

## REVIEW ARTICLE

# Normocalcemic hyper-parathyroidism "Diagnostic and therapeutic dilemma do's and dont's"

Aromal chekavar<sup>1</sup>, Suneel Mattoo<sup>1</sup>, Amit Agarwal<sup>1</sup>, Sabaretnam Mayilvaganan<sup>1</sup>,  
Pooja Ramakant<sup>2</sup>

## INTRODUCTION:

Primary hyperparathyroidism shifted from symptomatic severe bone disease to asymptomatic clinical presentation over last decade, but hypercalcemia was an essential part of biochemical diagnosis in both scenarios. Normocalcemic primary hyperparathyroidism (NPHPT) was first recognized at the time of the Third International Workshop on the Management of Asymptomatic PHPT in 2008.<sup>1</sup>

Even though it was poorly understood initially its importance increased due to high detection in the era of annual medical examinations. Due to various clinical scenarios like the incidental discovery of reduced bone mass, is typically reduced when it is measured by dual-energy X-ray absorptiometry (DXA), incidentally detected neck mass in routine neck ultrasonography, recurrent pancreatitis, renal stones and nephrocalcinosis lead to a diagnosis of hyperparathyroidism with normal ionized serum calcium. In bone mineral density findings involvement of cortical skeleton compared to cancellous skeleton favors suspicion of hyperparathyroidism. It is characterized by normal total and ionized serum calcium concentrations and consistently elevated PTH levels. It is mandatory to rule out other causes for secondary elevations of PTH, such as renal disease, malabsorption or vitamin D deficiency.

### Author information

1. Endocrine Surgery Department, SGPGIMS Lucknow, India
2. Endocrine Surgery Department, KGMU, Lucknow India

## Pathophysiology :

Even though there are assumptions regarding pathophysiology, exact mechanism still remains unknown in cases of NCPHPT. But early detection may be the cause of this entity and it's multifactorial causation.<sup>2</sup>

**Table 1: Differences between hypercalcemic HPT and NCHPT**

	NCPHPT	Hypercalcemic PHPT
<b>Target organ resistance to PTH</b>	+	-
<b>Bone turnover</b>	Less(+)	High(+++)
<b>Net skeletal calcium release</b>	+	+++
<b>Renal tubular reabsorption of calcium</b>	+	+++

## Diagnosis

The expert panel from the Fourth International Workshop on the Management of Asymptomatic PHPT recommended that the PTH level remains above the normal range on at least two subsequent measurements during a 3–6 month period to confirm hyperparathyroidism.<sup>3</sup>

1. Serum ionized calcium and albumin-corrected total calcium is always normal over the entire course of monitoring.

2. Additionally, secondary causes of an elevated PTH level must be ruled out. To diagnose NCPHPT the following conditions should be excluded, which includes
  1. Vitamin D deficiency.
  2. Renal failure
  3. Medications.
    - a. Hydrochlorothiazide
    - b. Lithium
  4. Hypercalciuria.
  5. Gastrointestinal calcium malabsorption disorders

### Clinical presentation & Epidemiology

Most of the cases of NCHPT were diagnosed while getting evaluated for a metabolic bone disease and most of the patients were postmenopausal women. However, unlike hypercalcemic HPT, normocalcemic hyperparathyroidism did not show cortical bone affinity in bone loss. Among NCHPT cases osteoporosis will be there in 9 to 50% and nephrolithiasis in 10-25%.<sup>(2,4-5)</sup>

According to the two-way hypothesis evolution of NCHPT is from normocalcemic to symptomatic hypercalcemia.<sup>(6)</sup>

In other words, the normocalcemic phase is an early presentation of the same disease. Prevalence of NCHPT ranges from 0.4 to 0.5% (Lundgren et al and Cusano et al study) and both these studies have the high number of subjects compared to studies shown prevalence as high as 6 to 8.9 %. So this discrepancy may be because of the difference in the number of study subjects and difference in diagnostic criteria.<sup>(5,7-9)</sup>

Since hypertension is one of the most important cardiovascular risk factors, and many studies suggest that the subjects with NPHPT had a higher risk of high BP than subjects with normal PTH, it seems reasonable to suppose that therapeutic intervention aimed to normalize PTH may have benefits in the short and long-term in NPHPT.

### Natural history

Even though limited data available regarding the natural history of the disease one study demonstrated progression only in 40 percent of cases in form of signs of primary hyperparathyroidism and 20 percent only

developed hypercalcemia.<sup>4</sup> In another study, 30 percent of patients with positive localization studies underwent successful parathyroidectomy, two third patients remained in conservative management.<sup>10</sup> In Garcia-Martin et al.<sup>5</sup> study, even though there was persistently high PTH after 1 year none developed hypercalcemia or symptoms. This discrepancy in natural history may be due to the differences in follow up period in these studies.

### Management

Management of NCHPT based mainly on confirmation of diagnosis and exclusion of secondary causes. Stepwise approach with caution is required in diagnosis and management. Clear cut evidence based on imaging guidelines are not available in NCHPT. Imaging plan should be similar to hypercalcemic primary hyperparathyroidism i.e. initial dual imaging using high-resolution ultrasonography and Tc99 SestaMIBI scan. If you are having suspicion on discordant imaging consider second-line investigations like 4 dimensional CT scan and methionine PET in cases with high level of suspicion, otherwise active surveillance and reimagine will be optimal.

- Step 1: Confirmation of diagnosis and exclusion of secondary causes
- Step 2: Imaging to identify the lesion
- Step 3: Most important to exclude cases without imaging evidence
- Step 4: Surgery or surveillance

In NCHPT management main components are

1. Surveillance
2. Medical management
3. Surgical management

### Surveillance

Annual serum calcium, PTH and bone mineral density determinations seem reasonable. If the disease evolves into the hypercalcemic form, then the published guidelines from the Third International Workshop would be reasonable to follow.<sup>3</sup>

### Medical management

Use of medical therapy in normocalcemic PHPT is controversial. Even though bisphosphonate has been shown to improve bone

density in few studies and one recent study has demonstrated benefit.<sup>(11,12)</sup> In one study use of cinacalcet along with dietary modifications reduced kidney stones in terms of number and diameter along with the reduction of PTH levels.  
13

### Surgical management

Indication for surgery arises once patients become hypercalcemic or symptomatic. So indications of surgery are

- Once the patient becomes hypercalcemic
- Among normocalcemic patients in case of progression of the disease in the form of
- Worsening bone density
- Fracture
- Kidney stone
- ? Recurrent pancreatitis

### POINTS TO REMEMBER

#### Caution in diagnosis

Evaluation to rule out secondary causes

Patient surveillance in image negative cases and cases who lack an indication for surgery

Surgery in image localized cases

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