Review Article

Investigating patients with normocalcemic hyperparathyroidism: When is a parathyroid scintigraphy indicated?

ABSTRACT

In clinical practice, physicians often encounter patients with persistent elevated serum parathyroid hormone levels and normal serum calcium levels, a state known as normocalcemic hyperparathyroidism (NHPT). The investigation of NHPT cases can lead to unnecessary use of parathyroid scintigraphy (PS) and consequently unnecessary health-care costs. In this clinical review, the most common causes of NHPT and the possible indications for PS performance in such cases are mainly presented and discussed.

Keywords: Normocalcemic hyperparathyroidism, parathyroid hormone, parathyroid scintigraphy, primary hyperparathyroidism, secondary hyperparathyroidism, Vitamin D

INTRODUCTION

In clinical practice, physicians often encounter not only symptomatic and asymptomatic patients with classic primary hyperparathyroidism (PHPT) characterized by elevated serum parathyroid hormone (PTH) levels in the setting of elevated serum calcium levels, but also patients with persistent elevated serum PTH levels and normal serum calcium levels, a state known as normocalcemic hyperparathyroidism (NHPT). Moreover, in some patients with PHPT, the classical biochemical hallmark of hypercalcemia is not always present. Furthermore, the investigation of patients with NHPT may lead to the unnecessary use of parathyroid scintigraphy (PS) and consequently unnecessary health-care costs.

In this brief review, we shall present and discuss mainly the most common causes of NHPT and the possible indications for PS performance in such cases.

COMMON CAUSES OF NORMOCALCEMIC HYPERPARATHYROIDISM

A common cause of NHPT is Vitamin D deficiency with serum 25(OH)D levels <20 ng/mL, or Vitamin D insufficiency with serum 25(OH)D levels between 20 and 30 ng/mL. Vitamin D deficiency or insufficiency is the known cause of secondary hyperparathyroidism (SHPT).[1-6] However, based on epidemiologic studies, approximately 75% of all adults worldwide have serum 25(OH)D levels <30 ng/mL.[7] Although an inverse relationship between serum 25(OH)D and serum PTH levels is well established, the exact serum 25(OH)D levels that lead to a rise in serum PTH levels remain controversial.[1] The World Health Organization (WHO) and the U.S. Endocrine Society consider a serum 25(OH)D level <20 ng/mL as Vitamin D deficiency and a serum 25(OH)D level higher than 30 ng/mL as normal because, at this level, PTH drops down to normal levels.[1,8,9] At present, it is believed that if serum 25(OH)D level is <30 ng/mL, the level of PTH should start rising.[1,5] With the successful management of

Elias E. Mazokopakis, Spyridon-Nikitas I. Skarakis
Department of Internal Medicine, Naval Hospital of Crete, Chania, Greece

Address for correspondence: Dr. Elias E. Mazokopakis, K. Mitsotaki 36, Chania 73 100, Crete, Greece.
E-mail: emazokopakis@yahoo.gr

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Vitamin D deficiency or insufficiency with cholecalciferol supplementation, the elevated serum PTH levels return to normal in a time period that varies depending on the severity of the condition.[1,5] Measurement of serum 25(OH)D levels should thus precede in the investigation of patients with NHPT in order to exclude SHPT due to Vitamin D deficiency and not to consider that the patient needs absolutely a 25(OH) D level of >30 ng/mL.[1,5]

Other secondary causes of elevated serum PTH levels, apart from Vitamin D deficiency or insufficiency, should also be considered in the initial investigation of patients with NHPT.[5] Impaired renal function represents a known cause of NHPT and SHPT.[5] Less often, the cause of NHPT and SHPT is renal calcium loss (e.g., idiopathic hypercalciuria and loop diuretics) or loss due to celiac disease, pancreatic disease (fat malabsorption), inflammatory bowel disease, or malabsorptive bariatric surgery (i.e., Roux-en-Y bypass).[3,5,6] However, in some cases of SHPT, if the parathyroid glands do not respond well to low extracellular calcium concentration, the increase in serum PTH cannot correct the plasma calcium, either due to a disorder in the organs responsible for transportation or deficiencies, and thus hypocalcemia develops. Therefore, the causes of SHPT may be associated with calcium concentrations that are within or below the reference range. The diagnostic value of PS in these situations of SHPT is very limited.[10] We underscore the necessity of serum creatinine measurement and estimated glomerular filtration rate calculation in the evaluation of elevated serum PTH levels independently from serum calcium levels.[2,5,10] In addition, when investigating a patient with NHPT, the intake of antiresorptive drugs (bisphosphonate, denosumab), hypomagnesemia (inducing resistance to PTH), and the coexistence of Vitamin D deficiency with intake of drugs which cause hypercalcemia, such as thiazide diuretics or lithium, deserve special consideration.[5]

If no cause of SHPT is evidenced, the diagnosis of normocalcemic primary hyperparathyroidism (NPHPT) should be considered as another known cause of NHPT. This form of hyperparathyroidism was first described in the 1960s by Wills *et al*.[11] and its prevalence may be between 0.4% and 3.1%.[2] It is characterized by elevated serum PTH levels with concomitant persistent normal levels of total and ionized serum calcium [Table 1].[3,4,12] Its defining difference from PHPT is that serum calcium levels (total albumin-corrected and ionized) remain normal whenever they are measured, provided that causes of SHPT have been ruled out or corrected.[12] Yet, NPHPT follows a biphasic course without a specific start and end of each phase. During the first phase, the patient seems to exhibit high levels of intact PTH (iPTH), whereas the calcium levels of the patient have not yet been affected. This phase may last for an unknown time period and the only symptom that leads the patient to the doctor might be skeletal pain resulting from the reduction of cortical bone density due to elevated levels of PTH. It is the second phase in which the calcium levels start to rise above the normal range and as a consequence classic symptoms of primary disease emerge.[13] Taking the aforementioned into consideration, NPHPT is presumed to represent the first phase of classic PHPT. Furthermore, due to increasing scientific interest of this entity, the condition was recognized as a distinct disease at the Third International Workshop of Asymptomatic Primary Hyperparathyroidism.[14,15] However, it must be pointed out that there are insufficient data on the natural history of this disease that could direct the diagnostic pathway and predict which patients are at risk of evolution to a more active form of the disease.[14] A calcium load test is a very useful tool for NPHPT diagnosis if it shows that serum PTH is not sufficiently decreased when calcemia rises above the upper normal limit.[5] In a normocalcemic patient with hypercalciuria and a high serum PTH concentration, a thiazide challenge test may help to differentiate SHPT due to a renal calcium leak from NPHPT.[5] If a PS is conducted in patients with NPHPT, the images will probably show a mild hyperplasia of the parathyroid glands due to the stimulating effect of the increased levels of PTH. However, the sensitivity of PS as a preoperative noninvasive localization technique in NPHPT patients who are candidates for surgery is low.[12] The combination of PS with neck ultrasound may increase the overall sensitivity of preoperative localization.[12]

Another cause of NHPT is the coexistence of PHPT with Vitamin D deficiency. Owing to Vitamin D deficiency, serum calcium levels cannot exceed the upper normal levels considering the key role of Vitamin D and its metabolites

Table 1: Differential diagnosis of normocalcemic hyperparathyroidism based on characteristic laboratory data

	iPTH	Blood Ca	Urine calcium (mg/24 h)	25(OH)D
PHPT	High	High	High (≥200 mg)	Normal
PHPT with Vitamin D deficiency	High	Normal	Normal-low or low (<100 mg)	Low (<20 ng/mL)
NPHPT	High	Normal or High	Normal	Normal
Hyperparathyroidism due to Vitamin D deficiency (SHPT)	High	Normal or Low	Low (<100 mg)	Low (<20 ng/mL)

Ca: Calcium; iPTH: Intact parathyroid hormone; NHPT: Normocalcemic hyperparathyroidism; NPHPT: Normocalcemic primary hyperparathyroidism; PHPT: Primary hyperparathyroidism; SHPT: Secondary hyperparathyroidism; 25(OH)D: 25-hydroxyvitamin D

in the gut absorption of calcium. As a result, the patient is normocalcemic, but this masked form of PHPT is revealed after Vitamin D restoration with cholecalciferol supplementation.[3] Urinary calcium levels are expected to be low (<100 mg/24 h) or low normal (<200 mg/24 h) if measured [Table 1].[3,4] The diagnosis and management of this cause of NHPT includes the measurement of serum 25(OH)D levels and cholecalciferol supplementation with goal serum 25(OH)D levels >30 ng/mL.[1,5] If PHPT is the cause, the patient, after achieving the goal serum Vitamin D levels, will develop hypercalcemia along with persistent high serum PTH levels. PS is indicated within the framework of PHPT management.[10,16,17]

LABORATORY CONSIDERATIONS

As far as the aforesaid laboratory parameters are concerned, the fragility of their interpretation should be noted. On the one hand, in the case of albumin concentration changes, discrepancies between ionized and total calcemia may occur. Furthermore, it is obligatory to use the following formula for the correction of total calcemia: corrected serum calcium = serum calcium + 0.8 × (4 − serum albumin).[18] On the other hand, it must be clarified that the reference range of PTH concentration depends on the PTH assay that is used,[5,19] and the method of serum 25(OH)D level measurement strongly influences Vitamin D levels.[20] Since the first radioimmunoassay, described in 1963 by Berson *et al*.,[21] several assays based on immunological identification have been published (first-generation assays). The routine assays used nowadays are immunoradiometric "sandwich-type" antibodies (IRMA), based on two different specific monoclonal antibodies: one amino terminal and the other carboxyl terminal specific,[19] and are widely used in most of the automation platforms. The specificity of the amino terminal antibody defines if the IRMA assay measures only the bioactive PTH circulating form (including the first amino terminal amino acids) or the iPTH, which includes, besides bioactive PTH, other "long" carboxyl-terminal forms, for example, 7-84-PTH.[19] These IRMA assays for the measurement of iPTH are widely available in clinical laboratories and have good sensitivity and reproducibility with well-defined normal reference.[19] The next (third) generation of assays will be based on different principles, mainly mass spectrometry in samples submitted to prior purification and fragmentation steps.[19] Another major issue concerning PTH assays is whether the reference range of a given PTH assay has been made in a population in which Vitamin D deficiency exclusion criteria had been considered.[12]

As 24 h urinary calcium levels depend on the calcium intake, it is advisable to evaluate this intake the day of the 24 h collection, which is difficult in routine practice though, and rarely done. It is also significant to measure urine sodium and urea since loop diuretics, a high sodium (salt) or protein diet, and excess tea or coffee consumption may cause hypercalciuria.[5,22,23] All these make the precise interpretation of calciuria not so easy. In all respects, calciuria that exceeds the level of 200 mg/24 h refers to PHPT and a PS is indicated for its management.[3,4] If levels of calciuria are lower than the threshold of 200 mg/24 h or even normal, other causes should be suspected.[3,4]

A common mistake made by several physicians in the evaluation of serum Vitamin D levels is the measurement of serum $1,25(OH)_2D$ levels instead of serum 25(OH)D levels. This seems significant as there is an inverse relationship between PTH and 25(OH)D, in that the lowering of serum Vitamin D levels <30 ng/mL triggers parathyroid glands to increase PTH secretion and vice versa.[12] It is essential to note though that some time may have to pass before PTH levels become normal after Vitamin D restoration.[5]

Two formulas have been created as supplementary diagnostic tools for the investigation of high PTH levels in clinical practice [Table 2].[24,25] On the one hand, MaxPTH is a multidimensional, mathematical nomogram developed in 2012 aimed at facilitating the diagnostic accuracy or recognition of less typical forms of PHPT such as NPHT [Table 2].[24,26] However, the maxPTH model could not be applied to a patient with SHPT. To overcome this limitation, the Mi-PTH formula was formed, which included all the variables of the original maxPTH equation with the inclusion of the patient's measured PTH level [Table 2].[25]

We must bear in mind that PS is specifically designed to localize hyperfunctioning parathyroid tissue (commonly adenomas

Table 2: Formulas appropriate for the management of elevated serum parathyroid hormone levels

Models	Interpretation
MaxPTH=120 - (6×calcium [mg/dL]) - (0.52 × 25(OH)D [ng/mL]) + (0.26×patient age [years])	If maxPTH ≤serum PTH: Suspect PHPT If maxPTH >serum PTH: Suspect normal/SHPT
Mi-PTH= $-32.6+0.0197 \times \text{age} + 0.00424 \times 25(OH)D + 2.85 \times Ca + 0.433 \times \sqrt{PTH}$	If Mi-PTH >0: High probability of PHPT If Mi-PTH <0: More likely to be normal or SHPT, depending on Vitamin D status If Mi-PTH=0: 50% chance of PHPT

Ca: Calcium; PTH: Parathyroid hormone; PHPT: Primary hyperparathyroidism; SHPT: Secondary hyperparathyroidism; 25(OH)D: 25-hydroxyvitamin D; Mi-PTH: Multidimensional predictive hyperparathyroid model; maxPTH: Upper limit of normal PTH

or hyperplasia) in patients with diagnosed PHPT, and the current method of choice is the dual-phase method using technetium-99 m-methoxyisobutylisonitrile (^{99m}Tc-MIBI).[10,16,17] This method is based on the differential washout rate of MIBI from the thyroid and abnormal parathyroid glands.[10,16,17] The reported sensitivity of this method ranges from 80% to 90% and is limited in cases with atypical washout, for instance, rapid parathyroid washout associated with parathyroid hyperplasia and P-glycoprotein expression, or delayed thyroid washout associated with thyroid diseases, such as thyroid adenoma, thyroid carcinoma, multinodular goiter, and Hashimoto thyroiditis.[10,17] Parathyroid scan is indicated among patients with biochemically proven PHPT, not as a diagnostic tool, but preoperatively as it reduces the duration or extent of surgical exploration.[1,10,16,17] Moreover, the combination of intraoperative PTH assays with minimally invasive radioguided parathyroidectomy improves success rates (less morbidity, shorter hospital stay time, and better cosmetic results) for a complete cure in patients with PHPT.[10,16,17] Parathyroid scan performance might be indicated in some cases with persistent isolated increases of PTH, when all the common etiologies of NHPT have been investigated and ruled out or corrected.

CONCLUSIONS

Vitamin D deficiency or insufficiency, NPHPT, and the coexistence of PHPT and Vitamin D deficiency are the main entities which must be investigated among patients with NHPT. Among the causes of NHPT, indications for PS performance bear the form of PHPT which is masked by Vitamin D deficiency after the successful restoration of Vitamin D serum levels and some NPHPT cases which are scheduled to undergo surgery.

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Conflicts of interest

There are no conflicts of interest.

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