CLINICAL COURSE OF PRIMARY HYPERPARATHYROIDISM IN POSTMENOPAUSAL WOMEN

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Abstract. Primary hyperparathyroidism (PHPT) is a common endocrine disorder and the leading cause of hypercalcaemia in the outpatient setting. The condition occurs predominantly in postmenopausal women and is often identified incidentally during routine biochemical testing, as many patients remain asymptomatic or experience only subtle, nonspecific symptoms for prolonged periods. PHPT is characterised by excessive secretion of parathyroid hormone (PTH), most frequently arising from a single parathyroid adenoma. The effects of PHPT on the skeleton are particularly important in postmenopausal women. Estrogen deficiency, which already accelerates bone loss after menopause, may act synergistically with PTH-induced bone resorption, further compromising bone strength and increasing the risk of osteoporosis and fragility fractures, especially at the spine, distal radius, and hip. In addition, vitamin D status plays a significant role in determining disease severity. Vitamin D deficiency is common among patients with PHPT and may aggravate skeletal involvement, influence biochemical abnormalities, and affect postoperative recovery after parathyroidectomy. This review discusses the current understanding of PHPT in postmenopausal women, focusing on its epidemiology, underlying mechanisms, impact on bone health, and available treatment options. Particular emphasis is placed on distinguishing the skeletal effects of menopause from those directly attributable to PHPT, as well as on the role of surgical and medical management in reducing fracture risk and improving long-term outcomes.

Keywords: primary hyperparathyroidism, postmenopausal women, parathyroid hormone, hypercalcaemia, osteoporosis, bone mineral density, vitamin D deficiency, parathyroidectomy, fracture risk

Introduction

Primary hyperparathyroidism (PHPT) is characterized by hypercalcemia accompanied by elevated serum parathyroid hormone (PTH) levels, resulting from excessive PTH secretion by one or more parathyroid glands. PHPT is recognized as the most common cause of hypercalcemia. The development of hypercalcemia in PHPT is mediated through several mechanisms, including increased renal tubular calcium reabsorption, enhanced bone resorption leading to the release of calcium and phosphate from the skeleton, and stimulation of renal synthesis of 1,25-dihydroxyvitamin D [$1,25(OH)_2D$]. Elevated levels of this active vitamin D metabolite subsequently increase intestinal absorption of both calcium and phosphate. Histopathologically, the majority of PHPT cases (approximately 80%) are caused by a single parathyroid adenoma, whereas multiglandular disease is observed more frequently in older individuals. The condition disproportionately affects women, with the highest incidence observed in those beyond the fifth decade of life, placing the postmenopausal period at the centre of its clinical epidemiology [1].

The clinical presentation of PHPT has shifted considerably over time. While the classical "bones, stones, abdominal groans, and psychic moans" presentation was once typical, most patients in contemporary practice present with mild, asymptomatic, or biochemically discovered disease. Nevertheless, even mild PHPT is associated with measurable skeletal consequences, and the postmenopausal hormonal milieu appears to amplify these effects through the convergence of two independent mechanisms of bone loss: oestrogen-deficiency-related remodelling imbalance and PTH-driven cortical bone resorption [1, 2].

Epidemiology and risk factors

PHPT is most frequently diagnosed in postmenopausal women, who represent the demographic group with the highest prevalence of the condition in virtually all population-based studies. The disease is increasingly identified during the evaluation of osteoporosis or low bone mineral density (BMD), a setting in which clinicians are specifically advised to consider PHPT as a secondary cause. A retrospective single-centre study comparing premenopausal and postmenopausal women undergoing parathyroidectomy found that postmenopausal patients presented with distinct clinical, laboratory, and operative characteristics compared with their premenopausal counterparts, reflecting the influence of the menopausal transition on disease expression [2,3].

Pathophysiology and skeletal effects

The pathophysiological hallmark of PHPT is a rightward shift in the set-point of the calcium-sensing receptor (CaSR) on parathyroid chief cells, resulting in continued PTH secretion despite hypercalcaemia. Chronically elevated PTH increases osteoclastic bone resorption, enhances renal tubular calcium reabsorption, and

stimulates renal 1α-hydroxylase activity, increasing the conversion of 25-hydroxyvitamin D to its active form, 1,25-dihydroxyvitamin D, and thereby augmenting intestinal calcium absorption [4].

In postmenopausal women, PHPT-related bone disease characteristically affects cortical bone to a greater extent than trabecular bone, in contrast to postmenopausal osteoporosis, which predominantly affects trabecular-rich sites such as the lumbar spine. A retrospective study evaluating forearm dual-energy X-ray absorptiometry (DXA) in postmenopausal women found that low cortical bone density at the distal radius was a useful discriminating feature for identifying underlying PHPT among women being evaluated for osteoporosis, supporting the inclusion of forearm BMD assessment as part of the diagnostic work-up in this population [5].

The interaction between PHPT and vitamin D status represents an additional layer of complexity. Numerous studies have documented that patients with PHPT frequently exhibit reduced concentrations of 25-hydroxyvitamin D, a finding that may reflect both increased catabolic conversion to the active hormone and altered feedback regulation rather than true nutritional deficiency. A 2025 single-centre study examining vitamin D metabolite profiles in patients with PHPT, including a substantial proportion of postmenopausal women, identified an inverse correlation between 25-hydroxyvitamin D and serum calcium, with both PTH and 25-hydroxyvitamin D independently predicting calcium concentrations, underscoring a complex bidirectional relationship between vitamin D metabolism and parathyroid function in this population [6].

Fracture risk in postmenopausal PHPT

The increased risk of fragility fracture represents one of the most clinically significant consequences of PHPT in postmenopausal women. A systematic review and meta-analysis of twelve studies found that PHPT was associated with an overall increase in fracture risk, with the most pronounced effects observed at the spine and forearm; notably, when the analysis was restricted to studies including postmenopausal women, the risk of vertebral fracture was particularly elevated, with an odds ratio exceeding eight compared with controls [7].

A subsequent meta-analysis incorporating studies published through 2024 confirmed an overall increase in fracture risk associated with PHPT across multiple age strata, including women aged 50-59 and 60-69 years, with elevated odds ratios observed for vertebral, foot, femoral, and overall osteoporotic fractures. These findings reinforce the clinical importance of considering PHPT in the differential diagnosis of postmenopausal women presenting with unexplained or recurrent fragility fractures, particularly at the spine [8].

A large retrospective cohort study examining fracture probability in patients with PHPT who did not undergo parathyroidectomy found that the risk of hip and major osteoporotic fracture remained elevated regardless of disease severity, although the

analysis also identified a competing increase in overall mortality risk that attenuated long-term fracture probability estimates—an observation with implications for risk communication and shared decision-making in older postmenopausal patients with mild PHPT [9].

Diagnosis

Primary hyperparathyroidism (PHPT) should be suspected in patients presenting with hypercalcaemia accompanied by elevated or inappropriately normal serum parathyroid hormone (PTH) concentrations. The diagnosis is based on the physiological relationship between circulating calcium and PTH levels, in which elevated calcium would normally suppress PTH secretion. Total serum calcium should be interpreted after correction for albumin concentration. In cases where albumin-adjusted calcium remains within the reference range despite elevated PTH levels, measurement of ionized calcium is recommended, as some patients with PHPT may exhibit isolated elevations in ionized calcium [9].

Accurate assessment of ionized calcium requires careful sample handling. Blood specimens should be collected under anaerobic conditions to preserve physiological pH, since acid-base disturbances can significantly affect the proportion of circulating ionized calcium. Samples should be analysed promptly or stored at 4°C for no longer than two hours to minimize alterations in calcium concentration. Although mathematical correction for pH changes can be applied when exposure to air occurs, such adjustments provide only an estimate and may not fully reflect the true ionized calcium level. Several disorders may resemble PHPT and should be considered in the differential diagnosis of hypercalcaemia. These include familial hypocalciuric hypercalcaemia (FHH), a hereditary condition characterized by lifelong mild hypercalcaemia, as well as medication-related hypercalcaemia associated with agents such as thiazide diuretics and lithium. Measurement of serum PTH using either second- or third-generation immunoassays remains a reliable diagnostic approach, with both assay types demonstrating comparable clinical performance in the evaluation of PHPT.

Preoperative imaging has become a standard component of the evaluation of patients with primary hyperparathyroidism (PHPT), primarily to localize abnormal parathyroid tissue and assist in surgical planning. Importantly, imaging studies are not used to establish the diagnosis of PHPT and are generally indicated only when surgical treatment is planned. Because parathyroid glands may be located in ectopic positions, imaging can facilitate identification of abnormal glands and support the selection of the most appropriate surgical approach. However, negative or inconclusive imaging findings should not preclude parathyroidectomy, as experienced surgeons can often successfully identify pathological glands intraoperatively.

The value of preoperative localization is particularly evident in patients undergoing repeat neck surgery, where postoperative scarring and distorted anatomical

landmarks can increase operative complexity. The most commonly used imaging modalities include neck ultrasonography, technetium-99m sestamibi scintigraphy, and computed tomography (CT). Combining imaging techniques improves localization accuracy, and concordant findings from ultrasound and sestamibi scintigraphy are associated with high predictive value for identifying the affected gland.

Technetium-99m sestamibi scintigraphy is one of the most commonly used imaging techniques for the preoperative localization of abnormal parathyroid tissue in patients with primary hyperparathyroidism. The method is based on the preferential uptake and prolonged retention of the radiotracer within mitochondria-rich parathyroid adenoma cells compared with surrounding thyroid tissue. Owing to its high sensitivity and diagnostic accuracy, sestamibi scintigraphy has become a key component of preoperative assessment, particularly in patients with biochemically overt disease and larger adenomas.

Several scintigraphic protocols have been developed, including dual-phase washout imaging and subtraction scintigraphy. Dual-phase imaging exploits the more rapid clearance of the tracer from thyroid tissue, whereas subtraction techniques use additional thyroid-specific tracers to improve differentiation between thyroid and parathyroid uptake. Among these approaches, subtraction scintigraphy has demonstrated superior performance for the detection of both single-gland and multiglandular disease.

The diagnostic value of sestamibi imaging can be further enhanced by combining it with single-photon emission computed tomography (SPECT) and low-dose computed tomography (CT). Hybrid SPECT/CT imaging provides both functional and anatomical information, allowing more precise localization of parathyroid lesions, including ectopic glands and lesions located posterior to the thyroid gland. These advantages are particularly important in patients undergoing reoperative neck surgery, where accurate localization can facilitate surgical planning and improve operative outcomes.

Management and Surgical Outcomes

Parathyroidectomy remains the only curative treatment for PHPT and is recommended according to internationally accepted criteria established by successive International Workshops on the management of asymptomatic PHPT, which incorporate serum calcium thresholds, evidence of skeletal involvement (including reduced BMD at the lumbar spine, hip, or distal one-third radius), nephrolithiasis or nephrocalcinosis, and age below fifty years [4].

Vitamin D status has emerged as a clinically relevant modifiable factor in the perioperative management of PHPT. A systematic review and meta-analysis of nine studies, including three randomised controlled trials encompassing 2,750 patients, found that preoperative vitamin D supplementation significantly reduced the risk of

postoperative hypocalcaemia and symptomatic hypocalcaemia, and was associated with a shorter postoperative length of stay, supporting the incorporation of vitamin D repletion into preoperative protocols for postmenopausal patients undergoing parathyroidectomy [10].

Age-related analyses of surgical outcomes have provided reassurance regarding the safety of parathyroidectomy in older postmenopausal women. A study comparing surgical and biochemical outcomes across age groups found no significant differences in postoperative complication rates, including transient hypoparathyroidism and hungry bone syndrome, between older and younger patients, with normalisation of calcium and PTH levels achieved in all age groups, supporting the view that advanced age alone should not preclude surgical referral in appropriately selected postmenopausal women [11].

For postmenopausal women with PHPT who are not candidates for surgery or who decline operative management, ongoing monitoring of serum calcium, renal function, and bone mineral density is recommended, alongside attention to adequate vitamin D repletion and calcium intake within recommended limits, in accordance with updated clinical practice guidance on vitamin D supplementation in the broader population [12].

Conclusion

Primary hyperparathyroidism in postmenopausal women presents a distinctive clinical picture shaped by the convergence of disease-specific hyperresorptive bone turnover and the independent skeletal consequences of oestrogen deficiency. Current evidence indicates that the duration of menopause may be at least as influential as biochemical disease severity in determining bone health outcomes, that cortical bone assessment at the forearm offers diagnostic value in differentiating PHPT-related from purely postmenopausal osteoporosis, and that fracture risk-particularly at the spine-is substantially elevated in this population. Parathyroidectomy remains the cornerstone of curative management, with preoperative vitamin D optimisation and age-inclusive surgical referral supported by recent evidence as means of improving perioperative outcomes. Continued attention to the interplay between menopausal status, vitamin D metabolism, and parathyroid hormone excess is essential for optimising the diagnosis and management of this common but often under-recognised endocrine disorder.

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