, years since menopause, body mass index, total serum calcium, PTH, 25(OH) vitamin D, lumbar spine BMD, and femoral neck.[2] Vertebral fractures were associated with lumbar spine BMD in patients with PHPT ($P = 0.002$) and controls ($P = 0.004$) and with age ($P = 0.04$) in controls. To determine whether PHPT was associated with an additional risk of vertebral fracture, logistic regression analysis was performed on the entire sample (patients and controls) using PHPT status as a covariate. Age ($P = 0.015$) and lumbar spine BMD ($P = 0.01$) remained associated with vertebral fractures, with a strong correlation between lumbar spine BMD and PHPT ($P < 0.0001$). A retrospective cohort study assessed fracture-free survival at 10 years in 533 patients with PHPT. Baseline mean calcium, PTH, and serum creatinine values were 11.1 mg/dL, 116 pg/mL, and 0.9 mg/dL, respectively. PTH was performed in 30% of patients, and 70% of them were followed up. Fracture-free survival at 10 years after PHPT diagnosis was 94% in the PTH group and 81% in the observation group ($P = 0.006$)[2]. Compared with observation, PTH improved 10-year fracture-free survival by 9.1% ($p = 0.99$), 12% ($p = 0.92$), and 12% ($p = 0.02$) in patients with a T-score ≥ -1.0, T-score -1.0 to -2.5, and T-score < -2.5, respectively. In multivariate analysis, PTH was independently associated with a reduced fracture risk (HR = 0.41, 95% CI 0.18–0.93), while in non-Black patients (HR = 2.94, 95% CI 1.04–8.30) and T-score < -2.5 (HR = 2.29, 95% CI 1.08–4.88) it remained independently associated with an increased fracture risk.[2] Studies

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evaluating different skeletal sites using different methods (3D micro-CT bone biopsy analysis, conventional 2D bone histomorphometry, and quantitative electron imaging) have shown differences in the impact of PHPT on trabecular bone [2]. Conventional 2D bone histomorphometry in patients with PHPT showed thinning and increased porosity of the cortex, endosteal resorption, and preservation of trabecular bone volume and connectivity. Analysis of 3D iliac bone biopsies using micro-CT in 29 women with PHPT compared with 20 controls and 15 men with PHPT showed that trabecular bone microarchitecture was preserved in patients with mild PHPT [2]. In contrast, in a cross-sectional study comparing 36 women with PHPT and 100 healthy controls, quantitative CT imaging of the radius showed a significant 20% reduction in volumetric BMD in trabecular bone and a significant 5% reduction in the cortical region of interest. In this same group, BMD as measured by densitometry was similar at the lumbar spine but decreased in the distal third of the radius compared with controls.[2] In another study comparing 52 women with PHPT (normocalcemic and hypercalcemic) and 56 controls, peripheral quantitative CT imaging of the tibia showed differences in trabecular and cortical volumetric BMD, consistent with a catabolic effect on both bone types in patients with hypercalcemic and normocalcemic PHPT.[2] However, a cohort study of 116 patients with PHPT (85% asymptomatic) followed for 15 years found that PTH was associated with improved BMD in both cortical and trabecular regions of the skeleton. The aim of this study was to evaluate BMD over 15 years in patients who did or did not undergo PTH[2]. BMD was measured at the lumbar spine, femoral neck, and distal radius. Patients who underwent PTH showed significant increases in BMD at 3 sites after 15 years of follow-up compared to controls. with baseline. In the non-PHPT group, BMD was unchanged at 3 sites over 8 years and remained stable at the lumbar spine after 15 years of follow-up, but 59% of patients experienced a 10% decrease in BMD at one or more sites over the 15-year period.[2]

Vitamin D deficiency is common in older adults, particularly in homebound and geriatric patients.[2] Differences in methods for measuring 25-hydroxyvitamin D hinder the establishment of strict diagnostic criteria. Skin synthesis of vitamin D3 from ultraviolet radiation declines with age due to insufficient sun exposure and decreased skin functionality. Diet provides a small portion of vitamin D requirements.[2] Vitamin D deficiency in older adults is less common in the United States than elsewhere due to milk fortification and the use of dietary supplements. Vitamin D deficiency causes secondary hyperparathyroidism, high bone turnover, bone loss, mineralization defects, hip fractures, and other fractures. Less well-defined consequences include myopathy and falls. A diet low in calcium may increase the turnover of vitamin D metabolites and thus worsen vitamin D deficiency.[2] Prevention is possible through exposure to ultraviolet radiation, food fortification, and dietary supplements. Vitamin D3 supplementation reduces serum PTH concentrations, decreases bone turnover, and increases bone mineral density. Vitamin D3 and calcium may reduce the incidence of hip fractures and other peripheral fractures in nursing home residents. Vitamin D3 is recommended for homebound older adults and may be cost-effective for the prevention of hip fractures in certain at-risk groups.[2] Vitamin D Deficiency and Secondary Hyperparathyroidism in the Elderly: Bone Consequences, Fractures, and Therapeutic Measures Vitamin D deficiency is common in the elderly, particularly in housebound and geriatric patients.[3] Differences in methods for measuring 25-hydroxyvitamin D hinder the establishment of strict diagnostic criteria. Skin synthesis of vitamin D3, induced by ultraviolet radiation, declines with age due to insufficient sun exposure and decreased skin functionality.[3] Vitamin D deficiency causes secondary hyperparathyroidism, high bone turnover, bone loss, mineralization defects, hip fractures, and other fractures. Less well-defined consequences include myopathy and falls.[3] A diet low in calcium can increase the turnover of

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Vitamin D Deficiency and Primary Hyperparathyroidism

In the mid-20th century, improved vitamin D availability in many Western countries led to a change in many characteristics of primary hyperparathyroidism.[4] Osteitis fibrosa cystica has become a rare manifestation of the disease, which is now often asymptomatic. At the same time, parathyroid hormone levels and parathyroid adenoma weight have decreased sharply in patients with this disease. Based on these and other observations, an association between vitamin D deficiency and the severity of primary hyperparathyroidism has been hypothesized.[4] The data support an association at two different levels. First, regardless of the clinical severity of primary hyperparathyroidism, the disease is more severe in patients with concomitant vitamin D deficiency. Second, vitamin D deficiency and insufficiency are more common in patients with primary hyperparathyroidism than in geographically comparable populations.[4] The association between vitamin D deficiency and primary hyperparathyroidism has clear implications. Concomitant vitamin D deficiency may result in serum calcium levels falling within the normal range, which may lead to diagnostic uncertainty.[4] With regard to treatment, preliminary data on vitamin D replacement in patients with mild primary hyperparathyroidism suggest that, in some cases, vitamin D deficiency can be replaced without worsening hypercalcemia. Patients with vitamin D deficiency who have undergone parathyroidectomy, are also at increased risk of postoperative hypocalcemia and "hungry bone syndrome," highlighting the importance of preoperative vitamin D assessment in all patients with primary hyperparathyroidism.[4]

The Calcium-Sensing Receptor Beyond Extracellular Calcium Homeostasis: Concept, Development, Adult Physiology, and Disease

The extracellular calcium-sensing receptor (CaSR) is the first identified G protein-coupled receptor that is activated by extracellular calcium ions (Ca2+).[5] Since the discovery of CaSR in 1993, genetic mutations in the CaSR gene and mouse models in which CaSR expression is regulated have clearly demonstrated the importance of this receptor in maintaining stable free ionized Ca2+ concentrations in extracellular fluids.[5] These functions are described in detail elsewhere. However, the distribution and expression patterns of CaSR in lower vertebrates strongly suggest that CaSR must play a role unrelated to mineral cation metabolism.[5] This review examines the involvement of CaSR in nutrient sensing, its proposed and demonstrated functions during conception, embryonic development, and birth, and its contribution to adult physiology and disease, including implications for CaSR-based therapies. Recent advances in understanding the role of CaSR in stem cell differentiation are also discussed.[5]

Cinacalcet for the Treatment of Primary Hyperparathyroidism

Primary hyperparathyroidism (PHPT) is the leading cause of hypercalcemia in the outpatient setting and is treated primarily with parathyroidectomy.[6] Several nonsurgical treatment options are available for patients who are unwilling to undergo surgery, have had unsuccessful surgery, or have contraindications for surgery. Cinacalcet sensitizes parathyroid calcium-sensing receptors to extracellular calcium, thereby lowering serum calcium levels.[6] We retrospectively reviewed medical records from 2004 to 2006 to examine the efficacy of

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cinacalcet in lowering total calcium, ionized calcium, and parathyroid hormone (PTH) serum levels in patients with primary hypercalcemia. Patients were eligible for cinacalcet if they had at least one indication for parathyroidectomy, including a T score less than −2.5 standard deviations from the mean, a serum calcium level 1 mg/dL above the upper limit of normal, a 24-hour urine calcium level greater than 400 mg/dL, age less than 50 years, or a creatinine clearance 30% lower than age- and sex-adjusted controls.[6] The primary outcome was normalization of serum calcium levels. A total of 18 patients with primary hyperparathyroidism were started on cinacalcet: 16 men and 2 women, with a mean age of 70 years.[6] The mean baseline serum calcium was 10.60 ± 0.53 mg/dL; serum ionized calcium was 1.45 ± 0.07 mmol/L; and serum parathyroid hormone was 141 ± 78 pg/mL. After treatment with cinacalcet, the mean serum calcium decreased to 9.46 ± 0.34 mg/dL, ionized calcium to 1.26 ± 0.06 mmol/L, and parathyroid hormone to 108 ± 64.5 pg/mL. In 94% of patients taking cinacalcet, total serum calcium levels were normal, in 81%, serum ionized calcium levels were normal, and serum parathyroid hormone levels were normal in only 25% of patients.[6] Cinacalcet normalizes serum calcium levels in most patients, while slightly reducing serum parathyroid hormone levels.[6]

Pathogenesis of secondary hyperparathyroidism.

Secondary hyperparathyroidism is a common complication in patients with chronic renal failure. These patients typically have parathyroid gland hyperplasia.[7] In the early stages of renal failure, impaired vitamin metabolism, decreased calcitriol levels, and a moderate decrease in ionized calcium levels can contribute to increased synthesis and secretion of parathyroid hormone. As the disease progresses, the number of vitamin D receptors (VDRs) and calcium receptors (CaRs) decreases.[7] A decrease in the number of VDRs and CaRs makes the parathyroid glands more resistant to calcitriol and calcium. Phosphorus causes parathyroid hyperplasia independently of calcium and calcitriol and, through a post-transcriptional mechanism, increases the synthesis and secretion of parathyroid hormone.[7] Experiments on rats with uremia have shown that when animals are fed a diet high in phosphorus, they develop not only secondary hyperparathyroidism, but also parathyroid cell hyperplasia. If the phosphorus content in the diet is reduced, the level of parathyroid hormone normalizes. However, parathyroid hyperplasia The cell turnover is maintained and apoptosis is not observed.[7] Thus, control of the three most important factors—calcium, calcitriol, and phosphorus—is crucial for preventing the development of secondary hyperparathyroidism and parathyroid hyperplasia. Parathyroid hyperplasia and high serum parathyroid hormone (PTH) levels are among the most significant pathogenetic factors affecting divalent ion metabolism in patients with chronic renal failure.[7] Elevated serum PTH levels are observed even in patients with mild to moderate renal failure, which was established back in the 1960s. Ionized calcium, 1,25-dihydroxyvitamin D3 (1,25D), and phosphorus are the three main regulators of PTH levels in humans.[7]

CONCLUSIONS: Primary hyperparathyroidism (PHPT) is one of the most common endocrine disorders, particularly in postmenopausal women, and in modern conditions, it often occurs asymptomatically or with minimal symptoms. The widespread adoption of biochemical screening, primarily serum calcium testing, has significantly increased the detection of the disease in its early stages, before the development of severe, classic bone and kidney complications.

Despite the absence of pronounced clinical symptoms, even mild and asymptomatic forms of PHPT are associated with increased bone remodeling, decreased bone mineral density (BMD), and an increased risk of fractures, primarily vertebral and proximal femoral. Cortical bone is the most vulnerable bone in PHPT, but modern imaging techniques (QCT, pQCT, and

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microcomputed tomography) indicate that trabecular bone is also affected in some forms of the disease, particularly in hypercalcemic and long-term cases.

Parathyroidectomy remains the only definitive treatment for PHPT and is significantly associated with reduced bone turnover, increased BMD in various skeletal regions, and a reduced risk of fractures over the long term. The greatest clinical benefit from surgical treatment is observed in patients with initially reduced BMD (T-score < -2.5). If surgical treatment is not possible, pharmacological approaches play a significant role, including the use of calcimimetics, which effectively lower serum calcium levels, although they have a limited effect on parathyroid hormone levels and bone health. Vitamin D deficiency is an important and often underestimated factor in both secondary hyperparathyroidism and a course modifier for primary hyperparathyroidism. In elderly patients, it contributes to increased PTH secretion, accelerated bone turnover, decreased BMD, and an increased incidence of fractures. Furthermore, vitamin D deficiency can mask hypercalcemia in PHPT, complicating diagnosis, and increases the risk of postoperative complications, including "hungry bone" syndrome. Therefore, assessment and correction of vitamin D status are essential in the management of patients with hyperparathyroidism.

Secondary and tertiary hyperparathyroidism, especially in the setting of chronic kidney disease, have independent clinical significance and are characterized by complex pathogenetic mechanisms, including disturbances in calcium, phosphorus, and vitamin D metabolism, as well as decreased expression of calcium-sensitive and vitamin D receptors. Control of these factors is key to the prevention of parathyroid hyperplasia and severe mineral metabolism disorders. Thus, hyperparathyroidism is a heterogeneous group of conditions that significantly impact bone tissue and fracture risk, even in the absence of overt clinical symptoms. Early diagnosis, thorough differential evaluation, correction of vitamin D deficiency, and timely selection of optimal treatment strategies, including surgical intervention, are key to preventing long-term skeletal complications and improving the prognosis in this patient population.

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