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Review

Evolving clinical profiles of primary hyperparathyroidism; a global perspective

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Abstract

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by the overproduction of parathyroid hormone (PTH), leading to disrupted calcium metabolism and hypercalcemia. Previously, PHPT was recognized as a symptomatic disease with severe skeletal, renal and neuromuscular manifestations. However, the advent of routine calcium screening has shifted the clinical profile toward milder, often asymptomatic presentations, particularly in developed countries. Despite this evolution, significant global disparities persist in the prevalence, clinical presentation and management of PHPT. In developing regions, symptomatic cases with advanced complications remain prevalent, driven by limited access to diagnostic resources, nutritional deficiencies and genetic factors. Exploring the evolving clinical profiles of this disease from a global perspective emphasizes regional variations in epidemiology, etiology and treatment approaches, examines the impact of socioeconomic, environmental, and genetic factors on the disease's presentation and outcomes and addresses the challenges of diagnosis and management in resource-limited settings.

Keywords: Primary hyperparathyroidism, Parathyroid hormone, Calcium metabolism, Hypercalcemia, Diagnosis

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Introduction

Primary hyperparathyroidism (PHPT) is a common endocrine disorder characterized by the overproduction of parathyroid hormone (PTH) due to abnormal parathyroid gland activity (1). This condition disrupts calcium metabolism, leading to hypercalcemia (1). The parathyroid glands, typically four small glands located near the thyroid, play a critical role in maintaining calcium homeostasis (2). Parathormone (PTH) regulates calcium levels by increasing calcium absorption in the intestines, reabsorption in the kidneys, and release from bones (3). In PHPT, excessive PTH secretion results in an imbalance, causing a range of clinical manifestations that can affect multiple organ systems (1,4). The understanding of endocrine disorders, particularly PHPT has evolved significantly over the past few decades, primarily driven by advancements in diagnostic technologies (5). Initially, PHPT is described as a rare and severe disease with overt symptoms such as bone abnormalities, kidney stones and neuromuscular dysfunction (6). This disease was recognized in its asymptomatic form and often diagnosed at advanced stages (7). The introduction of automated serum chemistry analyzers and routine calcium screening in the 1970s marked a turning point, leading to the identification of milder, asymptomatic cases (4). This shift in clinical presentation has transformed PHPT from a symptomatic disorder to one that is frequently detected incidentally through laboratory testing (8). Key milestones in its diagnosis and treatment include the development of PTH assays, advances in imaging techniques for localizing parathyroid adenomas, and the refinement of surgical and medical management strategies (9). Historical imaging methods such as ultrasound and X-rays were limited however these methods have evolved to include advanced modalities like four-dimensional CT (4DCT) and positron emission tomography (PET) imaging (10). A previous study by Prabhu et al highlights that the use of hybrid imaging techniques such as PET/CT increases the likelihood of accurate localization of parathyroid adenomas (11). Moreover, tools like the near-infrared camera system, which highlights the autofluorescence of parathyroid glands, have further refined surgical planning throughout a clear distinguishing parathyroid tissue from surrounding structures. This method therefore minimizes the unnecessary invasive procedures and its complications (12). Meanwhile, the emergence of molecular

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Implication for health policy/practice/research/medical education

The prevalence of asymptomatic primary hyperparathyroidism cases, has reportedly tripled in recent decades, indicating that efforts to inform the general alertness about this condition have been strengthen.

technologies has also altered the management landscape for asymptomatic PHPT. Genetic testing for mutations in genes like calcium-sensing receptor (CaSR), multiple endocrine neoplasia type 1 (MEN1), and hyperparathyroidism 2 (HRPT2) has provided essential information regarding the hereditary nature of this disease, enabling targeted screening in at-risk population (13). Furthermore, advances in PTH measurement techniques including various immunoradiometric tests have improved diagnostic accuracy, especially in determining the parathyroid cause of hypercalcemia (14). As an example, third-generation assays that specifically measure intact PTH levels offer a clearer interpretation of what constitutes abnormal parathormone levels in the context of hypercalcemia, further informing treatment decisions (15,16). Consequently, in developed countries, this endocrinopathy is often diagnosed at an early, asymptomatic stage due to widespread access to routine laboratory testing (17). In contrast, developing nations continue to see a higher prevalence of symptomatic PHPT, with patients presenting with severe skeletal and renal complications (5,17). These disparities highlight the need for a global perspective in understanding and managing PHPT. Socioeconomic factors, such as access to endocrinologists and nutritional status, play a significant role in shaping the disease's presentation and outcomes (18). Additionally, genetic predispositions (19) and environmental influences, such as vitamin D deficiency, further contribute to regional variations (20). This review sought to address these disparities and develop strategies to improve diagnosis, treatment, and outcomes for patients worldwide and find how public awareness initiatives impact the detection rates of asymptomatic PHPT.

Search strategy

For this review, we searched PubMed, Web of Science, EBSCO, Scopus, Google Scholar, Directory of Open Access Journals (DOAJ) and Embase, using different keywords like; primary hyperparathyroidism, parathyroid hormone, calcium metabolism, and hypercalcemia.

A short look at the evolution of PHPT

Significant changes in clinical presentation have occurred over the decades in PHPT, which is the third most common endocrine disorder (1). In developed countries, PHPT has shifted from a symptomatic disease affecting bones and kidneys to a predominantly asymptomatic condition, often detected incidentally (5). In developing countries, vitamin D deficiency plays a key role in shaping its clinical presentation (21). In Europe and North America, PHPT is largely asymptomatic (5). In contrast, regions such as South America, China, and Eastern Europe (e.g., Turkey, Bulgaria, and Russia) are transitioning from symptomatic to asymptomatic cases (16,22). Asia exhibits variability, for example symptomatic cases dominate in the Indian subcontinent, Middle East, and Southeast Asia, while transitional patterns with increasing asymptomatic cases are observed in China; Japan predominantly reports asymptomatic cases (5). In fact, factors driving these trends include advancements in diagnostic tools, incidental detection during thyroid ultrasonography, regional variations in vitamin D deficiency, dietary habits, genetic polymorphisms in calcium-sensing and vitamin D receptors, and environmental influences like climate-related nephrolithiasis prevalence (5). These parameters influence the clinical presentation and diagnosis of this disease through territories.

Epidemiology of PHPT

The prevalence and incidence of PHPT vary significantly across the world, reflecting differences in healthcare access, diagnostic practices and population characteristics (23). In developed countries, PHPT is relatively common, with an estimated prevalence of one to seven cases per 1000 individuals (24), largely due to the widespread use of routine calcium screening, which led to the identification of asymptomatic cases (4). In contrast, developing countries report lower prevalence rates of this disease, which is due to the underestimation owing to limited diagnostic resources and underreporting (25). In developing regions, this illness is often diagnosed at a more advanced stage, with patients presenting severe symptoms such as skeletal abnormalities and renal complications (5). Over time, the diagnosis of PHPT has increased globally, particularly in high-income countries, where advancements in medical technology and heightened awareness have facilitated early detection (26). However, this trend is less pronounced in low- and middle-income countries, where healthcare disparities persist (26,27). This condition exhibits notable demographic variations in terms of age, gender, and ethnicity (28). Moreover, this condition is most commonly diagnosed in postmenopausal women, with women being two to three times more likely to develop PHPT than men (29). This gender disparity is thought to be linked to hormonal changes and longer life expectancy in women (29,30). It is possible that, age acts as another factor, since the incidence of PHPT increases with age, particularly in individuals over 50 years (31). In addition, ethnic differences play a role, while previous studies suggesting higher prevalence rates among certain populations, such as African-Americans, who may have a greater

predisposition to vitamin D deficiency and subsequent secondary hyperparathyroidism (32). Regional disparities in access to diagnosis and treatment further complicate the epidemiological landscape. It should remember that, in resource-limited settings, delayed diagnosis and inadequate treatment options contribute to poorer outcomes, while in developed countries, early detection and advanced management strategies have significantly improved patient prognosis (33,34).

Clinical presentation of PHPT

Primary hyperparathyroidism has been associated with a range of classical symptoms, primarily affecting the skeletal, renal, and neuromuscular systems (35). Skeletal manifestations are among the most recognizable features, with patients often presenting with osteoporosis, bone pain, and an increased risk of fractures due to excessive bone resorption caused by elevated parathormone levels (36). The chronic excess of parathormone leads to increased osteoclast activity and bone resorption, potentially resulting in weakened bone structure (37). In severe cases, patients may develop osteitis fibrosa cystica, characterized by increased osteoclast activity, bone tissue replacement with fibrous tissue, and brown tumors (38). Renal involvement represents another classical manifestation of PHPT, including nephrolithiasis and hypercalciuria, which can lead to chronic kidney disease if left untreated (39). Prior studies indicated that up to 55% of patients have previously undiagnosed nephrocalcinosis or non-obstructing renal calculi (6). The development of kidney stones is influenced by various factors, including hypercalciuria, which affects approximately 40% of PHPT patients (39,40). Likewise, neuromuscular symptoms, such as muscle weakness, fatigue, and cognitive disturbances, further characterize the classical presentation of PHPT (41). These symptoms result from the direct and indirect effects of hypercalcemia and PTH, potentially through alterations in energy metabolism and protein synthesis on muscle and nerve function (42,43). In recent decades, the clinical profile of PHPT has shifted significantly, with an increasing prevalence of asymptomatic cases (5,44). This change is largely attributed to the widespread use of routine laboratory testing, which has enabled the early detection of hypercalcemia and elevated parathormone levels before the onset of overt symptoms (4,44). PHPT cases, typically have modestly elevated PTH levels, usually within 1.5-2 times the upper limit of normal (7). Asymptomatic PHPT is now the most common form of the disease in developed countries, where patients are often diagnosed incidentally during evaluations for unrelated conditions (45). Despite the absence of classical symptoms, these individuals may still be at risk for long-term complications, such as subclinical bone loss or mild renal dysfunction, underscoring the importance of regular monitoring and individualized management (46,47). Emerging evidence suggests that, this condition can also present with non-classical or atypical symptoms, reflecting its systemic effects beyond the skeletal and renal systems (31). On the other hand, cardiovascular manifestations, such as hypertension, left ventricular hypertrophy, and vascular calcification, have been increasingly linked to PHPT, raising concerns about its impact on long-term cardiovascular health (48,49). Neurocognitive symptoms, including depression, anxiety, memory loss, and reduced quality of life, are also reported, although their direct association with PHPT remains an area of active research (41,50). Additionally, gastrointestinal symptoms like peptic ulcers, pancreatitis, and constipation may occur due to hypercalcemia (51). These atypical presentations highlight the complex and multifaceted nature of PHPT, necessitating a comprehensive approach to diagnosis and management that considers its potential systemic effects (52).

Focus on asymptomatic PHPT

Asymptomatic PHPT has often been underdiagnosed leading to significant morbidity (53). As mentioned, in last few decades, across with increasing public awareness campaigns, the detection rates of asymptomatic PHPT have changed dramatically (45). In fact, in parallel with technological advancements, clinical guidelines have evolved to reflect the growing awareness of asymptomatic PHPT (54). In particular, patients educated about symptoms, such as kidney stones or fatigue, are more likely to discuss these concerns with their physicians, leading to increased testing and diagnosis of previously unrecognized cases (6). Educational initiatives that disseminate information about the relationship between calcium levels and bone health (55), kidney stones (56), and mood disturbances (57) have thus proven significant in driving the public to seek preventive care and screening for asymptomatic PHPT (6).

Diagnostic approaches for PHPT

The diagnosis of PHPT begins with laboratory testing to assess calcium and PTH levels (22). Hypercalcemia in conjunction with inappropriately high or normal parathormone levels is a hallmark of this endocrinopathy (1). Additionally, measuring vitamin D levels is crucial, as vitamin D deficiency can complicate the interpretation of PTH levels and influence disease severity (58). Once biochemical abnormalities are identified, imaging studies play a critical role in localizing parathyroid abnormalities (59). Ultrasound is often the first-line imaging modality due to its accessibility and non-invasive nature (59). For more precise localization, technetium-99m sestamibi scans are commonly used, as they can identify hyperfunctioning parathyroid tissue (59). In complex cases, advanced imaging techniques such as computed tomography (CT) or magnetic resonance imaging (MRI) may be employed to provide detailed anatomical information (59). Distinguishing PHPT from other forms

of hyperparathyroidism, such as secondary and tertiary hyperparathyroidism, is necessary for accurate diagnosis and management (22). Secondary hyperparathyroidism is characterized by elevated PTH levels due to conditions like chronic kidney disease or vitamin D deficiency, often accompanied by normal or low-serum calcium (60). Tertiary hyperparathyroidism, typically seen in patients with long-standing secondary hyperparathyroidism, involves autonomous parathormone secretion and hypercalcemia (61). Diagnosing normocalcemic PHPT, a variant where serum calcium levels remain within the normal range despite elevated PTH, presents additional challenges (62). This condition requires careful exclusion of other causes of secondary hyperparathyroidism, such as vitamin D deficiency or renal impairment, and often relies on repeated testing and clinical correlation (63). Diagnostic practices for PHPT vary significantly across several regions, influenced by differences in healthcare infrastructure, resource availability, and clinical guidelines. In developed countries, routine laboratory testing and advanced imaging techniques are widely accessible, facilitating early and accurate diagnosis (64).

Etiology and pathophysiology of PHPT

Genetic predisposition plays a significant role in the development of PHPT, particularly in familial syndromes (13). Multiple endocrine neoplasia type 1 (MEN1) and type 2A (MEN2A) are well-known genetic disorders associated with PHPT, often presenting with multiglandular parathyroid hyperplasia (65). MEN1 is caused by mutations in the MEN1 gene, while MEN2A is linked to mutations in the RET proto-oncogene (66). Another rare genetic condition, hyperparathyroidism-jaw tumor syndrome (HPT-JT), caused by mutations in the CDC73 gene, is characterized by parathyroid adenomas or carcinomas and fibro-osseous jaw tumors (67). In addition to these familial syndromes, sporadic mutations in genes such as cyclin D1 (CCND1) and CaSR have been implicated in the development of parathyroid adenomas, highlighting the complex genetic landscape of this illness (68-70). Environmental and lifestyle factors also contribute to the etiology and pathophysiology of PHPT (71). Vitamin D deficiency, a global health issue particularly prevalent in regions with limited sunlight exposure or poor dietary intake, is a significant risk factor (72). As mentioned above, low vitamin D levels lead to secondary hyperparathyroidism, which can progress to PHPT (73). Studies indicating that most of PHPT patients exhibit vitamin D insufficiency which appears to exacerbate disease severity, reflected in higher PTH levels and more pronounced clinical manifestations (74). Dietary habits, such as low-calcium intake, further exacerbate the risk by stimulating PTH secretion (75). Environmental chemicals present in urban environments have been detected in parathyroid tumors, suggesting potential causal links to tumor development (76). Additionally, challenges in urban environments, including pollution, artificial light exposure, and reduced natural light exposure, have been linked to lower vitamin D synthesis and calcium homeostasis and higher rates of PHPT (77). At the molecular level, PHPT is primarily driven by abnormalities in parathyroid gland function (78). The most common cause is a solitary parathyroid adenoma, accounting for approximately 80%-85% of cases (1). Less frequently in approximately 15% of cases, multiglandular hyperplasia or parathyroid carcinoma may be responsible (79). Dysregulation of the CaSR, a key regulator of PTH secretion, is a central mechanism in PHPT (80). This receptor, crucial for maintaining calcium homeostasis, enables parathyroid cells to sense and respond to changes in extracellular calcium levels (80). Inactivating mutations in the CASR gene or reduced expression of CaSR can impair the gland's ability to sense extracellular calcium levels, leading to excessive PTH secretion (81). Additionally, molecular alterations in cell cycle regulators, such as cyclin D1 overexpression, contribute to parathyroid cell proliferation and adenoma formation (82).

Management and treatment of PHPT

Surgical removal of the abnormal parathyroid gland, known as parathyroidectomy, is the definitive treatment for this endocrine disorder and is particularly recommended for symptomatic patients or those with complications such as osteoporosis, kidney stones, or significant hypercalcemia (83). Indications for surgery also include asymptomatic patients who meet specific criteria, such as markedly elevated serum calcium levels, reduced bone density, impaired renal function, or younger age (84). Minimally invasive parathyroidectomy has become the preferred surgical approach due to its high success rates, shorter recovery times, and reduced complications compared to traditional bilateral neck exploration (85). Preoperative imaging, such as sestamibi scans or high-resolution ultrasound, is often conducted to localize the affected gland, allowing for a targeted procedure (86). However, imaging results should not dictate surgical candidacy, as patients with negative imaging studies may still benefit from surgical intervention (87). Outcomes are generally excellent, with most patients experiencing normalization of calcium and parathormone levels and significant improvement in symptoms. For patients who are not candidates for surgery or prefer non-surgical options, medical management plays a crucial role in controlling PHPT (44). Calcimimetics, such as cinacalcet, have demonstrated effectiveness in lowering serum calcium levels and increasing phosphate concentrations (88). These agents are commonly administered to lower PTH by enhancing the sensitivity of CaSR on parathyroid cells (88). Likewise, bisphosphonate therapy has emerged as an important option for managing skeletal manifestations of PHPT (89). Studies indicate that bisphosphonates,

particularly alendronate, effectively improve bone mineral density at the lumbar spine without significantly altering serum calcium levels (89). Accordingly, vitamin D supplementation is often necessary, particularly in patients with coexisting vitamin D deficiency, to prevent secondary hyperparathyroidism and support overall bone health (90). Research demonstrates that careful vitamin D repletion in deficient patients can safely improve vitamin D status and potentially decrease PTH levels without increasing the risk of hypercalcemia or stone formation (91). Asymptomatic patients who do not meet surgical criteria are typically managed with regular monitoring of calcium, PTH, and bone density, along with lifestyle modifications to minimize complications (54). Importantly, renal function should also be monitored annually, with additional evaluations for stone formation in high-risk patients (39). Access to effective treatment for PHPT varies significantly across the world, with substantial disparities between high-income and low-resource settings (92). In developed countries, advanced diagnostic tools, surgical expertise, and medical therapies are widely available, leading to favorable outcomes for most patients (93). However, in low- and middle-income countries, limited healthcare infrastructure, lack of specialized surgical training, and high costs of medications pose significant barriers to care (94). Many patients in these regions are diagnosed at advanced stages of the disease, with severe complications that could have been prevented with earlier intervention (95).

Conclusion

This narrative review talked about advancements in diagnostic technologies have been instrumental in shifting the perception and clinical management of PHPT from a predominantly symptomatic disorder toward the recognition of asymptomatic cases. The introduction of multichannel serum autoanalyzers, improvements in imaging techniques, and the application of molecular diagnostics have all contributed to enhanced detection capabilities. Along with evolving clinical guidelines, these advancements reflect an ongoing commitment to refining the approach to PHPT, emphasizing the need for sensitive detection and appropriate management strategies for asymptomatic patients. As a result, the implications for long-term patient outcomes, including quality of life and potential complications, are becoming increasingly favorable in the context of improved diagnostic strategies.

Authors' contribution

Conceptualization: Parisa Tajdini, Majid Foroutan.
Data curation: Ali Valadkhani.
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Supervision: Parisa Tajdini.
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Visualization: Parisa Tajdini, Mohammad Reza Moonesan.
Writing—original draft: Mohammad Reza Moonesan, Majid Foroutan.
Writing—review and editing: Parisa Tajdini, Majid Foroutan.

Conflicts of interest

The authors declare that they have no competing interests.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Ethical issues

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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