

Asymptomatic Primary Hyperparathyroidism: A Misnomer

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Abstract

Primary hyperparathyroidism (PHPT) is an endocrine disorder marked by elevated secretion of parathyroid hormone (PTH), which results in hypercalcemia and may cause complications in the kidneys and bones. Diagnosing this condition involves ruling out secondary causes and understanding the complexities of the laboratory values associated with PHPT. The disease has become more recognizable to clinicians in an earlier phase thanks to updated screening guidelines. At present, patients can be diagnosed with “classic,” “normocalcemic,” “normohormonal,” or “asymptomatic” PHPT. Many patients are diagnosed through incidental findings of elevated calcium levels or PTH levels during routine blood tests rather than through the presentation of classic symptoms. If asked, patients will invariably harbor subtle or subclinical manifestations despite the absence of overt symptoms. There is debate on whether truly asymptomatic hyperparathyroidism exists.¹ We explore the definition and clinical patterns of asymptomatic hyperparathyroidism and propose concise recommendations for recognizing these patients.

Keywords

asymptomatic hyperparathyroidism, hyperparathyroidism, parathyroidectomy

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The prevalence of primary hyperparathyroidism (PHPT) is approximately 233 and 85 per 100,000 in women and men, respectively.^{1,2} The incidence of this condition has increased with routine laboratory screening for serum calcium and bone mineral density (BMD). The classic symptoms of primary hyperparathyroidism are primarily related to the effects of elevated calcium levels. They can be remembered by the mnemonic “Stones, Bones, Groans (abd. groans), Moans, Thrones, and Psychiatric Overtones!”

The disease has become more recognizable in an earlier phase thanks to updated screening guidelines. Patients may be diagnosed with “classic,” “normocalcemic,” “normohormonal,” or “asymptomatic” PHPT (**Table 1**).

“Asymptomatic primary hyperparathyroidism” refers to patients who do not exhibit apparent signs or symptoms associated with elevated calcium levels or parathyroid hormone (PTH). Many patients are diagnosed through incidental findings of elevated calcium levels or PTH levels during routine blood tests rather than through the presentation of classic symptoms. When asked, patients often harbor subtle manifestations despite the absence of overt symptoms. The cure for PHPT is parathyroidectomy, and it has been shown to improve all aspects of the disease with a high cure rate and minimal complications.³

Asymptomatic PHPT affects mainly women in their middle years within the first decade of menopause. Current guidelines for treatment of asymptomatic PHPT from the National Institute of Health (NIH) include the following indications for surgery: age <50 years, serum calcium concentration 1.0 mg/dL above the upper limit of normal, 24-hour urinary calcium greater than 400 mg, or a *t*-score <−2.5 at any bony site.⁴ Despite these guidelines, the impact of asymptomatic PHPT remains unclear.

As the detection of PHPT increased, patients with subtle symptoms have been identified. It is rare in this day and age for patients to present with the classic symptoms of renal stones and fractures due to earlier detection. However, many patients are deemed “asymptomatic” when, in fact, they suffer from albeit subtle but bothersome symptoms. Patients often do not recognize that they have symptoms until their “so-called” nonspecific manifestations diminish or disappear following surgery. One study found that over 90% of patients labeled “asymptomatic” have significant subclinical manifestations that may not be recognized.¹ Subtle manifestations of PHPT include signs

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of depression and poor mood, low energy levels, difficulty completing daily tasks, generalized weakness, and diffuse pain.⁵

Patients with primary hyperparathyroidism (PHPT) may experience various sleep-related issues, such as difficulty falling asleep, frequent awakenings during the night, and nonrestorative sleep.⁶ These disturbances can be attributed to several factors. Elevated calcium levels can disrupt normal sleep patterns, leading to insomnia or fragmented sleep. Additionally, symptoms like anxiety, depression, and irritability, which are common in PHPT, can negatively impact sleep quality.⁷

Studies have also shown that patients report improved quality of life following surgery for PHPT, including perceptions of general health and energy level.^{5,7} It is crucial to consider subjective and nonspecific measures in evaluating PHPT, and clinicians should have a lower threshold for suspecting this diagnosis. In addition to recommendations for initial workup (**Table 2**), the authors propose a series of questions asked of the patient and accompanying spouse or partner when evaluating these patients (**Table 3**). In most cases, these open-ended questions will elicit a positive response. Although no data exists on the validation of this metric, the author has had much success in utilizing it. Future studies will be conducted to further investigate the validity of this item.

Special attention must be given to elderly patients, as nonclassical symptoms such as nervousness and confusion are often overlooked or conflated with dementia. This population is also at a higher risk of subclinical vertebral fractures and bone degeneration, which have been detected

Table 1. Lab Values Corresponding to Presentation of PHPT

Presentation	PTH	Calcium
Classic PHPT	>60 pg/mL	>10.5 mg/dL
Normocalcemic PHPT	>60 pg/mL	8.5–10.5 mg/dL
Normohormonal PHPT	21–65 pg/mL	>10.5 mg/dL
“Asymptomatic” PHPT	>60 pg/mL	>10.5 mg/dL

Abbreviations: PHPT, patients with primary hyperparathyroidism; PTH, parathyroid hormone.

Table 2. Recommendations for Initial Workup of PHPT

Evaluation stage	Workup
Patients with suspected primary hyperparathyroidism	Measure albumin-adjusted serum calcium levels Measure PTH levels Measure vitamin D levels Exclude familial hypocalciuric hypercalcemia
Patients with a confirmed diagnosis of primary hyperparathyroidism	Measure eGFR (estimated glomerular filtration rate) or serum creatinine Obtain a DXA (dual-energy X-ray absorptiometry) scan of the lumbar spine, distal radius, and hip Obtain an ultrasound scan of the renal tract Assess symptoms and comorbidities

Abbreviations: PHPT, patients with primary hyperparathyroidism; PTH, parathyroid hormone.

in patients without specific symptoms.⁸ Postmenopausal women are already at a higher risk for fractures and PHPT may compound this risk. However, many of these symptoms should not only be attributed to age or menopausal status in the presence of a biochemical diagnosis of PHPT (ie, the presence of hypercalcemia and elevated PTH).

Shared decision-making is essential when considering the utility of surgery. Lorenz et al. found that 33.3% of patients with hypercalcemia who obtain PTH levels are at risk of PHPT. Their study showed that high-risk patients without a diagnosis of PHPT had a significantly increased risk of disease sequelae such as anxiety, hypertension, joint pain, abdominal pain, headache, and osteoporosis.⁸ This highlights the importance of prompt workup and diagnosis, even when patients appear asymptomatic. While underlying laboratory values for each patient should be considered and monitored, much debate exists over the correlation between laboratory values and symptom burden.^{8,9} Patients without evident symptoms or laboratory values should still be considered surgical candidates.

Neuropsychiatric symptoms, in particular, have been reported to improve quickly following parathyroidectomy, even in patients without typical signs and symptoms of PHPT. A prospective study investigating symptoms such as memory, attention, and verbal learning

Table 3. Recommended Questions to Ask Patients During the Initial Evaluation of PHPT

Recommended questions
How do you feel overall?
How is your energy level?
How is your mood of late? Ask the patient and accompanying spouse/partner about emotional lability or irritability that is out of character.
How is your memory of late?
Have you noticed any changes in your clarity of thought or concentration? (decreased ability to think clearly, focus, concentrate, remember, and pay attention)
How do you sleep at night? Please describe in further detail.

showed that improvements in these symptoms may occur as early as one week following surgery.¹⁰ In another study of patients with PHPT, Chan et al. used actigraphy to demonstrate significant improvements in objective measures of sleep following parathyroidectomy.⁷

Early evaluation of total calcium levels, as well as PTH in all patients, may help clinicians recognize the presence of PHPT. The authors conclude that “asymptomatic” PHPT may be a misnomer, and clinicians should take the time to recognize the subtle but significant symptoms that occur. Special care and counseling on all treatment options should be employed when discussing the possibility of surgery with patients.

Author Contributions


Hänel W. Eberly, writing—original draft, review and editing, conceptualization; **Bao Y. Sciscent**, writing—review and critical editing of the manuscript; **F. Jeffrey Lorenz**, writing—review and editing of the manuscript; **Neerav Goyal**, conceptualization, review and editing, supervision; **David Goldenberg**, conceptualization, supervision, writing—original draft, review, and editing.

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