DOI：10.6314/JIMT.202306_34(3).01 內科學誌 2023：34：141-156

Normocalcemic Primary Hyperparathyroidism-Mini Literature Review

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Abstract

While the great majority of the cases of primary hyperparathyroidism present with consistent and persistent hypercalcemia in laboratory test profile, a relatively new and rarer phenotype characterized by normal serum calcium concentrations in the face of persistently above-normal parathyroid hormone (PTH) levels has been recognized in a small proportion of patients in the past two decades and given the term normocalcemic hyperparathyroidism. Mostly, patients having this rare disorder could only be diagnosed incidentally or serendipitously during assessment of bone mineral disorders (osteoporosis or fragility fracture) or urolithiasis when serum calcium and PTH levels are measured for etiology finding. Long-term follow-up studies of this clinical entity in these patients have observed the natural course to be either stationary with persistent normocalcemia or developing into classical phenotype of hyperparathyroidism with time with steady or fluctuating pattern toward definitive hypercalcemia, and hence regarded by some investigators as a mild form of the classical phenotype of primary hyperparathyroidism at its initiation. Despite the status of normocalcemia, exposure to the excessive PTH concentrations of multiple tissues and organs could incur target organ damages in the long run which may manifest with disorders of bone mass or quality, fracture, or nephrolithiasis that in turn leads to impairment in renal function. Due to the largely unpredictable natural course and the odds of above-mentioned complications as may well-known to occur in classic primary hyperparathyroidism, it is prudent to keep periodic and continual follow-up and, when indicated, timely treatment of this specific phenotype of hyperparathyroidism. Surgical intervention by removal of identifiable parathyroid gland lesion(s) (hyperplasia or adenoma), or when surgical treatment is not feasible, pharmacological therapies aiming to inhibit bone resorption by osteoclasts with bisphosphonates to improve bone mineral density and reduce risk of fracture, or to reduce PTH back to normal levels by calcimimitics through its effect on calcium-sensing receptors at the parathyroid gland in hope of reducing urolithiasis burden, are all options available to ameliorate the risk of target organ damage by the excessive concentrations of PTH.

Key Words: Normocalcemic primary hyperparathyroidism, Osteoporosis, Fracture, Urolithiasis.

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Introduction

With its literally first introduction in the literature derived from a statement regarding the management of asymptomatic primary hyperparathyroidism (PHPT)[1], normocalcemic hyperparathyroidism (Nc-PHPT) has been drawing continual scientific attention to study its pathophysiology, natural course of development, clinical significance, and strategies of management that might help discern from those already clearly stated for patients with classical PHPT. As could be encountered in classical PHPT, patients with Nc-PHPT may also present as either being asymptomatic or suffering from target organ damage including osteoporosis, fragility fractures, urolithiasis, or decreased renal function thus incurred from exposure to excessive parathyroid hormone (PTH) concentrations, and, under the latter circumstances, should also receive optimal therapeutic intervention once the diagnosis is made[2,3]. Diagnosis of Nc-PHPT is primarily a laboratory one based on the finding of a combined normal serum calcium and above-normal PTH levels, which usually require repeated tests for confirmatory purpose[4].

Epidemiology of Nc-PHPT

According to a study conducted in a large cohort of population (n = 40,857) consisting of different ethnics enrolled in the Kaiser Permanente Southern California (KPSC) health care program, the incidence of classical PHPT increases with age as a whole cohort. For gender difference, the incidence ranged from 17.6 to 48.5 per 100,000 person-years among women, with corresponding figure from 7.2 to 20.9 among men, and higher prevalence is observed in postmenopausal women[5]. However, results of epidemiology of this disorder could vary widely due to different study designs, settings in which the studies are carried out, as well as the characteristics of the subjects recruited[6]. Similarly, with its debut in 2008 at the Third International Workshop on the Management of Asymptomatic Primary Hyperparathyroidism[1] and the following works carried out by enthusiastic researchers throughout all these years, the prevalence of Nc-PHPT has also been observed to vary widely among studies. With aims to identify prevalence and clinical features of patients with Nc-PHPT, researchers in a previous study had reviewed and analyzed the medical records from 179 women who had visited the health facility for purpose of screening for osteoporosis. After excluding patients who were taking medications such as bisphosphonates, diuretics, anticonvulsants and lithium, those suffering from kidney failure with estimated glomerular filtration rate (eGFR) < 40 mL/min/1.73 m^2 (calculated by Modification of Diet in Renal Disease Study formula) and those having serum concentrations of 25-hydroxy vitamin D (25(OH)D) < 30 ng/mL, the results showed that there were 14 patients who had met the diagnostic criteria of Nc-PHPT at a prevalence of 8.9% (14/156). Further analysis revealed that renal stones occurred in 28.6% of the patients with Nc-PHPT which was in contrast to only 0.7% in those without the diagnosis, and general fractures in 21.4% of the patients with Nc-PHPT versus 16.2% in those without. These findings had led the authors to conclude that Nc-PHPT possesses phenotypic presentation implying not being an "indolent" disorder due to the high rates of co-existence of renal stones and bone fractures[7]. On the other hand, in a more recent study that has been conducted retrospectively spanning 5 years in a cohort of 6,280 patients [mean age: 66 years (range, 16-100 years), gender: M/F:28/72%] who were referred for a bone mineral density (BMD) measurement in a referral metabolic center, only 11 patients (0.18%) were identified as Nc-PHPT after patients with eGFR < 60 mL/min/1.73 m^2 and 25(OH)D < 50 nmol/L (≈ < 20 ng/mL) had been excluded from analysis[8]. Furthermore, in a prospective study designed to evalu-

ate the prevalence of Nc-PHPT in 676 adults who would receive surgery for nodular lesions in thyroid gland and without a history of fractures or nephrolithiasis, initial diagnosis of Nc-PHPT was given to 46 patients (6.8 %) based on laboratory measurements (i.e. concomitant normocalcemia and higher PTH levels). However, further analysis after excluding those with lower vitamin D levels and/or eGFR had revealed a much lower prevalence rate at 0.74%, and the authors considered this rate of diagnosis more appropriate which agreed more with the surgical findings of altered parathyroid glands, among all the glands that had been fully explored by surgeons during the operations[9,10]. Nevertheless, with recognition and bearing in mind of Nc-PHPT as a distinct clinical entity, the diagnosis could reach a much higher rate among cohort originally diagnosed to have primary PHPT. In a cross-sectional, observational study designed to find the prevalence and clinical features of Nc-PHPT among a cohort of patients in a tertiary referral center originally diagnosed to be classical PHPT, the reviewing of medical record had identified 25 out of the 131 patients (prevalence 19%) to have fulfilled the diagnostic criteria for Nc-PHPT. Further analysis into clinical features showed high prevalence of nephrolithiasis (36%), fragility fractures (12%) and osteoporosis (25%)[11].

Several factors could have contributed to the wide variation in reported prevalence, including pre-specified selection of cohort (e.g. post-menopausal women and older patients), non-universal application of ionized calcium measurements, and varied threshold values for eGFR, vitamin D repletion status, serum calcium, and intact parathyroid hormone (i-PTH) concentrations. Also, during the evaluation and diagnosis of osteoporosis, PTH is commonly checked in order to find secondary causes for bone loss and such unavoidable confirmative diagnostic process could have biased the sample of patients with Nc-PHPT away from an unselected or general population in some of the studies[12].

Natural history of Nc-PHPT

In Nc-PHPT, hypercalcemia may be intermittent or evolving to classical PHPT with persistent hypercalcemic and the natural course of this disorder has always been an interesting issue to pursue. In a prospective follow-up study spanning over 6 years, 36 out of the 187 (19.3%) subjects who were originally diagnosed with Nc-PHPT became hypercalcemic. The changes occurred within 2 years in 24 of these 36 subjects, and later than 4 years in another 2 of the 36 subjects. The authors recommended that Nc-PHPT patients be monitored on a long-term basis, since it is unlikely to predict when and who of the subjects with initial normocalcemia would become hypercalcemic[13]. In an aforementioned study[8] that was conducted in a retrospective way among a total of 6,280 patients who were referred for an assessment of BMD, the natural course of development of Nc-PHPT was determined and the variability of serum calcium compared with a group of patients with classical PHPT and also with a control group consisting of 300 individuals having normal eGFR and being vitamin D replete. Two patterns of hypercalcemia variability were identified during the follow-up period: persistent normocalcemia and intermittent hypercalcemia. Of the 11 patients diagnosed with NcPHPT, only 4(0.06% of the whole population) had consistent normocalcemia throughout, but none had consistently high PTH concentrations, vitamin D replete status, as well as normal eGFR. Intermittent hypercalcemia was observed in the other 7 Nc-PHPT subjects. With these findings, the authors considered that, if the guidelines for the diagnosis were strictly applied, the prevalence of Nc-PHPT in this population would be zero[8].

Pathophysiology underlying Nc-PHPT

Target organ resistance to the actions of PTH

has long been raised as one of the main potential pathophysiological changes underlying Nc-PHPT. Studies have shown inadequate suppression of PTH secretion in response to an oral calcium load in Nc-PHPT as compared to the classical PHPT counterpart. Also, there were lower renal tubular calcium reabsorption, ability of PTH to reduce tubular phosphate reabsorption and stimulate 1,25-dihydroxyvitamin D (1,25(OH)2D3) synthesis, indicating also a resistance to PTH actions at renal level[14].

In an earlier study with aims to evaluate the response of PTH secretion to rising serum calcium levels, the dynamic changes in PTH concentrations to an oral calcium loading test were assessed in patients with hypercalciuric nephrolithiasis (n = 17) who had presented elevated PTH irrespective of the serum ionized calcium levels assessed at baseline. Blood samples were collected at baseline (0 min) and at 60 and 180 min after 1 gram of calcium was administered, and concentrations of serum PTH, total calcium, ionized calcium, 1,25(OH)2D3 were determined. Patients were stratified into normocalcemic (N = 9) or hypercalcemic (N = 8) group according to the initial ionized calcium levels. In the normocalcemic group, mean PTH levels at 0-, 60- and 180-min (95 ± 76, 56 ± 40, 57 ± 45 pg/mL, respectively) did not differ from those in the hypercalcemic group (130 ± 75, 68 ± 35, 80 ± 33 pg/mL, respectively) after the calcium loading, but were significantly higher than healthy controls (n = 6), despite a similar elevation in ionized calcium levels after 60- and 180-min vs baseline in all 3 groups. Mean 1,25(OH)2D3 levels were similar in the 3 groups. Additionally, 5 of the 9 normocalcemic patients presented a significantly higher concentration-time curve for serum PTH (area-under-the-curve derived from the study time frame at 0-, 60-, and 180-minute) than the other 4 patients and the healthy controls, indicating altered dynamics with non-suppressible PTH secretion in response to a similar calcium elevation at least in some of these patients. The authors concluded that there might exist a primary dysfunction of the parathyroid gland, suggesting a disturbance in calcium-sensing set point in the glands of normocalcemic patients[15].

It has been also postulated that resistance to the effect of PTH on renal tubular reabsorption of calcium may have contributed to higher urinary calcium excreted (hypercalciuria) in subjects with Nc-PHPT, which may partially play a role in the formation of urolithiasis in certain patients who are vulnerable to this complication of Nc-PHPT[16].

Diagnosis of Nc-PHPT

The diagnosis of Nc-PHPT is primarily based on a biochemical profile consisting of above-normal serum iPTH levels and concomitant normocalcemia, though with the latter mostly sitting at the upper end of the reference range. The measurement of i-PTH level (inclusion of full amino acid sequence 1-84 of the hormone) should be the one preferred to other fragments of PTH due to stable metabolism of the intact one (e.g. C-terminal PTH has much longer half-life in circulation in patients with kidney disease due to its primary metabolism site being in the kidneys)[17]. Serum calcium can be assessed as either albumin-corrected total or ionized concentrations when available. In ambiguous cases, the use of serum ionized calcium is favored over total serum calcium since ionized levels are more frequently elevated than total calcium levels in cases of PHPT, better correlated with PTH level and adenoma size, which weighs more when giving such a diagnosis[18]. To enhance the reliability of the diagnosis, an exclusion of secondary hyperparathyroidism due to underlying chronic kidney diseases (which first leading to imbalance in calcium and phosphorus metabolism, vitamin D deficiency, and could then be followed by a compensatory elevation in PTH concentrations) or medication-induced alteration in PTH secretion (e.g. diuretics, lithium, denosumab,

bisphosphonates, anticonvulsants, and phosphorus) is always demanded[19].

Since deficiency of vitamin D may contribute to activation of parathyroid gland with increased synthesis and secretion of PTH, it is prudent to evaluate the vitamin D status at the time of making a diagnosis to rule out hypovitaminosis D, which when present, may require supplement of this hormone with the expected normalization of overly secreted PTH when replete. Evidence derived from multiple studies had suggested a serum 25(OH) D level of 30 ng/mL or above be used to define vitamin D sufficiency state since serum PTH levels showed a plateau at approximately this vitamin D level, at which bone turnover markers are noted to be stable[20]. This strategy would help not only establish a correct diagnosis of Nc-PHPT at the beginning but also will facilitate setting of future plans regarding follow-up and/or treatment of Nc-PHPT when clinically indicated[21].

Another clinical scenario that may cause secondary Nc-PHPT could be encountered in patients who had received gastrectomy for various causes (most commonly gastric cancer and bariatric surgery). It has long been noted that a high rate of osteoporosis and fracture could develop in patients who had received gastrectomy for gastric adenocarcinoma[22,23]. Significant loss of BMD and increased risk of fracture have also been observed in patients who had received bariatric surgery, be it sleeve gastrectomy or Roux-en-Y gastric bypass procedure[24]. In addition to mechanical unloading of the skeleton after the weight loss as one of the underlying mechanisms of reduced BMD, the deficiency of calcium and vitamin D due to malabsorption of nutrients may eventually lead to an increased demand in PTH synthesis and secretion, with consequent development of secondary hyperparathyroidism.

In a previous retrospective study conducted in 140 patients who had received Roux-en-Y gastric bypass surgery, the researchers had found that hyperparathyroidism occurred in 5% of the patients as soon as 2 weeks after surgery, and the rate increased to 21% (30/140) at one year. In those 45 patients (32%) who had presented 25(OH)D deficiency (< 20 ng/mL) at initial postoperative assessment, their levels continued to be low as compared to the rest of the study population at one year. Among the 30 subjects who presented with hyperparathyroidism at study-end of one year, only two were diagnosed to be true primary hyperparathyroidism with both increased PTH levels and hypercalcemia, while most others presented with normocalcemia. This normocalcemia might have been obtained and maintained only at the expense of calcium stores in bone under the effect of excessive PTH, which increases osteoclast activity leading to the breakdown of bone[25]. In a more recent study that had prospectively evaluated the prevalence and predictive factors of persistence of secondary Nc-PHPT in 201 patients who had already had the diagnosis before surgery and undergone Roux-en-Y gastric bypass on vertical-banded gastroplasty, the periodic follow-up at 6, 12, and 18 months had found that 24% of the study subjects had persistence of Nc-PHPT into the study end of 18-month. Further analysis revealed that, in the majority rest of the patients, a successful pre-surgical dietary control (defined as leading to a loss of at least 10% of the initial overweight with subsequent weight maintenance for at least 6 months) that had been achieved no longer than 5 years before surgery determined the successful recovery from hyperparathyroidism within 6 months after the surgery. In those with persistence of Nc-PHPT, the PTH levels were still significantly higher than those who had recovered within 6 months after surgery (56.6 ± 2.2 vs 40.3 ± 1.5 mg/dL, $p < 0.05$), and there was a non-significant trend for lower vitamin D levels throughout the follow-up (baseline: 25.5 ± 2.5 vs 35.6 ± 1.8 ng/mL, 18-month: 32.1 ± 0.9 vs 43.7 ± 1.2 ng/mL), while the serum calcium levels were within normal range and

comparable with each other. From these findings, the authors concluded that evaluation and treatment of vitamin D insufficiency and the presence of secondary Nc-PHPT before bariatric surgery are recommended[26].

Clinical presentations in patients with Nc-PHPT

With rarity of the typical presentations caused by hypercalcemia (nausea and anorexia, cognitive impairment and irritability, and musculoskeletal manifestations)[27], and the wide application of multichannel biochemistry auto-analyzer, hyperparathyroidism-associated hypercalcemia is often an incidental diagnosis in the general population, and a higher diagnostic rate could thus be deviated to specific population who receive planned evaluation for clinical features including osteoporosis in postmenopausal women or in subjects having urolithiasis, both of which are considered to be the classical features in patients with classical PHPT. Similarly, with high rates of either of these two target-organ disorders that frequently accompany Nc-PHPT, there are good reasons to justify a potential diagnosis of Nc-PHPT when further investigations into such clinical presentations are aggressively pursued[7,11].

Health consequences of Nc-PHPT

In classical PHPT, concerns have been given to the consequences caused by prolonged exposure to both excessive PTH concentrations and hypercalcemia over different systems, notably urolithiasis, renal function impairment, disorder of bone mineral density that may cause osteoporosis and fracture, and metabolic disorders including glucose and lipid disorders that might be relevant to the development of pro-atherogenic changes and even cardiovascular (CV) events which have been observed to increase in hyperparathyroidism status as compared to the general population[28-32]. Not to be neglected, similar clinical attention should also be paid to patients with Nc-PHPT who have higher circulating PTH concentrations that may have direct impact on multiple, especially the CV, systems, despite absence of persistent hypercalcemia[33-37].

Bone health in subjects with Nc-PHPT

In Nc-PHPT, patients are frequently noted to present adverse bone health outcomes. A previous clinical study including 37 peri-menopausal and post-menopausal women had found that 57% of the cohort had osteoporosis and 11% fragility fractures. Assessment of BMD showed preferential bone loss at the lumbar spine (34%) and hip (38%)[38]. Even higher rates of bone disorders had been identified in another study which had recruited 63 patients with Nc-PHPT who would receive parathyroidectomy as a surgical cohort (88.7% women, median age 67 years), and 51% of the study subjects were found to have osteopenia and 41% osteoporosis[39]. Of note is that selection bias may have existed in studies recruiting populations consisting predominantly of peri- or post-menopausal women who potentially have a higher risk for development of osteopenia/osteoporosis independent of calcium and parathyroid status.

Comparable rate of fractures has been observed between subjects with Nc-PHPT and those with classical PHPT. In a retrospective study, rates of osteoporosis (25%) and fragility fractures (12%) in patients with normocalcemia were not statistically different from those in the hypercalcemic counterpart (32.5% and 13.2%, respectively)[11].

Hypovitaminosis D can be corrected with supplement of vitamin D3. A randomized clinical trial conducted in patients with PHPT had shown that 2,800 IU (70 μg) cholecalciferol/day for 6 months had effectively raised 25(OH)D from 20 ng/mL to 38 ng/mL, which was accompanied by significant decrease in i-PTH levels and improved lumbar spine BMD[6,40].

Urolithiasis in subjects with Nc-PHPT

Another clinical feature that deserves attention is the presence of urolithiasis, which may lead to impaired renal function if not treated in time.

In patients with classical PHPT, cross-sectional observation studies had found the prevalence of urolithiasis ranging between 17 and 21%[6], and the rate may rise to more than 50% in prospective study that had systematically screened patients who are diagnosed with PHPT[41]. Similarly, high rates of urolithiasis varying between 18% and 36% in subjects with Nc-PHPT were also noted in observational studies, figures that are significantly higher than those in healthy population which varied between 5% and 11%[7,17,29,42-45]. In a retrospective study evaluating both rates of urolithiasis and bone fracture among a cohort of 70 patients with PHPT (33 normocalcemic and 37 mild hypercalcemic), the results had revealed similar rate of urolithiasis in both groups (Nc-PHPT vs classical PHPT: 18.2 % vs 18.9%, p = 0.937), which was also true for the rate of previous history of bone fracture in normocalcemic patients when compared to the hypercalcemic counterpart (15% vs 10.8%, p = 0.726). These findings implicated that Nc-PHPT may not be an indolent disorder, with potential complications that need to be investigated and treated whenever indicated, despite absence of persistent hypercalcemia[42].

Hypercalciuria appears when the filtered calcium load exceeds the maximum ability of renal tubular reabsorption of calcium induced by PTH. One of the sequelae of increased daily urine calcium excretion is the potential for formation of insoluble calcium salts (calcium oxalate or calcium phosphate) in the urinary tract that may ultimately result in formation of nephrolithiasis or nephrocalcinosis[46]. In addition to the finding of higher activated 1,25(OH)2D levels in stone formers, there also existed a positive correlation between 24-hour urinary calcium excretion and 1,25(OH)2D levels in this study. The cause why stone-formers in PHPT have high 1,25(OH)2D levels is not yet clear, since PTH levels are not different in the two groups with and without higher 1,25(OH)2D levels. High 1,25 (OH)2D levels may increase intestinal calcium absorption which, when combining the effect of excessive PTH on bone resorption, could predispose to a greater filtered load of calcium in kidneys and hypercalciuria, then subsequent formation of urolithiasis[47]. Another mechanism of hypercalciuria may be related to calcium sensing receptors (CaSR) in the kidney[48-52]. Physiologically, CaSR functions as a direct inhibitor of para-cellular calcium permeability in the thick ascending limb and directly controls renal tubular calcium reabsorption. Polymorphisms in the CaSR gene itself presenting with different sensitivities to extracellular calcium may result in varying renal reabsorption and urinary calcium excretion[53,54]. One of the physiological functions of 1,25(OH)2D is to regulate CaSR and renal calcium channel expression which influence calcium reabsorption in the distal renal tubules[55,56]. One possible mechanism is that stone formers have dysregulation of the 1-alpha hydroxylase or 1,25(OH)2D 24-hydroxylase enzymes[57,58], an enzyme that inactivates 1α,25(OH)2D3 and, when in deficiency, may cause elevated 1α,25(OH)2D3 concentrations. This pattern of increased vitamin D levels in its active form is similar to the biochemical profile observed in patients with "idiopathic hypercalciuria" and suggests that stone formers in patients of PHPT could have risk factors not only limited to the functional disorders in the parathyroid gland per se[59]. However, whether similar mechanisms could be applied to patients with Nc-PHPT is debatable since neither total nor free form 25(OH)D levels are found to be higher in patients with Nc-PHPT than those in normal control subjects in a study aiming to comparing the status of and defining the pathophysiological role played by these hormones in patients with Nc-PHPT. It was noted that free form of 25(OH) D levels were in fact lower in the disease group than

the controls, and, along with an inversed correlation with i-PTH found in this study, the authors had concluded that a true vitamin D deficiency status may exist that predisposes patients with Nc-PHPT to a higher i-PTH level[60]. With the above research findings given, hypercalciuria per se may be only one of the multiple factors predisposing certain patients vulnerable to becoming stone formers in either classical PHPT or Nc-PHPT[61]. In a study that had compared the clinical and laboratory findings between the normocalcemic and mild hypercalcemic variants, all the patients recruited had a urinary calcium/creatinine (Ca/Cr) ratio of < 240 mg/g Cr that signified the absence of hypercalciuria, while the rates of urolithiasis in both groups were comparable (18.2% vs 18.9%, $p = 0.937$)[41]. In another study that was not specifically designed to evaluate the rate of urolithiasis but rather a role that parathyroid scintigraphy may play in enhancing the sensitivity of localization for pre-operative assessment, results from the laboratory tests had revealed both normal 24-hour urinary calcium excretion amount and serum 25(OH)D levels in patients with Nc-PHPT, as compared to patients with classical PHPT who had normal serum 25(OH)D but higher 24-hour urinary calcium levels[62].

For diagnostic purpose, ultrasonography (USG) of the urinary tract, as used in classical PHPT or other cases with urolithiasis, is also recommended as a practical tool to identify presence of renal stones in patients with Nc-PHPT due to its being a low-cost examination and not causing radiation exposure to the patient. Computed tomography (CT) may be considered alternative diagnostic modality when calculi are < 3 mm in diameter, which are usually not detectable on USG. However, CT should not be used routinely due to the risk of radiation exposure, and is reserved in cases with a high clinical suspicion of nephrolithiasis but negative findings on USG and abdominal x-rays.

Cardiometabolic disorders relevant to higher PTH levels

Classical hypercalcemic PHPT is associated with increased rate of CV disease risk factors, including hypertension, dyslipidemia, obesity, impaired glucose intolerance, diabetes mellitus (DM), and metabolic syndrome (MetS)[63,64]. Both hypercalcemia and excessive parathyroid hormone concentrations could have been associated with deleterious consequences in this regard[35,65,66]. Previous studies had demonstrated that parathyroidectomy could ameliorate CV risk factors in patients with mild or severe classical PHPT[67,68]. Similar findings of higher CV risk factors carried in patients with Nc-PHPT have also been observed. In a study conducted among a cohort of patients having classical PHPT (n = 81) or Nc-PHPT (n = 32), similar high rates of traditional CV risk factors including hypertension (61.7% vs 62.5%), hyperlipidemia (27.2% vs 31.3%), and DM or impaired fasting glucose (32.1% vs 19%, non-significant p values in all three parameters) were found between the two groups, although higher rate of CV or cerebrovascular disease existed in the classical group as compared to the normocalcemic counterpart (24.7 vs 3.1%, $p = 0.007$). In addition, arterial stiffness that was assessed by pulse wave velocity and vascular compliance indices did not show difference between the two groups. In this study, additional laboratory parameters of interest had found a higher urinary calcium excretion amount in the classical versus the Nc-PHPT patients (mean ± SD: 311 ± 144 vs 242 ± 139 mg/24h, $p = 0.003$), while both levels of serum 25(OH)-D and 1,25(OH)2-D were comparable[69]. Similar study investigating into the metabolic profile in patients with Nc-PHPT (n = 25), classical PHPT (n = 24), and age, gender and BMI-matched healthy controls (n = 30) had found no difference in the prevalence of MetS, glucose intolerance (DM or impaired glucose tolerance), history of hypertension, and prescription of antihypertensive medications between the two

hyperparathyroidism groups, while patients with Nc-PTHP had significantly higher prevalence of glucose intolerance, previous history of hypertension and prescription of anti-hypertensive medications as compared to the control group. In this study, the 24-hour urinary calcium excretion amount in the Nc-PTHP patients was not different from that in the hypercalcemic counterpart (212.71 ± 22.91 vs 281.70 ± 129.65 mg/24h, $p = 0.052$), as was finding in 25(OH)-D levels (17.04 ± 11.32 vs 13.51 ± 9.01 ng/mL, $p = 0.331$)[36].

As a critical risk factor for CV diseases, higher blood pressure (BP) has long been observed to be associated with PTH levels[70,71]. In a hospital-based study conducted in China which had enrolled 940 patients, the investigators had retrospectively surveyed results of the biochemical measurement of serum PTH and calcium level and found that, when subjects with normocalcemia and normal or higher PTH levels were analyzed (total number 307), 11 patients (3.6%) fulfilled the diagnosed of Nc-PHPT after interfering causes such as the use of thiazide diuretics, lithium, vitamin D deficiency, chronic kidney disease, hypercalciuria, and malabsorption syndrome had been excluded. Characteristics between the two groups with normal or high PTH did not differ in age, sex, BMI, as well as biochemistry profile including serum calcium, 25(OH)-D, creatinine, fasting plasma sugar (FPS), triglycerides (TG), total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), and low density lipoprotein cholesterol (LDL-C). However, a significant difference exists for both systolic (SBP) and diastolic BP (DBP) levels with higher readings in the Nc-PHPT group as compared to the normal PTH counterpart (SBP (141.9 ± 20.2 vs 131.2 ± 16.5, $p = 0.041$) and DBP (85.2 ± 12.4 vs 76.8 ± 10.3, $p = 0.026$), respectively. After adjustment for all potential confounders, risks (OR and 95% CI) of higher SBP and DBP in Nc-PHPT patients were 1.035 (1.000, 1.071) and 1.063 (1.004, 1.125), respectively ($p < 0.05$). Since PTH has been noted to play a significant role in BP rise, an aggressive therapeutic intervention aimed to normalize PTH in patients with Nc-PHPT would be a prudent strategy of management[72]. Other study investigating into the association between different PTH levels and BP had found a similar correlation between the two parameters of interest, and meanwhile hemodynamic study had revealed a direct relationship between PTH and systemic vascular resistance which was observed during the dynamic vasoconstriction response induced by upright posture[73].

To find whether surgical removal of parathyroid gland(s) with reduction of PTH levels would bring about comparable outcomes regarding the cardiometabolic parameters in a group of Nc-PHPT patients (N = 35), a prospective study has been conducted to compare those obtained from a counterpart of classical PHPT (N = 60). Traditional cardiometabolic risk factors were assessed, as were the changes in the Framingham cardiovascular risk score (CRS) before and 6 months after parathyroidectomy. At study entry, the rates of DM, dyslipidemia, hypertension, obesity, insulin resistance (IR), osteoporosis, and history of fractures were similarly increased in the hypercalcemic PHPT and Nc-PHPT groups ($p > 0.05$), which were higher than those in the controls (N = 60, selected from population-based screening programs, with subjects of DM and hyperparathyroidism excluded, $p < 0.05$). After parathyroidectomy, BP, serum TC, and homeostasis model assessment-insulin resistance index were decreased in both hyperparathyroid groups ($p < 0.05$). While baseline Framingham CRS was lower in the controls (5.74 ± 3.24, $p < 0.05$), it was noted to decrease in both normocalcemic (11.98 ± 10.11 vs 7.37 ± 4.48) and hypercalcemic (14.62 ± 11.06 vs 8.05 ± 7.72) PHPT groups after parathyroidectomy. The authors concluded that, both normocalcemic and hypercalcemic PHPT patients had similarly increased CV risk factors and parathyroidectomy had ameliorated

their severity in both groups[74].

Treatment of Nc-PHPT

Surgical treatment

Surgical intervention studies in patients with Nc-PHPT had found that the lesion(s) may present as a single adenoma, multiple adenomas, or multi-gland hyperplasia of the gland, just as may be encountered in the classical PHPT.

Prior to surgery in candidate patients with classical PHPT, USG and radionuclide scintigraphy scanning are routinely utilized in an attempt to localize parathyroid lesion(s). However, studies have shown that imaging in Nc-PHPT is less successful in giving diagnosis compared with classical PHPT and this certainly will pose an additional challenge from a surgical perspective[75]. Patients with Nc-PHPT have been shown not only to have higher rates of multi-glandular disease but also smaller lesions than those with the classical PHPT variant[76,77] and these features may contribute to the lower sensitivity of preoperative imaging in patients with Nc-PHPT[78]. A recent study that had tested the sensitivities of different imaging modalities had identified that four-dimension computed tomography had performed better than USG or Tc-99-Sestamibi scintigraphy in patients with Nc-PHPT with the following figures: 55.6%, 95% CI 23.1-88; 22%, 95% CI 0-44.9, and 11.1%, 95% CI 0-31.6, respectively[79].

In a study conducted in a total of 616 patients diagnosed with primary hyperparathyroidism, 119 (19.5%) of the cohort who had met the diagnostic criteria of Nc-PHPT had received surgical treatment for underlying parathyroid disorder. The surgical findings indicated that in subjects with Nc-PHPT, there were significantly higher rate of multi-gland hyperplasia (12% vs 4%, p = 0.002) and smaller gland size as compared with those in classical PHPT[80]. The primary goal of parathyroidectomy is to bring PTH levels back to normal range, since the long-term excessive exposure to PTH constitutes the major cause of urolithiasis formation and BMD reduction[81]. In classical PHPT, resection of pre-operatively identifiable parathyroid lesions can lead to a cure rate up to 99.2%[82]. Several studies have also shown clinical benefits in patients with Nc-PHPT after surgical removal of parathyroid lesions. In a cohort of 96 patients with Nc-PHPT, Lim et al[77] had found normalization of serum PTH levels in 93.8% of the patients at 6 months and further to 97.9% at 12 months, respectively. The rate of PTH normalization paralleled that obtained from patients with classical PHPT (N = 405) in the same study. However, not all studies have shown similarly high rate of PTH normalization after parathyroidectomy. In a prospective clinical study consisting of 71 patients diagnosed with Nc-PHPT, only 53.5% (38/71) had achieved normal serum PTH levels after parathyroidectomy that spanned over a median follow-up period of 23 months. It was also found that 53.5% (38/71) of this study cohort had multi-glandular lesions[39]. In another study comprising of 121 patients who were diagnosed with primary hyperparathyroidism, in patients with normocalcaemic variant (prevalence 13/121 = 10.7%) there was lower cure rate after surgery compared to the classical group (45% vs 93%, p=0.0006). In this study, a significantly higher rate of multinodular gland in patients with Nc-PHPT was also found as compared with the classical group (64% vs 13%, p = 0.0011)[83]. The relatively high prevalence of multi-glandular disease and smaller parathyroid glands reported in both these trials have been considered factors that may have lowered the sensitivity of preoperative parathyroid imaging study (dual-tracer scintigraphy with 99mTc-MIBI SPECT/CT) and hence the rate of surgical success. It was thus recommended that bilateral neck exploration should be performed in such population in order to improve the cure rate, even if the scintigraphy showed only single focus[84]. While some of these studies are relatively small and heterogeneous, parathyroid surgery has been shown

to correct PTH elevations in 45%-94% of patients with Nc-PHPT[12]. Following surgery, improvements in BMD and renal stones are generally observed[39,85]. In studies applying the same surgical criteria used for patients with hypercalcemic PHPT, outcomes in those with Nc-PHPT suggested that parathyroid surgery appears to be effective in normalizing elevated serum PTH and decreasing adverse renal and skeletal outcomes[75].

Pertaining to the impact of parathyroidectomy on CV risk factors in Nc-PHPT, although a study had observed improvements in BP, serum TC levels, IR, and Framingham CRS following parathyroidectomy in a cohort of 35 patients, the limited study results do not encourage the advice of parathyroid surgery for the sole purpose of improving CV outcomes to be listed in the updated guidelines[74].

Evidences gathered up to date had led the Fourth International Workshop Guidelines for the Management of Asymptomatic Primary Hyperparathyroidism to bringing up the following recommendations from surgical perspectives: monitoring the disease process by both biochemical and clinical features, including annual measurement of serum calcium, phosphate, alkaline phosphatase, 25(OH)D, creatinine, blood urea nitrogen and PTH concentrations, and BMD assessment by DEXA method every 1-2 years. It does not recommend performing parathyroid surgery until specific criteria are met (e.g. worsening of BMD or fracture, occurrence of kidney stone or nephrocalcinosis indicating progression of disease). When required, the surgical criteria for patients with classical hypercalcemic PHPT can be extended to those with the normocalcemic variant[85].

Medical Treatment

When surgery is not feasible due to various reasons, medical therapy with alendronate, a bisphosphonate which inhibits bone resorption and increases bone density has been shown to be effective in reducing bone loss. In a prospective, randomized clinical trial that compared effectiveness of combining alendronate and cholecalciferol versus cholecalciferol alone in postmenopausal women with Nc-PHPT (n = 15 in each group), BMD evaluated at lumbar spine, total hip, and femoral neck showed improvement in the combination therapy group after 12 months' therapy, an effect that was not observed in patients receiving cholecalciferol alone[86]. Another medical therapy regarded as effective in patients with Nc-PHPT is to decrease the risk of nephrolithiasis with the use of calcimimetics (e.g. cinacalcet, the only such agent available as far), which act as activators of the CaSR at level of both the parathyroid and the kidney and are capable of inducing a suppression of PTH secretion with a reduction also in serum calcium levels. In a pilot study of prospective and randomized design that was conducted in ten subjects (5 males: mean age 55.6 ± 8.3 years, 5 females: mean age 62.4 ± 11.8 years, all postmenopausal except one) who were diagnosed to have PHPT and also harboring nephrolithiasis, treatment with potassium citrate and allopurinol, and in combination with cinacalcet or not regardless of the serum calcium levels (4 hypercalcemic and 6 normocalcemic) were administered in a random fashion. Dosage of cinacalcet has been adjusted that was tailored to individual patient to obtain a reduction of PTH within normal range. At the end of the study period spanning a total of 20 months, cinacalcet treatment resulted in a statistically significant reduction in the overall number of stones as compared to the baseline (3 ± 2.5 vs 2.3 ± 2.8; $p = 0.045$) and in the larger diameter of the stones (0.47 ± 0.38 vs 0.805 ± 0.21 cm, $p = 0.002$) as measured by USG in both calcemic variants, while no such differences were found in patients not taking cinacalcet. The reduction in the number and size of kidney stones achieved by administration of cinacalcet is considered to be caused by bringing PTH levels effectively to within the normal limits[87]. With specific and dis-

tinct treatment target obtained through these two different agents (improved bone mass by bisphosphonates, and reduced calcemia and urolithiasis by calcimimetics), and potential that could be extrapolated from study results derived from the classical PHPT, it would make sense to combine the two drugs as a regimen in patients with Nc-PHPT who suffer from both bone loss and nephrolithiasis who are not feasible to undergo surgical intervention[61,88].

Conclusion

With the multiple health consequences associated with Nc-PHPT that parallel those encountered in classical PHPT, it would be prudent for clinicians to bear in mind of making such diagnosis in subjects having history of lower BMD, fracture of bone, or urolithiasis, the clinical features that potentially may harbor this milder form of parathyroid gland disorder. When time takes toll, the exposure to excessive PTH may ultimately cause inevitable target organ damage in a proportion of patients and periodic follow-up evaluation with vigilant watch on any of the development of relevant clinical presentations is recommended. However, with the currently data available which still lacks consensus regarding the optimal management of this relatively new and rare clinical phenotype, a reasonable approach would be to tailor treatment to the individual patient based on the presence of risk factors, including new or accelerated bone loss, formation of kidney stones, and development of CV disease. The reduction of PTH back to normal range obtained either by surgical or pharmacological intervention plays the key role in improving bone mass and reducing the burden of nephrolithiasis, two major complications that should be addressed aggressively and effectively in patients with Nc-PHPT to improve their quality of life[89,90].

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正常血鈣性副甲狀腺高能症 - 小型文獻回顧

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摘 要

典型的原發性副甲狀腺高能症皆以高血鈣症做為實驗室及臨床診斷之依據，但是近十餘年來，一種較少見的正常血鈣性原發性副甲狀腺高能症已持續引起臨床關注，諸多研究的結果認為此疾病是典型病例的初期或較輕微的表現型，在長期追蹤過程中發現，部份個案持續維持正常血鈣，其他則可呈現波動但逐漸升高、終至於高血鈣程度之疾病發展史。在持續性副甲狀腺素濃度過高的影響下，即使血鈣濃度正常，臨床表現仍類似於典型原發性副甲狀腺高能症患者，其罹患骨質疏鬆，骨折，尿路結石，及腎功能因而受損的風險明顯增加，因此，在追蹤病程發展的過程中，應警覺注意是否已有相關併發症之呈現，考慮予以治療。當前述受到副甲狀腺素調控的終端器官已有明顯臨床表徵時，以手術治療摘除副甲狀腺腺瘤或增生性病變後，將副甲狀腺素濃度降回正常範圍，可以獲得改善；若患者不適合接受手術治療，可嘗試藥物療法，包括作用於副甲狀腺細胞之鈣離子受體，可以減少副甲狀腺素分泌的擬鈣劑，對於減少尿路結石的數目及體積大小已證實有其臨床成效。另外，用於治療骨質疏鬆症的雙磷酸鹽類藥物則可減緩骨質流失，降低骨折風險。兩者合併使用的臨床效益則需待更多臨床實驗證實。