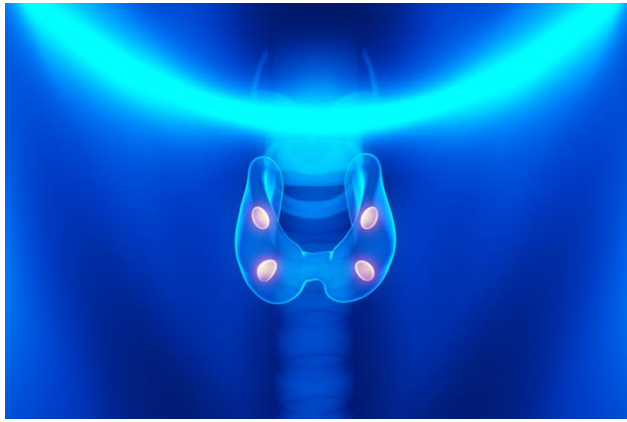

IN THE NAME OF GOD



Normocalcemic Hyperparathyroidism

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Normocalcemic Hyperparathyroidism(NHPT)

- Normocalcemic primary hyperparathyroidism (NHPT) was first described over 10 years ago, but uncertainties still remain about its
- definition,
- prevalence, and
- rates of complications

Hypotheses

Clinical concern

- A common clinical concern is whether NHPT should be treated surgically when complications are already present at first recognition of the disorder, rather than following patients clinically over time.

Normocalcemic Hyperparathyroidism(NHPT)

- The literature on NHPT is based mostly on larger studies of **population-based cohorts** and **smaller studies** from referral centers. **Lack** of rigorous **diagnostic criteria** and **selection bias** inherent in populations seen **at tertiary referral centers** may explain the heterogeneity of reported rates of bone and renal complications in relation to consistently mild laboratory alterations.

Unresolved questions

- Unresolved questions remain about the significance of NHPT when it is diagnosed biochemically **without evident** *bone* or *kidney* complications.

NHPT may revert to normal?

- Moreover, its natural history remains to be elucidated because a proportion of what is classified as NHPT may **revert to normal** spontaneously revealing previously **unrecognized secondary hyperparathyroidism.**
- These issues indicate that caution should be used in recommending surgery for NHPT.

Heterogeneous results about NHPT complications

- may be explained by **two factors**:
- 1The widespread failure of many studies to include subjects that rigorously fulfilled the full **diagnostic criteria** for NHPT, and
- 2-The persistent uncertainty regarding the **pathophysiology underlying** NHPT.

Definition and Diagnosis of NHPT

- Normocalcemic hyperparathyroidism was first acknowledged to
- be part of the diagnostic spectrum of PHPT during the **Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism in 2008**, and further defined and characterized at the Fourth International Workshop that followed
- in in 2014.

Definition and Diagnosis of NHPT

- NHPT is characterized by **persistently** increased serum **PTH** levels in the setting of **normal albumin adjusted** and **ionized serum Ca**, after *secondary causes* of PTH elevation have been **excluded**. The consensus statement from the Fourth International Workshop indicated that these laboratory findings should be confirmed on at least two occasions over a time frame of at least 3 to 6 months.

- Based on this definition, NHPT is necessarily a diagnosis of **exclusion**.

Secondary hyperparathyroidism

- Because **multiple causes** of increased **PTH secretion**
- have been identified, and because the disorder does not generally
- *warrant immediate* ***surgical action***, it is advisable to thoroughly
- rule out all possible factors contributing to secondary
- hyperparathyroidism.

Secondary hyperparathyroidism

- vitamin D deficiency (<20 to 30 ng/mL)
- Insufficient Ca intake or Ca malabsorption
- chronic kidney disease (eGFR <60 mL/min)
- medications including loop diuretics, thiazide diuretics, lithium, bisphosphonates, or denosumab
- idiopathic hypercalciuria with or without nephrolithiasis

Vitamin D deficiency in PHPT

- may lower serum Ca or increase PTH levels in PHPT
- By increasing vitamin D levels into an optimal range, Ca levels may increase because **of improved** *intestinal Ca absorption*, thereby changing the presumed diagnosis of NHPT to PHPT.

What is the minimum threshold of vitamin D necessary for skeletal health?

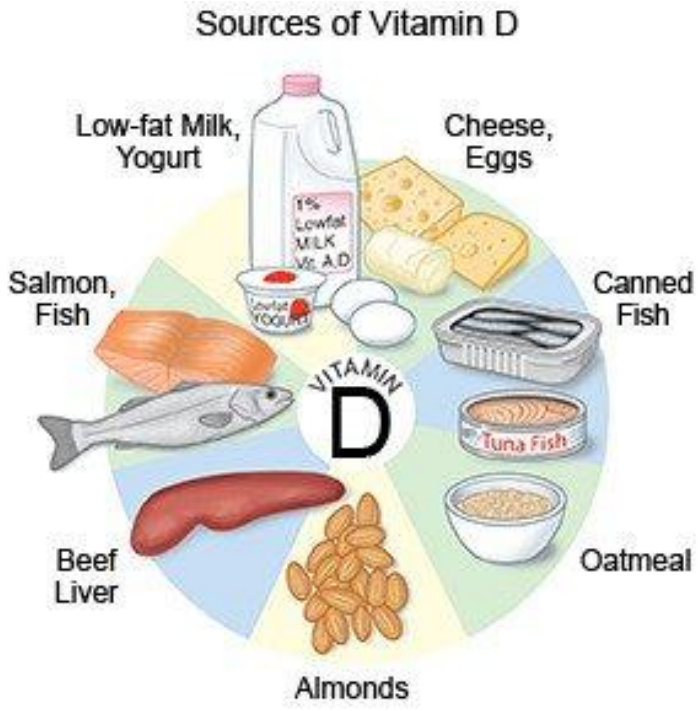
- Some guidelines favor ≥ 20 ng/ mL, whereas others recommend ≥30 ng/mL.
- However, these threshold levels may not be sufficient to normalize PTH in all patients.

Serum 25-hydroxyvitamin D

- To be confident of a diagnosis of NHPT, it is necessary that serum [25(OH)D] be within the optimal range defined by the **laboratory**, with a **minimum level of 30 ng/ mL**. Some patients might require higher levels within the optimal range to normalize their PTH secretion, suggesting that a **range of optimal vitamin D values** rather than a single threshold might be appropriate for an accurate diagnosis of NHPT.
- **Accurate vitamin D assays**

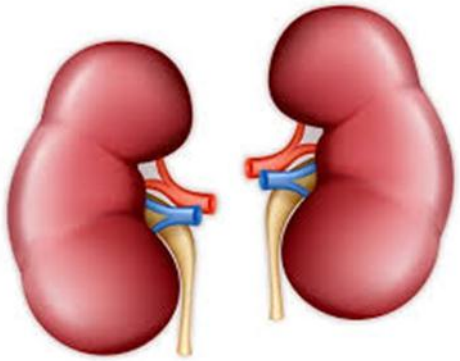
Adequate dietary Ca intake

- Moreover, proper counseling of patients regarding adequate dietary Ca intake may result in improved Ca intake and absorption, with retrospective recognition of a previous secondary form of hyperparathyroidism rather than PHPT.



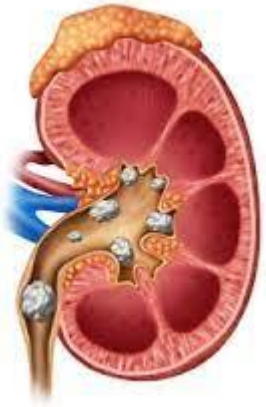
Hypercalciuria→chronic secondary HPT

- which ultimately leads to **parathyroid autonomy** with resultant **multigland parathyroid hyperplasia**.
- Therefore, before confirming a diagnosis of NHPT when urinary Ca is significantly increased (>350 mg/day in females, or > 400 mg/day in males, or >4 mg/kg/day), a **short-term trial** of a **low-dose thiazide** should be considered to block or reduce urinary Ca loss, which may restore normal biochemical values, as well as limit the risk of development or progression of **renal stones**.



Hypercalciuria

- In this circumstance, **parathyroidectomy** may **not** significantly reduce urinary Ca levels or renal stone risk, as the primary driver of **parathyroid overactivity continues** to be renal loss of Ca in urine.



Albumin-adjusted Ca/P ratio > 3.5

- without requiring **measurement** of **PTH**
- A ratio cut-point above 3.5, when Ca and P were measured in **mg/dL,** had a sensitivity of 89% and specificity of 91% for detecting patients in the cohort with either PHPT or NHPT.
- When the ratio was tested in 35 patients with NHPT, the sensitivity **dropped to 67%,** while retaining the same specificity as that of the entire cohort.
- during high-volume screening
- low cost because of its lack of need for measuring PTH
- less useful in NHPT (single Ca and phosphate (PO4) measurements)

Albumin-adjusted Ca/P ratio > 3.28

- 142 patients
- multicenter cross-sectional study
- sensitivity (80.8%)
- However, the positive predictive value was much lower at 47.4% compared to 73% in the previous study, suggesting a limited ability of this tool to identify PHPT when **albumin-adjusted Ca** is **within the normal range**.

Ca/P ratio

Study	N of Patients	(Ca/P) ratio	sensitivity	specificity	Conclusion
single-center, case–controlled retrospective	97 (PHP& NHP)	>3.5	89%	91%	*high-volume Screening/low cost PPV=73.3%,NPV=88%
"	35 (NHP)	>3.5	67%	91%	*less useful PPV=73.3%,NPV=95%
multicenter cross-sectional study	142 (PHP & NHP)	3.28	87.7%	87.5%	high accuracy. PPV=82.4%,NPV= 91.1% was suggesting a limited ability of this tool to identify PHPT when albumin-adjusted Ca is within the normal range.

PPV= positive predictive value , NPV=negative predictive values, *exclude rather than confirm NHPT

PFindex

- discriminate PHPT from vitamin D-deficient secondary HP
- Pfindex = Ca × PTH/P
- Ca and P reported in mmol/L, and PTH in pg/mL.
- Guo and colleagues
- **PFindex of > 34** was able to discriminate
- **NHPT** from vitamin D-deficient **secondary** hyperparathyroidism
- with a *sensitivity* of 96.9% and a *specificity* of 97.6%.

Limitation of these studies for discriminate between NHPT, PHPT

- **Retrospective design**
- **Lack** of measurement of **serum ionized Ca**.
- This may have led to **overestimation** of NPHT cases in these studies.

Single measurements of serum Ca and PTH,

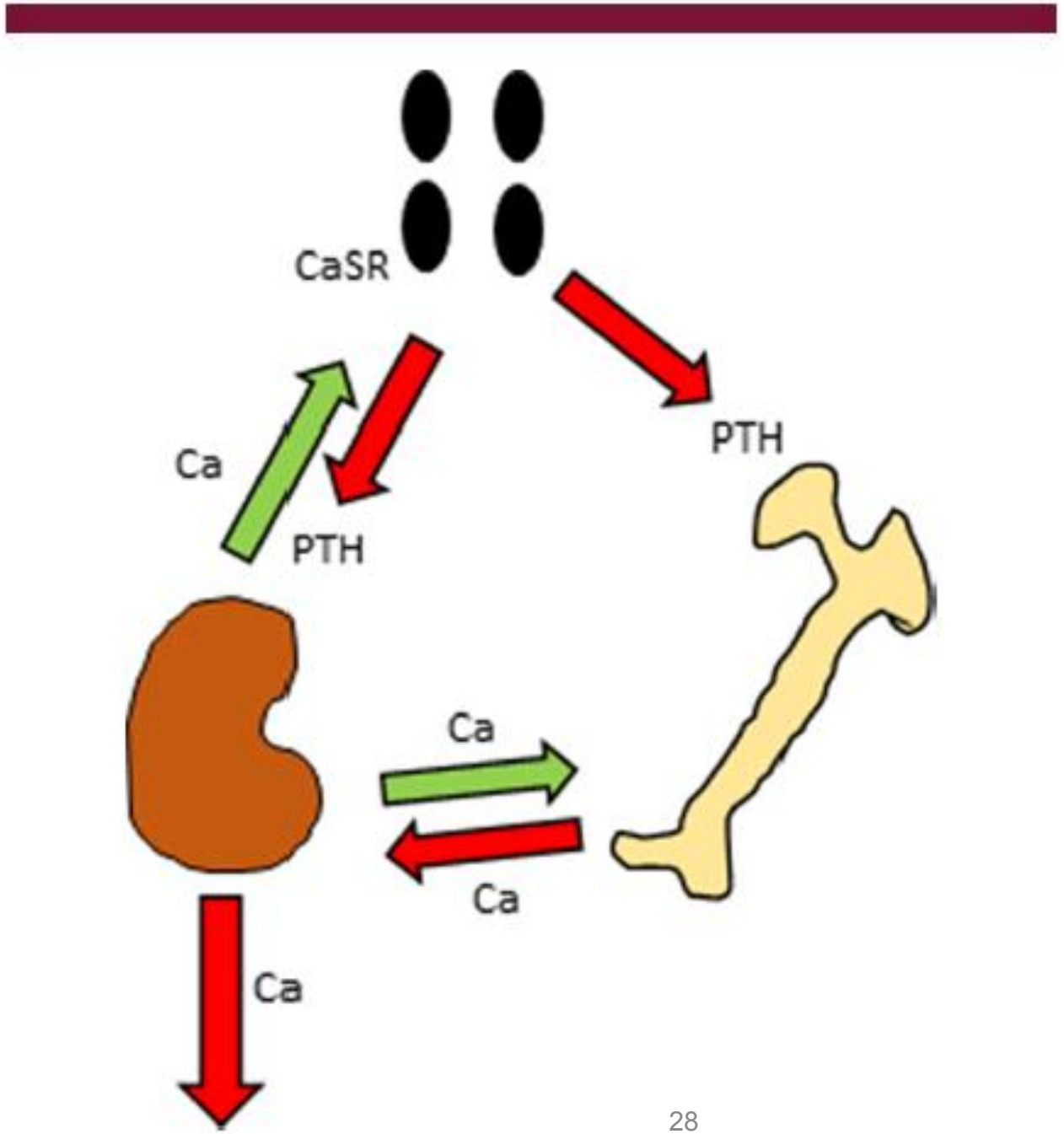
- The current definition of NHPT requires **persistently** normal serum total and ionized Ca over **3 to 6 months**.
- Because **PHPT** is often characterized by **fluctuating** serum Ca levels in the upper-normal and above-normal ranges, a single Ca measurement in the **upper-normal range** with **high PTH** should be interpreted as suspicious for **PHPT** rather than NHPT.

Pathogenetic Hypotheses

Pathogenetic Hypotheses

- The mechanism(s) underlying development of NHPT are currently not yet known.

As shown,
Ca reabsorption is maintained by the renal tubules to prevent
oversecretion of PTH, and thereby preserve bone density and
reduce the risk of hypercalciuria and kidney stones.



NHPT represents anearly or milder form of classical PHPT

- **The most widely accepted**
- gradually develop the classical form over time, with an eventual increase in serum and urine Ca levels

The most hypotheses about NPHP

- Given that the normal population has mean serum Ca concentrations ranging over an approximately **2 mg/dL interval**, it is possible that **increased** serum **PTH levels** increase serum Ca to a mild extent within the normal range that is not clinically detectable within the general population, but significant enough to explain the pathophysiology of patients with NHPT.
- This hypothesis presumes that those with serum Ca in the upper-normal range might be more likely to convert to the hypercalcemic phenotype over time.

A second view

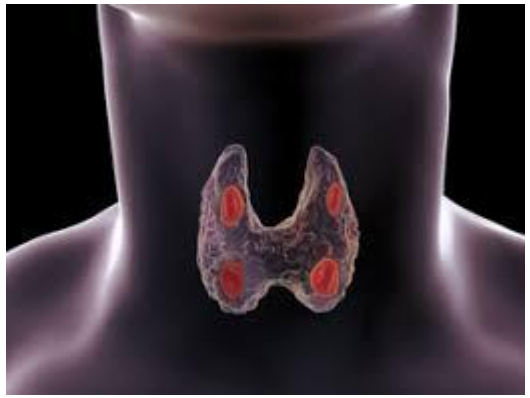
- A second view is that **advancing age** and **menopausal** status play a role in the increase in serum PTH levels.
- In 1994, Ledger and colleagues reported the phenomenon known as secondary hyperparathyroidism of **aging**.
- Secretory dynamics of PTH were evaluated in small groups of elderly postmenopausal (mean age 73 years) and younger premenopausal women (mean age 30).

Secondary hyperparathyroidism of aging

- Besides having greater **mean baseline PTH** values, **elderly women** showed a **greater sensitivity** of response of **PTH** levels to intravenous EDTA-induced hypocalcemia.
- These abnormalities in the elderly women were completely reversed by a **1-week** treatment course with 1,25(OH)2D (**calcitriol**), which completely restored normal PTH dynamics by improving Ca absorption and transcriptionally suppressing PTH secretion.

Secondary hyperparathyroidism of aging

- These PTH dynamics suggest that the more vigorous response
- of older postmenopausal women might be attributable to
- decreased suppression of baseline PTH secretion, which could
- also possibly be caused by **mild parathyroid gland hyperplasia**.



Secondary hyperparathyroidism of aging

- Aging could lead to **decreased 1,25(OH)2D action** on **intestinal Ca absorption** or **reduced 1,25(OH)2D levels** because of compromised **renal function**, resulting in a **chronic stimulus** to the parathyroid glands.
- This study was more consistent with **intestinal resistance to vitamin D** action, which was promptly overridden by a short course of calcitriol.

Estrogen

- Cosman and colleagues analyzed a cohort of postmenopausal women with osteoporosis to evaluate the regulation of PTH secretion by estrogen.
- Subjects receiving hormone therapy were found to have lower baseline PTH levels compared with those that were untreated. Moreover, the women receiving hormone therapy showed a blunted PTH response to the induction of EDTA-mediated hypocalcemia. These findings suggested that **parathyroid glands** might be **less sensitive** to **hypocalcemia** under the influence of **estrogen.**

Estrogens

- Another study by Khosla and colleagues addressed whether the effect on PTH secretion was direct or indirect. **EDTA-stimulated PTH** secretion was evaluated in 10 postmenopausal women before and after 3 days of estrogen therapy. The study showed that estrogens did not have significant effect on either basal or stimulated PTH secretion. The authors concluded that PTH levels were indirectly affected by **estrogens**, possibly by **increasing intestinal** and **renal Ca absorption**.

Estrogens

- PHPT and NHPT may be diagnosed **more commonly** in **postmenopausal** women based on the unmasking of **mild hyperparathyroidism** caused by loss of the protective effect of estrogen on bone, leading to a **negative Ca balance**.

Stimulation of PTH with PO4 or suppression with Ca

- Invernizzi and colleagues showed that patients with NHPT
- maintained their PTH physiologic feedback in response to stimulation
- with PO4 or suppression with Ca. This study treated three
- patient cohorts with an oral peptone load rich in PO4 or an oral
- Ca load, respectively, in an effort to stimulate or suppress PTH secretion.

	patients	oral Ca loading (↓Mean PTH)
first cohort (PHPT)	22	Failed
second cohort (NHPT)	20	↓sign
third cohort (healthy controls)	30	↓sign

In addition, the mean PTH response to PO4 loading was more pronounced in the PHPT cohort than in the NHPT or healthy control cohorts. Because PTH was only sampled during the oral Ca load (for 120 min), it is possible that the response to Ca in PHPT may take longer than what usually occurs in NHPT and healthy people. The rapid response to Ca in the NHPT cohort is consistent with physiology, pointing toward a form of **secondary rather than PHPT**.

Another hypothesis
over-production of PTH

- Another hypothesis is that **over-production of PTH** by patients with NHPT may be **lower** compared with that in patients with PHPT.
- one cohort studied by Maruani and colleagues. This study suggested that **relatively lower secretion of PTH** in NHPT might result in serum Ca concentrations remaining within the normal range.

Resistance to PTH

- The study also proposed combined **renal** and **bone resistance** to **PTH** as a mechanism to explain NHPT, because, after matching the cohorts of PHPT and NHPT for PTH level, the normocalcemic cohort
- showed **lower markers of bone turnover** and **lower serum 1,25**
- **(OH)2D levels**, as well as lower **capacity** to increase **urinary Ca reabsorption** and **blunted** ability **to increase urinary PO4 excretion**

Serum free 25(OH)D levels

- **lower serum-free 25(OH)D levels**
- measured by an immunometric assay
- These patients and controls all had normal serum total 25(OH)D levels in the range of 30 to 40 ng/mL. PTH levels correlated with free, but not total 25(OH)D levels ($r = -0.415$; $p < 0.05$). The study concluded that some NHPT patients might have a form of **secondary hyperparathyroidism** caused by lower serum free 25(OH)D levels. This finding could be explained by higher concentrations of **vitamin D-binding protein** that might mask vitamin D deficiency.

calcium-sensing receptor (CaSR)

- The study demonstrated that the **A986S polymorphism** in the CaSR was an independent predictor of PTH level in NHPT, but not in asymptomatic PHPT.
- This polymorphism affects the intracellular domain of the CaSR, and appears to cause **reduced CaSR function**, thereby inducing **lower sensitivity** to extracellular serum Ca and stimulating increased PTH secretion in response. This resistance-inducing polymorphism was not observed in the control group with asymptomatic PHPT, suggesting that these disorders might have different pathogenetic mechanisms.

- Patients with hyperparathyroidism may present with different
- phenotypes.

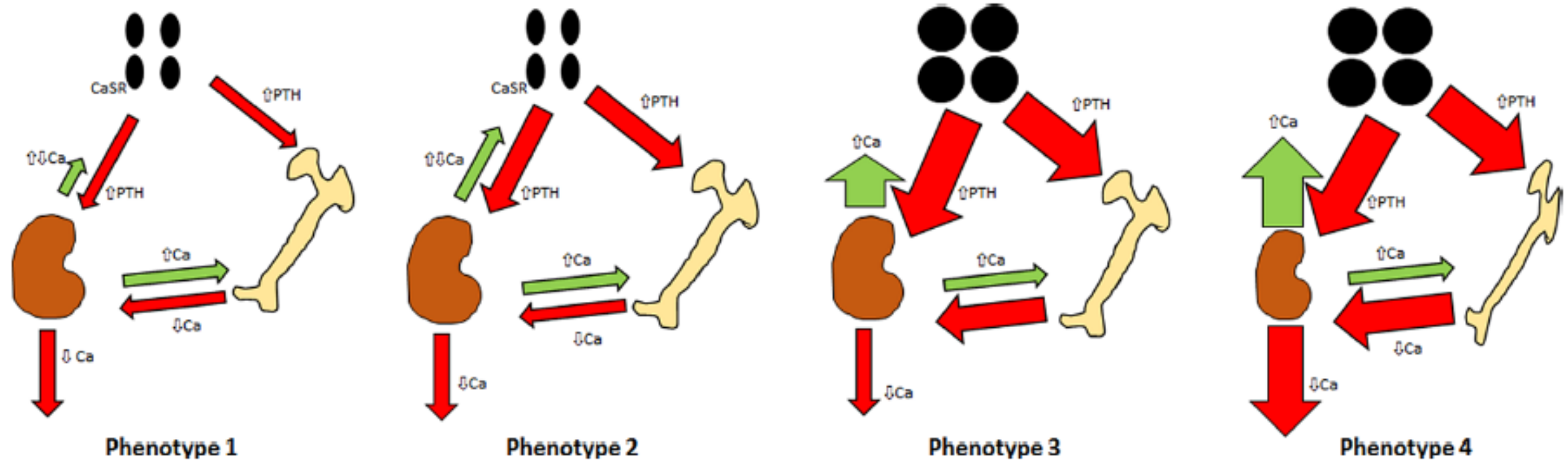


Fig 2. Patients with hyperparathyroidism appear to present with different phenotypes. It has not yet been observed that the recognized phenotypes progress to more severe phenotypes, or regress to less severe forms over time, with the possible exception of classical mild primary hyperparathyroidism regressing to normal when observed over years without surgery. Phenotype 1. Mild changes within the physiologic range: Subclinical increased renal calcium (Ca) losses stimulate the parathyroid glands to secrete increased PTH within the physiologic range. Phenotype 2. Normocalcemic hyperparathyroidism: PTH oversecretion stabilizes at a new set-point, in which renal Ca filtration and reabsorption are increased to allow preservation of bone density, but not enough to cause Ca-sensing receptor function to inhibit the parathyroid glands. Phenotype 3. Asymptomatic primary hyperparathyroidism: PTH oversecretion is associated with parathyroid gland enlargement and eventual parathyroid autonomy, with no evidence of bone or renal complications. Phenotype 4. Primary hyperparathyroidism: Clinical features of classical primary hyperparathyroidism with possible kidney malfunction and bone loss starting with the cortical sites.

phenotypes1 and 2

- Given a sufficient and constant amount of **dietary Ca,** phenotypes1 and 2 would explain why PTH remains increased, after having excluded all known secondary causes.
- Changes of normal **aging** might explain biochemical changes seen in some patients.
- It is not evident that NHPT **evolves** into PHPT or **reverts** to
- normal.

Table 1. Putative Mechanisms Underlying Normal Calcium and High PTH When Common Secondary Causes Have Been Ruled Out. Clinical and Biochemical Values of Each Study are Reported

Source	Hypothesis	Age (yrs)	F/M ratio	PTH (pg/ml)	sCa (mg/dL)	sP (mg/dL)	25(OH)D (ng/mL)	1,25 $(OH)_2D$ (pg/mL)	Ionized calcium (mmol/L)	eGFR (ml/min)	Explanation	Implications
Lowe et al.[22] (n = 7)[a]	Early form of PHPT	64 ± 2	95% F	96 ± 15	9.7 ± 0.2	3.4 ± 0.2	29 ± 3	62 ± 11	No	>40	PTH is secreted autonomously. It might progress to frank hypercalcemia.	Feedback on PTH is assumed not to be present.
Ledger et al.[17] (n = 10)[b]	Aging	73.7 ± 0.6	100% F	3.8 ± 0.5 pmol/L	2.32 ± 0.02 mmol/L	1.22 ± 0.04 mmol/L	40.9 ± 4.8 nmol/L	65.8 ± 6.3 pmol/L	1.22 ± 0.04	Creatinine 83.1 ± 4.2 µmol/L	Aging may cause a reduced effect of 1,25-OH vitamin D on intestinal calcium absorption, thus raising PTH inducing a chronic stimulus on the parathyroid glands	Feedback on PTH might be restored with 1,25-OH vitamin D, through a greater calcium absorption
Cosman et al.[18] (n = 9)[c]	Low estrogen status (menopause)	61 ± 3	100% F	5.08 ± 0.51 pmol/L	NR	NR	58 ± 6 nmol/L	77 ± 8 pmol/L	1.281 ± 0.022	NR	Low estrogens have been associated with a lower sensitivity to hypocalcemia. Women receiving HT were found to have lower PTH in the setting of induced hypocalcemia. Besides the known protective effect on bone, better intestinal and renal calcium absorption, rather than direct effects on parathyroid glands seems to link estrogen with PTH dynamics.	Feedback on PTH is dependent on estrogen status
Vincent et al.[19] (n = 10)		76.4 ± 1.9	100% F	≈5-7.5 pmol/L	2.36 ± 0.02 mmol/L	NR	NR	NR	≈1.2-1.25 mmol/L	Creatinine 88.4 ± 3.2 µmol/L		
Invernizzi et al.[20] (n = 20)	Nutritional (feedback preserved)	55.3 ± 6.2	65% F	≈100	NR	≈3	36.7 ± 6.78	NR	≈1.3	81 ± 7.1	Oral calcium loading reduced PTH rapidly as opposed to PHPT, where this did not occur over 120 min. Oral phosphate loading increased PTH similarly in NHPT and controls.	That would point toward an unrecognized form of secondary hyperparathyroidism, with a physiologic response to minerals
Maruani et al.[23] (n = 34)	A partial resistance to PTH from bone and kidney in NHPT but not in PHPT	53 ± 14	68% F	75 ± 19	9.62 ± 0.22	3.3 ± 0.4	33(17-86)	103 ± 30 pmol/L	1.32 ± 0.03	Creatinine 0.80 ± 0.13 mg/dL	Lower secretion of PTH so that calcium can remain in the normal range	Lower impact on biochemistry and bone turnover markers
Wang et al.[24] (n = 10 NHPT *vs* n = 20 controls)[e]	Low free 25-hydroxivitamin D	59.9 ± 5.4	90% F	98.1 ± 31.7	9.3 ± 0.3[d]	NR	31.9 ± 1.7 vs 32.7 ± 3.3 *(total Vit. D)* 5.0 ± 0.9 vs 6.2 ± 1.3 *(free Vit. D)*	NR	NR	'normal'	PTH levels correlate with free, but not total vitamin D	It is an unrecognized secondary form, therefore feedback on PTH is preserved.

(Continues)

Table 1. Continued

Source	Hypothesis	Age (yrs)	F/M ratio	PTH (pg/ml)	sCa (mg/dL)	sP (mg/dL)	25(OH)D (ng/mL)	1,25 $(OH)_2D$ (pg/mL)	Ionized calcium (mmol/L)	eGFR (ml/min)	Explanation	Implications
Diaz-Soto et al.[27] (n = 41, 17 of whom with A986S polymorphism of CaSR)	Altered parathyroid sensing	63 ± 11	83% F	103 ± 25	9.23 ± 0.43	3.39 ± 0.48	34.0 ± 10.9	47.2 ± 15.8	1.22 ± 0.04	89.3 ± 28.1	Some polymorphisms in CaSR may lower sensitivity of the CaSR to serum calcium levels, thereby physiologically leading to a greater secretion of PTH.	No feedback on PTH.

To convert calcium from milligrams per deciliter to millimoles per liter, multiply by 0.25.
To convert phosphorus from milligrams per deciliter to millimoles per liter, multiply by 0.323.
To convert 25-hydroxyvitamin D from nanograms per milliliter to nanomoles per liter, multiply by 2.496.
To convert 1,25-dihydroxyvitamin D from picograms per milliliter to picomoles per liter, multiply by 2.6.
To convert PTH from picograms per milliliter to picomoles per liter, multiply by 0.105.
To convert creatinine from µmol per liter to millimgrams per deciliter, multiply by 0.113.
[a]Characteristics of patients who became hypercalcemic.
[b]Values of the 'elderly women group' who responded to calcitriol are reported.
[c]Basal values of untreated postmenopausal women undergoing EDTA-induced hypocalcemia.
[d]Albumin-adjusted calcium.
[e]NHPT data are shown.
CaSR = Calcium-sensing receptor; NHPT = normocalcemic primary hyperparathyroidism; HT = hormone therapy; NR = not recorded.

Prevalence

Prevalence

- a rare condition
- 0.1% and 6%.
- These studies suggest that **repeating laboratory** evaluation over time is essential in confirming the diagnosis of NHPT.

Classical Complications

Classical Complications

- referral centers→ selection bias
- Notably, population-based studies to date have shown either **no** evidence or **less** evidence of substantial **bone** or **renal** complications.
- Thus, it
- appears that NHPT identified solely by **biochemical criteria**,
- rather than by recognized **bone disorders** or **renal stones**, may
- not be associated with significant complications.
- cut-offs for 25(OH)D sufficiency
- without consistently measuring ionized Ca

BONE

- Patients with NHPT having **low** bone density, osteoporosis, or
- low-trauma fractures have mostly been reported in small cohorts
- in selected referral centers that evaluated limited numbers of
- cases of NHPT.
- Most of these studies ranged between 6 and 37 patients.

BONE

- The study by Siprova and colleagues
- reported the largest number of NHPT patients with low bone
- density, osteoporosis, or fractures.
- This study included 137 NHPT
- patients (81% female), of whom 36 converted to PHPT within
- 6 years. Of these, 42% were described as having reduced bone
- density, without specifying whether they had osteopenia or
- osteoporosis. Bone quality may also have been affected in these
- patients, with increased risk of fracture.

Cortical and trabecular sites

- Charopoulous and colleagues evaluated the effects of
- NHPT and PHPT on cortical and trabecular sites in postmenopausal
- women using **pQCT scans** of the tibia in postmenopausal
- women. They demonstrated catabolic actions on both cortical
- and trabecular compartments in NHPT and PHPT, as well as deterioration
- in cortical geometry in both phenotypes, with relative
- preservation of trabecular architecture. These findings suggest
- that bone loss occurs silently over time in NHPT. As a result, NHPT may be responsible for the onset and progression of the same
- **skeletal complications** as described in classical PHPT.

Nephrolithiasis in NHPT

- In referral cohorts, → high as 18% to 29%.
- NHPT →10% or slightly more
- . In some cohorts, the
- small numbers of patients and the heterogeneous ways of defining
- or **excluding hypercalciuria** in these cohorts may have led to
- **overestimation** of the prevalence of nephrolithiasis. The study by
- Siprova and colleague suggested that nephrolithiasis was
- **more common in patients with hypercalcemic PHPT, with 22%**
- **reported to have kidney stones, whereas only 4% of the NHPT**
- **patients had nephrolithiasis.**

NHPT → PHPT

- It is still **not yet clear** whether NHPT progresses toward hypercalcemic

The study by Schini and colleagues

- highly variable rates of evolution of NHPT into classical
- PHPT ranging between **zero** and **19**%, so that it was difficult to draw a definitive conclusion
- 1-incorrect diagnosis at baseline based on single biochemical measurements or
- 2-selection bias.

Palermo and colleagues

- This study was **unable** to identify hyperparathyroidism-related **bone disease** in the cohort with NHPT.

Nonclassical Manifestations

- Response to parathyroidectomy:
- Hypertension → might be beneficial
- IHD → excluded an influence of NHPT on the **coronary calcium score**
- No improvement in **cerebrovascular** or **neuropsychological** function
- Quality of life → mild improvement in certain physical symptoms
- Quality of life → no effect was seen on mood-related symptoms
- Thirst and fatigue → improved in patients with NHPT

Parathyroidectomy response in PHPT

- improved
- mental status,
- Ameliorating physical symptoms and
- improving a greater number of nonspecific symptoms (anxiety, fatigue, muscle-wasting, thirst, weight loss, loss of appetite, bone pain, constipation, and headaches)

Surgical and Medical Outcomes

Surgical and Medical Outcomes

- Few data
- In the largest study, **Pandian** and colleagues confirmed that NHPT is characterized by a higher prevalence of **multigland** disease, which has been associated with **lower cure rates**.
- **Smaller gland size** may also be more common in NHPT as compared with PHPT

Pandian and colleagues

- concluded that **routine bilateral neck exploration** was necessary, in addition to using **intraoperative PTH monitoring** (ioPTH) in all patients affected by NHPT.
- Alternatively, another study suggested proceeding with bilateral neck exploration (BNE) if ioPTH did not drop by 50% within 10 min of removal of the suspected overactive parathyroid gland(s).
- overly aggressive

slower decline PTH in NHPT

- The authors acknowledged that long-term studies are needed to clarify the role of surgery in NHPT. The basis for recommending ioPTH monitoring with or without BNE is the observation that the decline in ioPTH observed in patients with NHPT may be slower than in patients with PHPT.
- This slower decline has been associated with lower cure rates

Improvement of bone complications after parathyroidectomy,

- Sho S et al →NHPT → reported that increased PTH levels were
- common (46.5%) after parathyroidectomy for NHPT, and that they
- were associated with a lack of BMD improvement after parathyroid
- removal.

Postoperative hyperparathyroidism (**PHPT**)

- Postoperative hyperparathyroidism is not an uncommon finding after parathyroidectomy for classical **PHPT**, with a mean **prevalence** of **23.5%** among various studies, mostly related to vitamin
- D deficiency or
- insufficiency or lack of Ca through diet or supplements.

Postoperative hyperparathyroidism (NHPT)

- As opposed to PHPT where this finding invariably
- represents a form of secondary hyperparathyroidism because the
- Ca normalizes, elevated PTH levels found after surgery for NHPT
- may be the only sign of disease persistence, possibly hinting at a
- previously unidentified cause of **secondary hyperparathyroidism**
- involving multiple glands.

NHPT

- significant increase in BMD?
- Another study showed a mild (2.3% 5.0%), but significant increase in lumbar spine BMD in NHPT patients undergoing successful parathyroidectomy.
- A large surgical single-center retrospective study found that after parathyroidectomy, as many as 41.7% and 40.0% of patients showed
- improvements in BMD and kidney stones, respectively.
- However, this study did not provide T-scores or BMD percentage changes.

oral alendronate and cholecalciferol

- One study evaluated the effects of oral alendronate and cholecalciferol in a small cohort of postmenopausal women. All skeletal sites improved with alendronate therapy **after 12 months**, with lumbar spine BMD improving by 4.7%, total hip BMD improving by 4.0%, and femoral neck BMD improving by 2.6%.
- The control group receiving cholecalciferol alone experienced significant BMD loss of 1.6% at the lumbar spine, 1.4% at the total hip, and 1.7% at the femoral neck. The other study investigated the effectiveness of cinacalcet in improving nephrolithiasis. Although the study consisted of
- only 10 patients with hyperparathyroidism, 6 of whom were normocalcemic, cinacalcet reduced the number and size of urinary stones in both the hypercalcemic and normocalcemic groups over a follow-up period of 10 months

Cinacalce

- Cinacalcet reduced the number and size of urinary stones in both the hypercalcemic and normocalcemic groups over a follow-up period of 10 months

parathyroid carcinoma

- A single case of parathyroid carcinoma was reported to present with NHPT.
- A large surgical series compared outcomes in
- NHPT (n = 733) versus PHPT (n = 6836) patients.
- Among those with parathyroid cancer or atypical adenoma (n = 212), 26.8% (n = 57) were categorized as having NHPT.
- This histologic category was not further analyzed to distinguish between cancers and atypical adenomas. The authors commented that this unexpected finding might have been caused by **pathological misclassification.**

Summary

- There is a strong scientific and clinical need to determine **a precise definition for NHPT.**
- Ca, PTH, vitamin D ranges, P, and the number of sequential Ca measurements over a specified period need to be derived by consensus.
- Short of such an endeavor, there will always be misclassification of NHPT and PHPT. This is a major obstacle to the ability to phenotype this condition, understand its pathophysiology and complications, and make clinical management recommendations.

- . The **symptomatic form** of NHPT has mainly been reported by referral centers for **metabolic bone disorders**; therefore, selection biases could have led to an overestimation of the clinical impact of the disease.

DD of NHPT from secondary hyperparathyroidism

- NHPT is a biochemical diagnosis of exclusion, and laboratory testing over time is necessary to distinguish this from secondary hyperparathyroidism.
- Follow-up frequently reveals resolution of hyperparathyroidism.

Conclusions

- A precise definition for NHPT has been derived by consensus.
- Prospective studies are needed that include patients based on this definition.
- • The pathophysiology of NHPT may be heterogeneous.
- • NHPT is a biochemical diagnosis of exclusion, with appropriate long-term follow-up frequently revealing resolution of hyperparathyroidism.
- • The natural history of NHPT remains unknown.
- • Caution should be used in recommending surgery for NHPT, but when surgery is done, multigland disease has been reported.