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**Mini-Review**

# Normocalcemic primary hyperparathyroidism; a mini-review

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**Abstract**

Normocalcemic primary hyperparathyroidism (NPHT) is a subtype of primary hyperparathyroidism (PHPT) characterized by elevated levels of parathyroid hormone (PTH) within the normal range of serum calcium. In traditional PHPT, high serum calcium levels are typically seen, whereas in normocalcemic PHPT, calcium levels are within the normal range. NPHT is often diagnosed incidentally when routine blood tests reveal elevated PTH levels while calcium levels remain normal. The exact prevalence of NPHT is not well established due to variations in diagnostic criteria and inconsistent screening practices. The clinical significance and management of NPHT are still a subject of debate. Some studies suggest that NPHT may have similar long-term complications as traditional PHPT, such as kidney stones, osteoporosis, and cardiovascular disease. However, other research indicates that NPHT may have a more benign course with a lower risk of developing these complications

**Keywords:** Normocalcemic primary hyperparathyroidism, Hyperparathyroidism, Parathyroid hormone, Calcium, Diagnosis, Management

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## Introduction

Primary hyperparathyroidism (PHPT) is a disorder characterized by excessive secretion of parathyroid hormone (PTH) from one or more parathyroid glands, leading to hypercalcemia (1). Traditionally, the diagnosis of PHPT has been based on elevated serum calcium levels. However, there is increasing recognition of a subset of patients with normal serum calcium levels but elevated PTH levels, known as normocalcemic PHPT. This review paper aims to summarize the current literature on normocalcemic PHPT, including its prevalence, clinical presentation, diagnostic challenges, and management options (2-4).

## 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 such as normocalcemic primary hyperparathyroidism, hyperparathyroidism, parathyroid hormone, calcium, diagnosis, management.

## Prevalence of normocalcemic PHPT

The prevalence of normocalcemic PHPT varies widely across different studies, ranging from 5% to 30% of all cases of PHPT. This variability can be attributed to differences in study populations, diagnostic criteria, and assay methods for measuring PTH and calcium levels. Normocalcemic PHPT is more commonly observed in older individuals and women (5,6).

## Molecular mechanisms

The molecular mechanisms underlying normocalcemic primary hyperparathyroidism (NPHT) are still not fully understood and are an area of active research. However, several potential factors have been proposed to contribute to the development of NPHT (5,7).

Here are some of the molecular mechanisms that have been suggested;

### *Parathyroid cell proliferation*

In NPHT, there may be an increased proliferation of parathyroid cells, leading to the overproduction of PTH. Abnormalities in cell signaling pathways, such as dysregulation of the cyclin D1/CDK4/retinoblastoma protein (RB) pathway or the Wnt/β-catenin pathway, have been implicated in promoting parathyroid cell growth (8,9).

### *Calcium-sensing receptor (CaSR) abnormalities*

The calcium-sensing receptor plays a crucial role in regulating parathyroid cell function. Mutations or

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**Implication for health policy/practice/research/medical education**

Normocalcemic primary hyperparathyroidism (NPHPT) is an increasingly recognized variant of primary hyperparathyroidism (PHPT). Although the optimal management approach is still evolving, early detection and close monitoring are crucial to identify patients who may benefit from intervention. Further research is needed to better understand the natural history, long-term outcomes, and optimal management strategies for NPHPT. NPHPT is a relatively newly recognized variant of PHPT. PHPT is characterized by excessive secretion of parathyroid hormone (PTH) from the parathyroid glands, leading to hypercalcemia. However, in NPHPT, serum calcium levels remain within the normal range, making it challenging to diagnose.

dysregulation of the CaSR gene can result in altered sensitivity to calcium, leading to excessive PTH secretion even in the presence of normal serum calcium levels (10,11).

### *Vitamin D and calcium homeostasis*

Disturbances in the vitamin D and calcium homeostatic mechanisms may contribute to NPHT. Dysregulation of vitamin D metabolism, such as impaired conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, can affect calcium absorption and feedback regulation of PTH secretion (12,13).

### *Genetic factors*

Studies have suggested a potential genetic predisposition to NPHT. Specific genetic variations or mutations in genes involved in parathyroid cell regulation, calcium metabolism, or signaling pathways have been identified in some individuals with NPHT. However, the genetic factors contributing to NPHT are not yet well-defined and require further investigation (14,15).

### *Parathyroid hormone resistance*

Some individuals with NPHT may exhibit resistance to the actions of PTH at the target tissues, leading to a compensatory increase in PTH secretion. The exact mechanisms underlying PTH resistance in NPHT are not fully understood but may involve alterations in PTH receptors or downstream signaling pathways (16,17).

## Clinical presentation

Normocalcemic PHPT is often asymptomatic and diagnosed incidentally through routine laboratory testing or imaging studies. However, some patients may present with nonspecific symptoms such as fatigue, bone pain, muscle weakness, or cognitive impairment. It is important to note that the absence of symptoms does not exclude the presence of complications associated with PHPT, such as osteoporosis, kidney stones, or cardiovascular disease (1,18).

## Diagnostic challenges

The diagnosis of normocalcemic PHPT can be challenging due to the lack of consensus on diagnostic criteria. Various thresholds for defining elevated PTH levels have been proposed, ranging from the upper limit of normal to two standard deviations above the mean. Additionally, there is ongoing debate regarding the optimal reference range for serum calcium levels in this population. Further research is needed to establish standardized diagnostic criteria for normocalcemic PHPT (3,5).

## Management of normocalcemic PHPT

The management of normocalcemic PHPT remains controversial due to the limited evidence available. Current guidelines recommend a conservative approach with regular monitoring of serum calcium and PTH levels, along with assessment of bone mineral density. Surgical intervention may be considered in select cases with evidence of complications or progressive disease. However, the long-term outcomes and benefits of surgery in normocalcemic PHPT are not well-established (7,19,20).

## Conclusion

Normocalcemic PHPT is a distinct entity within the spectrum of PHPT, characterized by elevated PTH levels in the presence of normal serum calcium levels. The prevalence, clinical presentation, and optimal management of normocalcemic PHPT are still areas of active research and debate. Further studies are needed to better understand the natural history, complications, and treatment outcomes in this patient population.

### Conflicts of interest

The author declare that she has no competing interests.

### Ethical issues

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

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