# The Changing Landscape of Primary, Secondary, and Tertiary Hyperparathyroidism: Highlights from the American College of Surgeons Panel, "What's New for the Surgeon Caring for Patients with Hyperparathyroidism"

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The management of primary, secondary, and tertiary hyperparathyroidism (HPT) has become an ever-changing landscape that all parathyroid surgeons need to recognize and understand. A panel of surgical experts in HPT assembled at the 2015 Clinical Congress of the American College of Surgeons in Chicago. Their task was to address the rarer diagnostic and therapeutic challenges facing the parathyroid surgeon today. Highlights from those presentations and discussions are provided in the current review.

Primary hyperparathyroidism (PHPT) is the third most common endocrine disorder, with a lifetime risk of 1%. In North America, severe manifestations of the disease are rare, with most patients presenting with a mild form of the disease.[1-3] The diagnosis of PHPT is biochemical, characterized by an elevated total serum calcium and an elevated or inappropriate normal parathyroid hormone (PTH) level. The only curative treatment for PHPT is the surgical removal of a single parathyroid adenoma (75% to 80%) or multiple hypercellular glands (15% to 20%). The surgical approach has evolved with the use of preoperative imaging and intraoperative PTH (IOPTH) measurements from a standard bilateral exploration to a more focused image-directed approach.[1] Preoperative imaging, such as ultrasound, sestamibi, or 4-dimensional CT, have no role in confirmation of the diagnosis. Preoperative imaging should be used solely for the purpose of surgical planning. The use of IOPTH has allowed the surgeon to know when all autonomously functioning parathyroid tissue has been removed without the need for exposure of all 4 parathyroid glands. Although these adjuncts have helped minimize the surgical trauma of a parathyroidectomy, surgical expertise and experience are still required to achieve a high surgical cure rate of >95%. Recognition of some of the diagnostic and therapeutic challenges facing the parathyroid surgeon today is necessary to avoid surgical failure.

With increased awareness and PTH screening in metabolic bone clinics, a small portion of PHPT patients present with only elevated PTH and normal calcium levels. Not only is the diagnosis of this "new" entity—normocalcemic HPT—a challenge for our endocrinology colleagues, it poses a greater challenge to define the treatment end point(s) of surgical therapy. Secondary HPT (SHPT) occurs as an adaptive response of the parathyroid glands to a hypocalcemic or hyperphosphatemic stimulus.[2] Among the many causes of SHPT, renal failure is the most common for patients referred for surgical evaluation. As the renal failure progresses, so does the SHPT, until it reaches a point where the response is no longer adaptive but pathologic, resulting in end-organ manifestations. Data suggest that early surgical intervention benefits these complex patients.[4,5] However, it can be difficult to define when SHPT becomes a nonadaptive process. Tertiary HPT (THPT) is a state of autonomously functioning parathyroid tissue typically manifesting as hypercalcemia after either prolonged SHPT or successful renal transplantation, when calcium levels fail to normalize within the first year. When to intervene with surgery has been a source of debate in the recent literature. Older studies reported a greater risk of renal graft failure and reduced graft function after parathyroidectomy, however,

**Disclosure information: Nothing to disclose.**

Received January 2, 2016; Revised February 11, 2016; Accepted February 12, 2016.

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http://dx.doi.org/10.1016/j.jamcollsurg.2016.02.024
ISSN 1072-7515/16

**Abbreviations and Acronyms**

HBS = hungry bone syndrome
HPT = hyperparathyroidism
IOPTH = intraoperative parathyroid hormone
NCHPT = normocalcemic hyperparathyroidism
PHPT = primary hyperparathyroidism
PTH = parathyroid hormone
SHPT = secondary hyperparathyroidism
THPT = tertiary hyperparathyroidism
TPTx = total parathyroidectomy

the results of recent studies run counter to this finding.[5-7] In addition, the recent increased use of the calcimimetic, cinacalcet, has altered the surgical referral patterns of both THPT and progressive SHPT.[8-10] Finally, the choice of the ideal operation for these complex patients is also evolving in the face of improving medical therapies and surgical adjuncts.[11-15]

## Normocalcemic hyperparathyroidism

Normocalcemic hyperparathyroidism (NCHPT) is considered a precursor of classic PHPT and is characterized by an elevated intact PTH concentration and persistently normal ionized and total serum calcium concentrations with normal vitamin D levels. Very few studies describe NCHPT, and the majority that do have failed to properly rule out secondary causes of PTH elevation, such as vitamin D deficiency.[16,17] The latest International Workshop on the Management of Asymptomatic PHPT officially recognized NCHPT as a variant of classic PHPT.[1] Although early recognition of this condition can be useful to prevent and treat bone loss, patients with NCHPT often do not meet the guideline criteria for surgical intervention. Ultimately, the recommendation from the International Workshop was to practice caution when recommending parathyroidectomy in cases of NCHPT because the disease course has not been clearly defined and the benefit of surgical intervention is yet to be established with long-term outcomes data.[1] Although there is a role for surgical intervention in carefully selected patients, the diagnosis can be challenging. As such, this is a population of patients that would benefit from the involvement of a multidisciplinary team.

## How to make the diagnosis, and what are the indications for imaging and surgery?

Classic PHPT often presents as a disorder of mild hypercalcemia. The biochemical profile and bone mineral density usually remain stable over time. However, because both hypercalcemia and low bone mineral density are generally present at the time of diagnosis, it has been postulated that NCHPT might have a biphasic disease course that progresses over an unpredictable time period to the classic hypercalcemic, hyperparathyroid state.[3,18] During the first, subclinical phase, when the PTH concentration is initially elevated, hypercalcemia is not yet present. The elevated PTH concentration in this phase is suggested to cause minimal reduction in cortical bone density and no progression of biochemical markers. This initial phase is thought to be followed by a second, clinical phase in which patients become hypercalcemic and establish the biochemical profile of classic PHPT. The natural history of PHPT in most patients is consistent with this theory, as progression of the disease after diagnosis of NCHPT is seen in approximately 22% to 41% of patients.[18,19]

As awareness of the importance of skeletal health has increased, clinicians have started measuring the serum PTH concentration in patients with low bone density. A subset of these patients with low bone density have subsequently been identified with NCHPT. Other patients with NCHPT have been diagnosed due to relative hypercalciuria, high serum PTH values, nephrolithiasis, or an incidental discovery of an enlarged parathyroid on ultrasound imaging of the neck.[20] However it is important to note that vitamin D deficiency is the most likely cause of an elevated PTH in a background of normal serum calcium.[18] The first priority in these patients is to correct any vitamin D deficiency before considering a diagnosis of NCHPT. Once vitamin D has been repleted, NCHPT can be considered when all other causes of elevated serum PTH concentration have been excluded, including the use of bisphosphonates, thiazide diuretics, lithium, or anticonvulsants; a glomerular filtration rate of >60 mL/min; and the absence of metabolic, malabsorption, and liver diseases.[3] The other potential pitfall in the diagnosis of NCHPT is a urinary calcium leak. It is important to note that patients with a normal serum calcium concentration, history of kidney stones, and marked hypercalciuria should not be considered to have NCHPT. They likely have a renal tubular dysfunction resulting in urinary calcium leak. The biochemical differences of the varying causes of elevated serum PTH concentration are shown in the Table 1. As with other cases of HPT, imaging studies should not be used to establish a diagnosis of NCHPT or the need for surgery. The diagnosis should always be established clinically and biochemically. Once the diagnosis is confirmed, localization studies before surgery can help guide the surgical approach.

Currently, there are no published guidelines for the management of NCHPT. Common clinical practice is to observe these patients initially and offer surgery if there