DR NARDEEN DAWOOD (Orcid ID : 0000-0002-1762-6144)
DR ANGELA LEUNG (Orcid ID : 0000-0001-8935-9332)

Article type : Requested Review

Corresponding author mail id: amleung@mednet.ucla.edu

Normocalcemic Primary Hyperthyroidism: An Update on Diagnostic and Management Challenges

Nardeen B. Dawood[1]; Kimberly L. Yan[1]; Albert Shieh[2]; Masha J. Livhits[3]; Michael W. Yeh[3]; Angela M. Leung[4,5]

[1] UCLA David Geffen School of Medicine, Los Angeles, CA, U.S.A.

[2] Division of Medicine, Geriatric Medicine, UCLA David Geffen School of Medicine, U.S.A.

[3] Section of Endocrine Surgery, Department of Surgery, UCLA David Geffen School of Medicine, Los Angeles, CA, U.S.A.

[4] Division of Endocrinology, Diabetes, and Metabolism; UCLA David Geffen School of Medicine, Los Angeles, CA, U.S.A.

[5] Division of Endocrinology, Diabetes, and Metabolism; VA Greater Los Angeles Healthcare System, Los Angeles, CA, U.S.A.

Short Running Title: Normocalcemic primary hyperparathyroidism

Summary

Normocalcemic primary hyperparathyroidism likely represents a condition that may evolve into its hypercalcemic counterpart and recent studies have shown that patients can present with intermittent hypercalcemia. This milder biochemical entity remains an incompletely understood condition because of a lack of long-term health outcomes regarding both medical and surgical approaches to its management. Medical therapies have shown some efficacy. A limited number of studies have found that bisphosphonates increase bone mineral density and calcimimetics may decrease

the risk of nephrolithiasis in patients with normocalcemic primary hyperparathyroidism. Other studies have described patient outcomes after applying the same surgical criteria used for patients with hypercalcemic primary hyperparathyroidism to those with the normocalcemic form of the disease. These few studies suggest that parathyroid surgery appears to be effective in normalizing elevated serum PTH concentrations and decreasing adverse renal and skeletal outcomes in patients with normocalcemic hyperparathyroidism. Given the available data and overall lack of consensus regarding the optimal management of these patients, a reasonable approach is to tailor management to the individual patient by considering their risk factors for new or accelerated bone loss, kidney stones, diminished quality of life, and cardiovascular disease.

MeSH Key Words: Hyperparathyroidism; Hyperparathyroidism, primary; Calcium-regulating hormones and agents; Parathyroid hormone; Osteoporosis; Bone diseases, metabolic; Nephrolithiasis

Background

Classic (hypercalcemic) primary hyperparathyroidism is a well-characterized disease with an estimated prevalence of 0.23% among women and 0.085% among men.[1] The related biochemical condition of normocalcemic primary hyperparathyroidism has not been as extensively studied, but is thought to range in prevalence from 0.4-6% in asymptomatic patients.[2-4] The wide variation in supposed prevalence rates can be attributed to selective cohorts of post-menopausal women and older patients, absence of ionized calcium measurements, inclusion of patients with hypercalciuria, and varied threshold values for eGFR, vitamin D, calcium, and PTH. Rosario et al. accounted for these areas of potential error and found the prevalence of normocalcemic primary hyperparathyroidism amongst patients without nephrolithiasis or fractures to be .74% in an adult population.[5]

Among patients with skeletal or renal disease (i.e. osteoporosis, fragility fractures, or renal calculi), normocalcemic primary hyperparathyroidism appears to be more prevalent (8.9%) than hypercalcemic primary hyperparathyroidism.[7] A recent study from a metabolic bone referral center challenged these figures by uncovering a much lower prevalence of normocalcemic primary hyperparathyroidism of 0.18% (n=6,320).[8] The purpose of this review is to expand previous discussions of the pathophysiology, diagnostic challenges, clinical sequelae, and management strategies in patients with normocalcemic primary hyperparathyroidism[9-11]

Pathophysiology

A common hypothesis describes normocalcemic primary hyperparathyroidism as an early, "subclinical" manifestation of its more widely described counterpart, hypercalcemic primary hyperparathyroidism. The latter is a disease characterized by elevated serum calcium levels with concurrently elevated or inappropriate normal parathyroid hormone (PTH) levels. The normocalcemic form of the disease is characterized by elevated PTH levels in the setting of

normal serum calcium concentrations, although hypercalcemia may develop in a subset of individuals over time.[12-14] One risk factor for progression to hypercalcemia is the degree of calcium elevation within the normal range. A longitudinal cohort study of 37 individuals followed for a median of three years reported that those with baseline calcium levels at the upper limit of normal were more likely to develop overt hypercalcemia over time.[13] In this study, however, hypercalcemia was determined by elevated total serum calcium, rather than the preferred method of using ionized calcium in conjunction with total adjusted calcium as discussed below.

A second hypothesis posits that PTH action in normocalcemic primary hyperparathyroidism has an attenuated ability to increase the serum calcium level because of skeletal and renal tissue resistance to the hormone.[6] In a cohort of 178 hyperparathyroid patients in France, investigators observed substantial overlap of PTH concentrations between the normocalcemic and hypercalcemic groups. When compared to the hypercalcemic group, those with normocalcemia exhibited reduced renal tubular calcium reabsorption, markers of bone turnover, 1,25-dihydroxyvitamin D levels.[6] These findings suggest that the normocalcemia may be attributed to a blunted target-tissue response to PTH. Thus, do elevated PTH levels in the presence of end-organ tissue resistance truly represent a pathologic condition, or is this merely a variant of calcium homeostasis at a higher PTH set point?

Diagnosis

The diagnosis of normocalcemic primary hyperparathyroidism relies on a biochemical profile of concurrently elevated serum PTH and normal serum calcium concentrations, both of which hinge on several assay-related and additional factors. Evaluation further requires the exclusion of secondary hyperparathyroidism.

a. Parathyroid Hormone

The first PTH immunoassay was developed in the 1960s and 1970s. It indiscriminately detected both intact PTH (iPTH, the full amino acid sequence 1-84) and smaller C-PTH fragments on the peptide. This poses an issue as these fragments can be produced by chronic hypercalcemia; thus, they cannot effectively distinguish between hyperparathyroidism and nonparathyroid hypercalcemia.[15] Second- and third- generation assays have since replaced the first-generation assays and now remain the preferred methods of PTH testing. Second-generation assays employ two-site specificity that recognizes PTH fragments near their termini in order to capture intact PTH (1-48). However, they have also been shown to cross-react with large PTH fragments (most notably, PTH (7-48)). Third-generation assays achieve specificity by using a labeled antibody that detects whole, "bioactive" PTH (1-84) peptides, without noticeably cross-reacting with PTH (7-48). However, the third-generation assay has been shown to detect a post-translation modified form of PTH that can be overproduced in parathyroid carcinoma or severe hyperparathyroidism (N-PTH). [15] Few studies have been done to compare the diagnostic sensitivities of second- and third- generation assays.[16-19] Using these analyses, the Fourth International Workshop described these two assays as equivalently useful modalities for diagnosis of PHPT.[20]Despite these new developments, the inter-method variability between different commercially-available PTH assays poses another threat to consistent PTH measurements. Assays vary by antibody affinities and specificities across

manufacturers.[21] This highlights the importance of appropriate reference ranges for each assay in order to determine PTH elevation.

b. Calcium

Serum calcium can be assessed as either total or ionized concentrations. The use of serum ionized calcium in conjunction with total adjusted calcium is favored over total serum calcium alone in diagnostically ambiguous cases because ionized levels are more frequently elevated than total serum calcium levels in patients with primary hyperparathyroidism. A study showed that 27 of 144 patients with elevated ionized serum calcium were found to have total calcium values within the normal range.[6] In light of this discrepancy, the Fourth International Workshop Guidelines for the Management of Primary Hyperparathyroidism advises clinicians to assess both ionized serum calcium and albumin-adjusted total serum calcium to confirm the diagnosis of normocalcemic primary hyperparathyroidism; however, the report acknowledges the limitations of measuring ionized calcium using blood gas machines in outpatient clinics.[20] Other limitations of using ionized calcium include the need for immediate handling, the lack of good quality control, and frequent electrode dysfunction.[22]

Serum calcium must also be measured at least twice within a six-month period in order to distinguish true normocalcemic disease from hypercalcemic primary hyperparathyroidism.[2,9] Furthermore , albumin assessment must accompany total serum calcium measurements to correct for calcium levels obscured by hypo- or hyperalbuminemia.

c. Exclusion Criteria (Secondary Hyperparathyroidism, Calcium Malabsorption, Medications):

Integral to diagnosis of primary hyperparathyroidism (whether normocalcemic or hypercalcemic) is the exclusion of secondary hyperparathyroidism, which is commonly seen with vitamin D deficiency. The regulatory pattern of increased PTH response with insufficient serum 25-OHD levels is well understood. In the absence of primary hyperparathyroidism, elevated serum PTH concentrations should be physiologically suppressible after three months of vitamin D repletion, although specific dose recommendations of vitamin D vary by race.[23] A diagnosis of primary hyperthyroidism can be made with greater certainty only if serum 25-OHD levels are consistently replete; the U.S Institute of Medicine advises a serum 25-OHD level ≥50 nmol/L.[24] However, Rosario et al. assessed preoperative Vitamin D levels in patients with normocalcemic PHPT and found that Vit D>75 nmol/L more appropriately predicted altered parathyroid pathology. Importantly, however, the surgeons were aware of the biochemical profiles of the subjects and determined if parathyroid morphology was abnormal by macroscopic appearance alone--resection and histologic analysis were only conducted for grossly enlarged glands.[5]

Renal insufficiency is another known cause of elevated PTH levels (resulting in secondary hyperparathyroidism) and thus may confound the diagnosis of normocalcemic primary hyperparathyroidism. The Kidney Disease Outcomes Quality Initiative (KDOQI) and Kidney Disease Improving Global Outcomes (KDIGO) guidelines describe that serum PTH elevation tends to occur with estimated glomerular filtration rates (eGFR) <60 mL/min/1.73m2.[5,25,26]

The diagnosis of primary hyperparathyroidism requires exclusion of some additional renal and gastrointestinal conditions, as well as use of medications that may alter serum PTH and/or calcium levels. Calcium deficiency resulting from a malabsorptive disorder (i.e. celiac disease, cystic fibrosis, biliopancreatic diversion complications) may raise PTH levels. [27-30] Some studies have also shown that idiopathic hypercalciuria is associated with parathyroid hyperactivity and should therefore be excluded.[31,32] Medications such as loop diuretics, lithium, bisphosphonates, denosumab, and antiepileptic medications are known to increase serum PTH levels, and their use should similarly be investigated as confounding factors.[15,33,34]

Clinical Features

Hypercalcemic primary hyperparathyroidism is traditionally understood to present either asymptomatically or with renal and/or skeletal complications. Some authors have proposed cardiovascular and neurocognitive complications of the disease as well. However, most of the available data on this condition come from referral cohorts, rather than unselected individuals from the general population. The central question here is, why would the PTH level be checked in a patient who has a normal serum calcium level? The frequent answer is because the managing physician is motivated to confirm or exclude a specific diagnosis that they suspect clinically. For example, PTH is commonly checked in the diagnosis of osteoporosis, to assess for secondary causes of bone loss. This unavoidable ascertainment process biases the entire sample of patients with normocalcemic primary hyperparathyroidism away from an unselected population. For this reason, an unanswered question is whether normocalcemic primary hyperparathyroidism can be compared in its natural history and clinical presentation to its hypercalcemic counterpart, which is often discovered through biochemical screening of unselected individuals.

In patients with hypercalcemic primary hyperparathyroidism, nephrolithiasis has largely been attributed to hypercalciuria resulting from elevated serum calcium concentrations. So, how might hypercalciuria exist in the context of normocalcemia? It may be the case that both exist but without any relation to one another. The high baseline prevalence of nephrolithiasis (10.6% in men and 7.1% in women) makes this possibility all the more compelling.[35] If, however, an association does exist, the mechanism of kidney stone formation in individuals with normocalcemic primary hyperparathyroidism is poorly understood. One possible cause for this phenomenon could be PTH resistance at the level of the renal tubule. Another explanation attributes a higher risk of kidney stone formation to several polymorphisms of the calcium-sensing receptor (*CASR*) gene.[36]

In a cohort of 37 individuals with normocalcemic primary hyperparathyroidism, 14% of patients presented with nephrolithiasis, in contrast to a higher rate (35%) in another study (n=34).[6,13] A much larger cohort of 137 patients with normocalcemic primary hyperparathyroidism showed a prevalence of only 4%.[12] Thus, the degree to which normocalcemic primary hyperparathyroidism correlates with nephrolithiasis is too diversely reported to point to a clear association between the two conditions.[7,12,37,38]

Similarly, patients with normocalcemic primary hyperparathyroidism show a wide range of adverse bone health outcomes. The aforementioned study of 37 primarily peri-menopausal and post-menopausal women reported that 57% of

the cohort had osteoporosis and 11% had fragility fractures.[13] Bone mineral density (BMD) assessment showed preferential bone loss at the lumbar spine (34%) and hip (38%), and less commonly at the distal radius (28%).[13] In a surgical cohort of 63 patients (88.7% women, median age 67 year [IQR 62-72]), 51% were found to have osteopenia and 41% showed osteoporosis.[39] Both of these studies, however, were made up of peri- or post-menopausal women who have the greatest propensity for development of osteopenia/osteoporosis independent of calcium and parathyroid status.

In summary, the literature reports great variation in the prevalence of renal and skeletal complications of normocalcemic primary hyperparathyroidism, due in part to the selection bias inherent in referral populations.[3] The factors that predispose specific patients with normocalcemic primary hyperparathyroidism to develop nephrolithiasis, osteopenia/osteoporosis, and fragility fractures remain unclear.[37,38,40]

Renal and skeletal disease are the complications most traditionally associated with primary hyperparathyroidism. However, normocalcemic primary hyperparathyroidism may also increase cardiovascular risk. This may be due to the physiologic effects of PTH and/or calcium on the cardiomyocyte, cardiac conduction system, and endothelial cells.[41] Some studies suggest that hypercalcemic primary hyperparathyroidism is associated with cardiovascular-related morbidity and mortality.[42] However, a recent study compared the two variants and found that a cohort of patients with normocalcemic primary hyperparathyroidism had more prominent coronary artery calcification than those with the hypercalcemic form of the disease,[43] although other data suggest the lack of an association.[44] Beysel et al. conducted a small case-control study (n=95) that challenges these findings: patients with normocalcemic and age- and sex- matched hypercalcemic PHPT were found to have similarly elevated blood pressure, glucose, insulin, HOMA-IR (homeostatic model assessment of insulin resistance), lipid profiles, and cardiovascular risk scores ($p>.05$) when compared with controls ($p<.05$).[45] Because the normocalcemic group was made up of only 35 patients, it is unclear how generalizable these findings are to all patients with normocalcemic hyperparathyroidism. Thus, it appears that patients with hyperparathyroidism may have worse cardiovascular outcomes, however, it remains uncertain whether the pathophysiology is related to serum calcium elevation or not.

Management

The appropriate management of normocalcemic primary hyperparathyroidism is difficult to discern, as the long-term outcomes of therapeutic options have not been sufficiently studied. The Fourth International Workshop Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism recommends monitoring the disease process (with both biochemical and clinical measures) and does not recommend performing parathyroid surgery until specific criteria are met or the disease cannot be medically managed.[20] In this model, it is recommended to assess serum calcium, phosphate, alkaline phosphatase, 25-OH vitamin D, creatinine, BUN, and PTH concentrations annually, and to perform a bone density (DXA) scan every 1-2 years. The guidelines suggest that the surgical criteria for patients with hypercalcemic primary hyperparathyroidism ought to be extended to those with the normocalcemic variant of the condition. These criteria advise that patients who develop kidney stones, nephrocalcinosis, fracture, or reductions in BMD would benefit

from treatment by parathyroidectomy. The observed biochemical and clinical outcomes of medical versus surgical management of normocalcemic primary hyperparathyroidism are discussed below.

Medical Treatment of Normocalcemic Primary Hyperparathyroidism

Very few studies have evaluated the benefit of medical therapy in this population. These reports and case series suggest that alendronate and cinacalcet may be useful in improving bone health and decreasing nephrolithiasis risk (Table 1), but they are limited by their very small sample sizes. The effects of medical therapies on cardiovascular and neurocognitive symptoms associated with normocalcemic primary hyperparathyroidism are unknown.

a. Bone Mineral Density

In a prospective, open-label, randomized clinical trial of 30 post-menopausal women with normocalcemic primary hyperparathyroidism, 15 received alendronate with concurrent vitamin D supplementation (treatment group), and 15 received vitamin D alone (control group).[46] After 12 months, those who had received the combination of alendronate and vitamin D showed improvements in BMD at the lumbar spine (+4.7%), femoral neck (+2.6%), and total femur (+4.0%), compared to the control group. This small study suggests a potential benefit of bisphosphonates in normocalcemic primary hyperparathyroidism, but larger scale studies are required. Furthermore, alendronate is a widely used treatment for decreased bone mineral density and is expected to improve osteoporosis independent of etiology. Thus, it is unlikely that these findings are specific to normocalcemic primary hyperparathyroidism.

The effect of cinacalcet on bone health has not been studied in patients with normocalcemic primary hyperparathyroidism. However, because cinacalcet has not been shown to increase BMD in patients with hypercalcemic primary hyperparathyroidism, it is not expected to benefit patients with normocalcemic primary hyperparathyroidism.[47,48]

b. Nephrolithiasis

Similarly, it is unclear if patients with normocalcemic primary hyperparathyroidism benefit from medical treatment of nephrolithiasis. One Italian report of six adults with normocalcemic primary hyperparathyroidism reported a reduction in the diameter and quantity of kidney stones after 10 months of cinacalcet use.[49]

Parathyroid Surgery in Normocalcemic Primary Hyperparathyroidism

The surgical management of normocalcemic primary hyperparathyroidism has been better studied than the medical management of this condition (Table 2). In general, these case series reported improvements in bone mineral density, nephrolithiasis, cardiovascular risk factors, and quality of life.

However, parathyroidectomy performed in patients with normocalcemic primary hyperparathyroidism is associated with lower long-term cure rates when compared to surgical treatment of the hypercalcemic form. This may be due to an increased frequency of multiglandular disease observed in patients with normocalcemic primary hyperparathyroidism.[50] Multiglandular disease requires four-gland exploration, which may be a more challenging

operation. Surgical intervention is similarly complex in cases of single parathyroid adenomas because patients with normocalcemic primary hyperparathyroidism have been shown to have smaller lesions than those with the hypercalcemic disease variant.[51-53] These features may contribute to the lower sensitivity of preoperative imaging in patients with normocalcemic PHPT compared to hypercalcemic PHPT.[40,54-56] A study by Bezerra et. al supported these previous findings and also compared the sensitivity of three preoperative imaging modalities (4DCT, CT-99-Sestamibi scintigraphy, and ultrasonography) in patients with normocalcemic primary hyperparathyroidism. 4DCT was found to have the greatest sensitivity (55.6%, CI 23.1-88), when compared to scintigraphy (11.1%, CI 0-31.6) and ultrasonography (22%, CI 0-44.9%).[57] Thus, parathyroid surgery appears to be performed less commonly in cases of normocalcemic primary hyperparathyroidism, compared to the hypercalcemic form, due to the more complex morphology, technical challenges of surgery, poor sensitivity of preoperative imaging, and the lack of a clear and sustained benefit over medical management.[58]

a. Normalization of Serum PTH Concentrations

In studies of mostly hypercalcemic primary hyperparathyroidism, resection of an identified parathyroid adenoma results in decreased, and in most cases, normalized serum PTH concentrations.[13,39,40,53,55,59] Several studies have shown similarly beneficial results among those with the normocalcemic form of the disease. Lim. et al reported that of 96 patients with normocalcemic primary hyperparathyroidism, serum PTH levels normalized in 86.5% of patients in the immediate postoperative period, which further improved to 94% at 12 months.[55] Another study showed that in 8 patients with normocalcemic primary hyperparathyroidism who underwent parathyroidectomy, 6 achieved normal serum PTH levels during a mean follow-up period of 73 months.[59] Other studies have shown slightly less effective results. One report of 75 patients with normocalcemic primary hyperparathyroidism demonstrated that only 53.5% were able to achieve normal serum PTH levels after parathyroid surgery, although authors noted a relatively high prevalence of multiglandular disease and smaller parathyroid glands in this cohort.[39] Another study of 121 patients showed that those with the normocalcemic variant were less likely to have normal PTH levels six months after surgery compared to those with hypercalcemic primary hyperparathyroidism (7% vs 55%).[60] While these studies are still relatively small and heterogeneous, parathyroid surgery was shown to correct PTH elevations in those with normocalcemic primary hyperparathyroidism in 45-94% of cases.

b. Bone Mineral Density

After parathyroidectomy, BMD tends to improve in patients with normocalcemic primary hyperparathyroidism. One study of 39 individuals showed BMD improvements both at the spine (2.3±5.0%; P=0.016) and femoral neck (1.9%±5.7; P=0.048), but no change at the distal radius, one year following the operation.[52] In another cohort (n=23), Sho et al. demonstrated that patients whose serum PTH concentrations normalized after surgery had an associated mean BMD increase of 5.6% (from 0.706±0.036 g/cm^2 to 0.745±0.037 g/cm^2; P=0.006) at the site of lowest preoperative T-score by DXA (spine, femoral neck, or hip).[39]

c. Nephrolithiasis

Whether parathyroidectomy improves renal outcomes in patients with normocalcemic primary hyperparathyroidism remains much less understood. Traini et al. followed a small cohort of patients (n=10) and found that 40% of patients with preexisting nephrolithiasis no longer had stones after parathyroid surgery.[59] Another study of 48 patients with normocalcemic primary hyperparathyroidism demonstrated an 80% cure rate in nephrolithiasis following removal of parathyroid adenomas and hyperplastic glands.[61]

d. Cardiovascular Health

Cardiovascular dysfunction is a proposed manifestation of primary hyperparathyroidism. Literature pertaining to cardiovascular risk in this population is very limited. Therefore, the 2014 guidelines do not advise parathyroid surgery for the sole purpose of improving cardiovascular outcomes.[20] Pertinent to this discussion, however, is a study by Beysel et al. that evaluated the association of parathyroidectomy and cardiovascular risk factors in patients with normocalcemic primary hyperparathyroidism. The study observed improvements in blood pressure, serum total cholesterol levels, insulin resistance, and Framingham cardiovascular risk scores following parathyroidectomy in 35 patients with the normocalcemic disease.[45]

e. Quality of Life (QoL)

In addition to renal and skeletal complications, primary hyperparathyroidism is associated with a variety of potential neurocognitive and nonspecific physical symptoms (abdominal complaints, musculoskeletal pain, depression, and anxiety). In a prospective, multicenter study of four French academic medical centers, parathyroid surgery was associated with a greater improvement in physical QoL outcomes (but less so in mental health-associated QoL) among patients with the normocalcemic variant compared to those with hypercalcemic primary hyperparathyroidism.[62]

Summary

Normocalcemic primary hyperparathyroidism is defined by elevated serum PTH levels, normal albumin-adjusted total and ionized calcium, and exclusion of secondary causes of hyperparathyroidism. From the limited available literature on the topic, this condition is believed by some to represent the first phase of hypercalcemic primary hyperparathyroidism, given their overlapping adverse clinical outcomes (nephrolithiasis, bone loss, cardiovascular disease, and impaired quality of life). However, the clinical benefits of medical and surgical interventions in patients with normocalcemic primary hyperparathyroidism remain poorly understood. The available literature suggests that bisphosphonates, calcimimetics (cinacalcet) and parathyroid surgery may be effective in ameliorating some complications of normocalcemic primary hyperparathyroidism, but the condition requires further large-scale study with extended follow up. Subject inclusion methods for future studies should be carefully crafted to minimize the effects of selection bias.

Table 1. Biochemical and clinical outcomes following medical therapy of patients with normocalcemic primary hyperparathyroidism.

STUDY	N	TREATMENT	BASELINE (INCLUSION CRITERIA)	BIOCHEMICAL OUTCOMES		CLINICAL OUTCOMES	
				SERUM CALCIUM	SERUM PTH	BMD	NEPHROLITHIASIS
Cesareo (2015)	15	Alendronate for 12 months	Total calcium <2.6 mmol/L PTH >6.9 pmol/L Vit D>75nmol/L	2.3±0.1 mmol/L	11.7±1.4 pmol/L	Lumbar (+4.7%) Femoral neck (+2.6%) Total femur (+4.0%)	
Brardi (2015)	6	Cinacalcet for 10 months	Total calcium 2.1-2.6 mmol/L PTH >8.4 pmol/L eGFR >50ml/min Vit D >50 nmol/L	2.16±0.12 mmol/L	7.3 pmol/L		Reduced size and number (from 3+/-2.5 stones at enrollment to 2.3+/-2.8 at end of study period)

Table 2. Biochemical and clinical outcomes following parathyroid surgery in patients with normocalcemic primary hyperparathyroidism.

STUDY	N	% MULTI-GLAND DISEASE	BASELINE (INCLUSION CRITERIA)	POST-SURGICAL BIOCHEMICAL OUTCOMES		POST-SURGICAL CLINICAL OUTCOMES	
				SERUM CALCIUM	SERUM PTH	OSTEOPENIA/ OSTEOPOROSIS (BMD)	NEPHROLITHIASIS
Grimelius (1976), Johansson (1975)	84	49% (95% hyperplasia, 5% double adenoma)	Total calcium 2.2-2.6 mmol/L	Uniform decrease			100% cured (parathyroid adenomas), 74% cured (parathyroid hyperplasia), 54% cured ("normal")
Wade (2012)	58*	14%	Total calcium 2.12-2.62 mmol/L (N=58), ionized calcium 1.19-1.33 mmol/L (N=8), PTH >7.6 pmol/L	Median total Ca: 2.4 mmol/L, range 2.15-2.69 mmol/L (N=7)	Median PTH: .0668 pmol/L, (N=6)		
Rejnmark (2013) [63]	24	8%**	Total calcium 2.22-2.55 (and 2.25-2.54***) mmol/L, ionized calcium 1.18-1.32 mmol/L, PTH >5				

			pmol/L			
Koumakis (2013)	39	28%	Total calcium ≤2.6 mmol/L, ionized calcium ≤1.30 mmol/L, PTH >4.88 pmol/L eGFR >40mL/min, Vit D >50 nmol/L	Total calcium 2.32±0.08 mmol/L, ionized calcium 1.23±0.03 mmol/L	Normal in all pts evaluated at 3 month follow-up (n=8)	Spine: +2.3± 5.0%, Femoral neck: +1.9±5.7%, Distal radius: no significant change
Lim (2017)	96	45%		Normal in 95 pts at 6 months	Normal in 90 pts at 6 months	
Sho (2018)	71	54%	Total calcium <2.54-2.64 mmol/L***, PTH 1.8-5.8 pmol/L, eGFR >60mL/min, Vit D >50nmol/L	Median total calcium in pts with normalized PTH: 2.32 mmol/L Median total calcium in pts with persistently elevated PTH: 2.4 mmol/L	Of those normalized (N=38), median PTH 4.2 pmol/L, range 3.8-4.98 Of those persistently elevated (N=33): median PTH 7.561 pmol/L, range 6.5-8.3	+2.6% in entire cohort (+5.6% in pts with normalized PTH, no significant change in pts with persistently elevated PTH)
Kiriakopolous (2018)[51]	23	21.7%	Total calcium < 2.54 mmol/L,		Normalized in 22 pts	

			ionized calcium < 1.3 mmol/L , PTH >6.9 pmol/L, eGFR >60mL/min, Vit D >50 nmol/L				
Traini (2018)	154	13% (55% hyperplasia and 45% double adenoma)	Total calcium 2.62 mmol/L, PTH >6.9 pmol/L, Vit D>50 nmol/L	Total 2.27±0.15 mmol/L, range 1.8-2.7 (N=96)	3.3±2.8, range 0.2-16.4 pmol/L (N= 93)	11/12 pts stable or improved	10/10 pts stable or resolved

* Only 8 patients within this cohort had a normal iCa in addition to a normal total Ca. The outcomes listed pertain to the subgroup with normal iCa.

** 4 patients had unknown pathology

***Variance dependent on reference values from multiple laboratories

References

1. Yeh MW, Ituarte PH, Zhou HC, et al. Incidence and prevalence of primary hyperparathyroidism in a racially mixed population. *The Journal of clinical endocrinology and metabolism.* 2013;98(3):1122-1129.
2. Cusano NE, Maalouf NM, Wang PY, et al. Normocalcemic hyperparathyroidism and hypoparathyroidism in two community-based nonreferral populations. *The Journal of clinical endocrinology and metabolism.* 2013;98(7):2734-2741.
3. Garcia-Martin A, Reyes-Garcia R, Munoz-Torres M. Normocalcemic primary hyperparathyroidism: one-year follow-up in one hundred postmenopausal women. *Endocrine.* 2012;42(3):764-766.
4. Lundgren E, Rastad J, Thrufjell E, Akerström G, Ljunghall S. Population-based screening for primary hyperparathyroidism with serum calcium and parathyroid hormone values in menopausal women. *Surgery.* 1997;121(3):287-294.
5. Rosário PW, Calsolari MR. Normocalcemic Primary Hyperparathyroidism in Adults Without a History of Nephrolithiasis or Fractures: A Prospective Study. *hmr.* 2019;51(04):243-247.
6. Maruani Gr, Hertig A, Paillard M, Houillier P. Normocalcemic Primary Hyperparathyroidism: Evidence for a Generalized Target-Tissue Resistance to Parathyroid Hormone. *The Journal of Clinical Endocrinology & Metabolism.* 2003;88(10):4641-4648.
7. Marques TF, Vasconcelos R, Diniz E, Rego D, Griz L, Bandeira F. Normocalcemic primary hyperparathyroidism in clinical practice: an indolent condition or a silent threat? *Arquivos brasileiros de endocrinologia e metabologia.* 2011;55(5):314-317.
8. Schini M, Jacques RM, Oakes E, Peel NFA, Walsh JS, Eastell R. Normocalcemic Hyperparathyroidism: Study of its Prevalence and Natural History. *The Journal of clinical endocrinology and metabolism.* 2020;105(4):e1171-1186.
9. Babwah F, Buch HN. Normocalcaemic primary hyperparathyroidism: a pragmatic approach. *Journal of Clinical Pathology.* 2018;71(4):291-297.
10. Cusano NE, Cipriani C, Bilezikian JP. Management of normocalcemic primary hyperparathyroidism. *Best practice & research Clinical endocrinology & metabolism.* 2018;32(6):837-845.
11. Pawlowska M, Cusano NE. An overview of normocalcemic primary hyperparathyroidism. *Current opinion in endocrinology, diabetes, and obesity.* 2015;22(6):413-421.
12. Šiprová H, Fryšák Z, Souček M. Primary Hyperparathyroidism, With A Focus On Management Of The Normocalcemic Form: To Treat Or Not To Treat? *Endocrine Practice.* 2016;22(3):294-301.

13. Lowe H, McMahon DJ, Rubin MR, Bilezikian JP, Silverberg SJ. Normocalcemic Primary Hyperparathyroidism: Further Characterization of a New Clinical Phenotype. *The Journal of Clinical Endocrinology & Metabolism.* 2007;92(8):3001-3005.
14. Silverberg SJ, Bilezikian JP. "Incipient" Primary Hyperparathyroidism: A "Forme Fruste" of an Old Disease. *The Journal of Clinical Endocrinology & Metabolism.* 2003;88(11):5348-5352.
15. Eastell R, Arnold A, Brandi ML, et al. Diagnosis of Asymptomatic Primary Hyperparathyroidism: Proceedings of the Third International Workshop. *The Journal of Clinical Endocrinology & Metabolism.* 2009;94(2):340-350.
16. Gao P, Scheibel S, D'Amour P, et al. Development of a novel immunoradiometric assay exclusively for biologically active whole parathyroid hormone 1-84: implications for improvement of accurate assessment of parathyroid function. *Journal of bone and mineral research : the official journal of the American Society for Bone and Mineral Research.* 2001;16(4):605-614.
17. Boudou P, Ibrahim F, Cormier C, Chabas A, Sarfati E, Souberbielle JC. Third- or second-generation parathyroid hormone assays: a remaining debate in the diagnosis of primary hyperparathyroidism. *The Journal of clinical endocrinology and metabolism.* 2005;90(12):6370-6372.
18. Carnevale V, Dionisi S, Nofroni I, et al. Potential clinical utility of a new IRMA for parathyroid hormone in postmenopausal patients with primary hyperparathyroidism. *Clinical chemistry.* 2004;50(3):626-631.
19. Silverberg SJ, Gao P, Brown I, LoGerfo P, Cantor TL, Bilezikian JP. Clinical utility of an immunoradiometric assay for parathyroid hormone (1-84) in primary hyperparathyroidism. *The Journal of clinical endocrinology and metabolism.* 2003;88(10):4725-4730.
20. Bilezikian JP, Brandi ML, Eastell R, et al. Guidelines for the management of asymptomatic primary hyperparathyroidism: summary statement from the Fourth International Workshop. *The Journal of clinical endocrinology and metabolism.* 2014;99(10):3561-3569.
21. Garrett G, Sardiwal S, Lamb EJ, Goldsmith DJA. PTH—A Particularly Tricky Hormone: Why Measure It at All in Kidney Patients? *Clinical Journal of the American Society of Nephrology.* 2013;8(2):299-312.
22. Calvi LM, Bushinsky DA. When Is It Appropriate to Order an Ionized Calcium? *Journal of the American Society of Nephrology.* 2008;19(7):1257-1260.
23. Chandler PD, Agboola F, Ng K, et al. Reduction of Parathyroid Hormone with Vitamin D Supplementation in Blacks: A Randomized Controlled Trial. *BMC nutrition.* 2015;1.

24. Ross AC, Manson JE, Abrams SA, et al. The 2011 report on dietary reference intakes for calcium and vitamin D from the Institute of Medicine: what clinicians need to know. *The Journal of clinical endocrinology and metabolism.* 2011;96(1):53-58.
25. Isakova T, Nickolas TL, Denburg M, et al. KDOQI US Commentary on the 2017 KDIGO Clinical Practice Guideline Update for the Diagnosis, Evaluation, Prevention, and Treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *American journal of kidney diseases : the official journal of the National Kidney Foundation.* 2017;70(6):737-751.
26. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD). *Kidney international Supplement.* 2009(113):S1-130.
27. Nuti R, Martini G, Valenti R, Giovani S, Salvadori S, Avanzati A. Prevalence of undiagnosed coeliac syndrome in osteoporotic women. *Journal of Internal Medicine.* 2001;250(4):361-366.
28. Aris RM, Ontjes DA, Buell HE, et al. Abnormal bone turnover in cystic fibrosis adults. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2002;13(2):151-157.
29. Balsa JA, Botella-Carretero JI, Peromingo R, et al. Role of calcium malabsorption in the development of secondary hyperparathyroidism after biliopancreatic diversion. *Journal of endocrinological investigation.* 2008;31(10):845-850.
30. Steingrimsdottir L, Gunnarsson O, Indridason OS, Franzson L, Sigurdsson G. Relationship between serum parathyroid hormone levels, vitamin D sufficiency, and calcium intake. *Jama.* 2005;294(18):2336-2341.
31. Worcester EM, Bergsland KJ, Gillen DL, Coe FL. Evidence for increased renal tubule and parathyroid gland sensitivity to serum calcium in human idiopathic hypercalciuria. *American journal of physiology Renal physiology.* 2013;305(6):F853-860.
32. Coe FL, Canterbury JM, Firpo JJ, Reiss E. Evidence for secondary hyperparathyroidism in idiopathic hypercalciuria. *The Journal of clinical investigation.* 1973;52(1):134-142.
33. Bisphosphonates: an overview with special reference to alendronate. *Annals of Clinical Biochemistry.* 2001;38(6):608-623.
34. Yacobi-Bach M, Serebro M, Greenman Y, Tordjman K, Stern N. Letter to the editor: Thiazides are not inducers of PTH secretion: a comment on normocalcemic hyperparathyroidism. *The Journal of clinical endocrinology and metabolism.* 2015;100(2):L27-28.

35. Scales CD, Jr., Smith AC, Hanley JM, Saigal CS. Prevalence of kidney stones in the United States. *European urology.* 2012;62(1):160-165.
36. Cong X, Shen L, Gu X. Current opinions on nephrolithiasis associated with primary hyperparathyroidism. *Urolithiasis.* 2018;46(5):453-457.
37. Tordjman KM, Greenman Y, Osher E, Shenkerman G, Stern N. Characterization of normocalcemic primary hyperparathyroidism. *The American journal of medicine.* 2004;117(11):861-863.
38. Amaral LM, Queiroz DC, Marques TF, Mendes M, Bandeira F. Normocalcemic versus Hypercalcemic Primary Hyperparathyroidism: More Stone than Bone? *Journal of osteoporosis.* 2012;2012:128352.
39. Sho S, Kuo EJ, Chen AC, Li N, Yeh MW, Livhits MJ. Biochemical and Skeletal Outcomes of Parathyroidectomy for Normocalcemic (Incipient) Primary Hyperparathyroidism. *Annals of Surgical Oncology.* 2019;26(2):539-546.
40. Wade TJ, Yen TWF, Amin AL, Wang TS. Surgical Management of Normocalcemic Primary Hyperparathyroidism. *World journal of surgery.* 2012;36(4):761-766.
41. Pepe J, Cipriani C, Sonato C, Raimo O, Biamonte F, Minisola S. Cardiovascular manifestations of primary hyperparathyroidism: a narrative review. *European journal of endocrinology.* 2017;177(6):R297-r308.
42. Walker MD, Rubin M, Silverberg SJ. Nontraditional manifestations of primary hyperparathyroidism. *Journal of clinical densitometry : the official journal of the International Society for Clinical Densitometry.* 2013;16(1):40-47.
43. Koubaity O, Mandry D, Nguyen-Thi PL, et al. Coronary artery disease is more severe in patients with primary hyperparathyroidism. *Surgery.* 2020;167(1):149-154.
44. Mesquita PN, Dornelas Leao Leite AP, Chagas Crisostomo SD, Veras Filho E, da Cunha Xavier L, Bandeira F. Evaluation of coronary calcium score in patients with normocalcemic primary hyperparathyroidism. *Vascular health and risk management.* 2017;13:225-229.
45. Beysel S, Caliskan M, Kizilgul M, et al. Parathyroidectomy improves cardiovascular risk factors in normocalcemic and hypercalcemic primary hyperparathyroidism. *BMC cardiovascular disorders.* 2019;19(1):106.
46. Cesareo R, Di Stasio E, Vescini F, et al. Effects of alendronate and vitamin D in patients with normocalcemic primary hyperparathyroidism. *Osteoporosis international : a journal established as result of cooperation between the European Foundation for Osteoporosis and the National Osteoporosis Foundation of the USA.* 2015;26(4):1295-1302.

47. Marcocci C, Chanson P, Shoback D, et al. Cinacalcet reduces serum calcium concentrations in patients with intractable primary hyperparathyroidism. *The Journal of clinical endocrinology and metabolism.* 2009;94(8):2766-2772.
48. Peacock M, Bolognese MA, Borofsky M, et al. Cinacalcet Treatment of Primary Hyperparathyroidism: Biochemical and Bone Densitometric Outcomes in a Five-Year Study. *The Journal of Clinical Endocrinology & Metabolism.* 2009;94(12):4860-4867.
49. Brardi S, Cevenini G, Verdacchi T, Romano G, Ponchietti R. Use of cinacalcet in nephrolithiasis associated with normocalcemic or hypercalcemic primary hyperparathyroidism: results of a prospective randomized pilot study. *Archivio italiano di urologia, andrologia : organo ufficiale [di] Societa italiana di ecografia urologica e nefrologica.* 2015;87(1):66-71.
50. Singh Ospina NM, Rodriguez-Gutierrez R, Maraka S, et al. Outcomes of Parathyroidectomy in Patients with Primary Hyperparathyroidism: A Systematic Review and Meta-analysis. *World journal of surgery.* 2016;40(10):2359-2377.
51. Kiriakopoulos A, Petralias A, Linos D. Classic Primary Hyperparathyroidism Versus Normocalcemic and Normohormonal Variants: Do They Really Differ? *World journal of surgery.* 2018;42(4):992-997.
52. Koumakis E, Souberbielle JC, Sarfati E, et al. Bone mineral density evolution after successful parathyroidectomy in patients with normocalcemic primary hyperparathyroidism. *The Journal of clinical endocrinology and metabolism.* 2013;98(8):3213-3220.
53. Trinh G, Rettig E, Noureldine SI, et al. Surgical Management of Normocalcemic Primary Hyperparathyroidism and the Impact of Intraoperative Parathyroid Hormone Testing on Outcome. *Otolaryngology--head and neck surgery : official journal of American Academy of Otolaryngology-Head and Neck Surgery.* 2018;159(4):630-637.
54. Gómez-Ramírez J, Mihai R. Normocalcaemic primary hyperparathyroidism: a diagnostic and therapeutic algorithm. *Langenbeck's archives of surgery.* 2017;402(7):1103-1108.
55. Lim JY, Herman MC, Bubis L, et al. Differences in single gland and multigland disease are seen in low biochemical profile primary hyperparathyroidism. *Surgery.* 2017;161(1):70-77.
56. Carneiro-Pla DM, Irvin GL, 3rd, Chen H. Consequences of parathyroidectomy in patients with "mild" sporadic primary hyperparathyroidism. *Surgery.* 2007;142(6):795-799; discussion 799.e791-792.
57. Cunha-Bezerra P, Vieira R, Amaral F, et al. Better performance of four-dimension computed tomography as a localization procedure in normocalcemic primary hyperparathyroidism. *Journal of medical imaging and radiation oncology.* 2018.

58. Yan H, Calcatera N, Moo-Young TA, Prinz RA, Winchester DJ. Degree of hypercalcemia correlates with parathyroidectomy but not with symptoms. *American journal of surgery.* 2019;217(3):437-440.
59. Traini E, Bellantone R, Tempera SE, et al. Is parathyroidectomy safe and effective in patients with normocalcemic primary hyperparathyroidism? *Langenbeck's archives of surgery.* 2018;403(3):317-323.
60. Trebouet E, Bannani S, Wargny M, et al. Mild sporadic primary hyperparathyroidism: high rate of multiglandular disease is associated with lower surgical cure rate. *Langenbeck's archives of surgery.* 2019;404(4):431-438.
61. Grimelius L, Ejerblad S, Johansson H, Werner I. Parathyroid adenomas and glands in normocalcemic hyperparathyroidism. A light microscopic study. *The American journal of pathology.* 1976;83(3):475-484.
62. Bannani S, Christou N, Guerin C, et al. Effect of parathyroidectomy on quality of life and non-specific symptoms in normocalcaemic primary hyperparathyroidism. *The British journal of surgery.* 2018;105(3):223-229.
63. Rejnmark L, Amstrup AK, Mollerup CL, Heickendorff L, Mosekilde L. Further insights into the pathogenesis of primary hyperparathyroidism: a nested case-control study. *The Journal of clinical endocrinology and metabolism.* 2013;98(1):87-96.