Asymptomatic Primary Hyperparathyroidism

Diagnostic Pitfalls and Surgical Intervention

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KEYWORDS

• Asymptomatic primary hyperparathyroidism • Parathyroid hormone
• Parathyroidectomy • Hypercalcemia • Nonclassic primary hyperparathyroidism

KEY POINTS

- In most cases, primary hyperparathyroidism can be diagnosed by measuring serum calcium and parathyroid hormone.
- Nearly half of cases of primary hyperparathyroidism have a "nonclassic" presentation, with hypercalcemia and inappropriately normal parathyroid hormone levels.
- Parathyroidectomy has become a more commonplace and safe procedure, but many patients, especially elderly patients, are not appropriately referred for surgical consultation.

INTRODUCTION

Primary hyperparathyroidism (PHPT) is a disease caused by the excess production of parathyroid hormone (PTH), resulting in the dysregulation of calcium metabolism. The current estimated prevalence of PHPT is as high as 1 in every 400 women, and 1 in 1000 men.[1] Symptoms caused by hypercalcemia and elevated PTH levels manifest insidiously over an extended period of time; most patients with PHPT are asymptomatic, with only a small fraction exhibiting classic signs and symptoms. Patients with asymptomatic disease were largely undiagnosed until the advent of the multichannel autoanalyzer in the 1970s, which subsequently led to the adoption of routine serum calcium measurements. Detection of hypercalcemia on routine serum calcium screening has greatly facilitated the diagnosis of PHPT: from 1995 to 2010, the

The authors have nothing to disclose.
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Surg Oncol Clin N Am 25 (2016) 77–90
http://dx.doi.org/10.1016/j.soc.2015.08.004 **surgonc.theclinics.com**
1055-3207/16/$ – see front matter

incidence of PHPT tripled.[1] This article addresses the diagnosis and surgical management of asymptomatic PHPT.

BIOCHEMICAL DIAGNOSIS OF PRIMARY HYPERPARATHYROIDISM

Our standard biochemical panel for the initial workup of suspected PHPT is shown in **Box 1**. Most ambulatory patients have normal serum phosphorus, creatinine, and albumin. Hence, the diagnosis can be determined by serum calcium and serum PTH in most cases. We routinely measure the serum 25-hydroxy (25-OH) vitamin D level to clarify the diagnosis in borderline cases, and to help differentiate between primary and secondary hyperparathyroidism.

Calcium

Suspicion of asymptomatic hyperparathyroidism typically begins with incidental detection of elevated serum calcium. A single elevation of the serum calcium is frequently spurious. Therefore, repeat testing of the serum calcium is recommended before proceeding further in the diagnostic workup of PHPT. Because 40% to 45% of serum calcium is protein-bound, total serum calcium should be corrected for serum albumin. Corrected serum calcium is calculated by the following: measured total serum calcium (mg/dL) + 0.8 (4.0 – measured serum albumin [g/dL]). Per the recent 2013 guidelines established by the Fourth International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism, total serum calcium should be used to establish the diagnosis and not ionized calcium, because ionized calcium testing is not widely available.[2]

Ionized calcium directly measures the bioactive (free) fraction of serum calcium, which more accurately reflects patients' true calcium status than albumin-corrected total calcium, particularly for patients with hyperparathyroidism.[3] Among patients with histologically confirmed PHPT, up to 24% have elevated ionized calcium levels despite normal total calcium levels.[4,5] Additionally, ionized calcium may be informative in hypoalbuminemic patients (ie, patients with cirrhosis or nephrotic syndrome) with suspected PHPT. However, we have noted greater intra-assay variability when

Box 1
Initial diagnostic workup of hyperparathyroidism

Routine tests

Serum calcium

Parathyroid hormone

Serum phosphorus

Serum creatinine

Serum albumin

Optional tests

Ionized calcium (hypoalbuminemic patients, borderline diagnoses)

25-OH vitamin D (nonclassic presentation or suspected vitamin D deficiency)

Urinary calcium excretion (suggestive family history for FHH)

Abbreviation: FHH, familial hypocalciuric hypercalcemia.