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REVIEW ARTICLE

Elevated parathyroid hormone levels after successful parathyroidectomy for primary hyperparathyroidism: a clinical review

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Abstract

Introduction Surgery for primary hyperparathyroidism (PHPT) is traditionally deemed to be successful if serum calcium levels return to normal 6 months after parathyroidectomy. Regular monitoring of serum calcium and parathyroid hormone (PTH) in the follow-up of patients after parathyroidectomy for PHPT has drawn attention to the presence of a normocalcemic group of patients with elevated PTH (NCePTH) during the post-operative period. The etiological factors and mechanisms underlying this condition, its consequences, and the possibility of treatment are the object of this study.

Materials and methods We conducted an unlimited PubMed search updated on March 31, 2017, which yielded 1628 results. We selected 37 articles, 33 of which included cases of NCePTH in their series and 23 performed statistical studies to assess factors associated with NCePTH.

Results The maximum mean prevalence of NCePTH in the various series was 23.5%, ranging from 3 to 46%. Many factors were associated with NCePTH. The most important were higher pre-operative PTH, low pre-operative 25 (OH) D3, lower pre-operative creatinine clearance and greater adenoma weight. The origin of NCePTH may be multifactorial, since several factors were implicated in the etiology. NCePTH does not seem to be related to an increase in PHPT recurrence, although this possibility should not be dismissed. Vitamin D deficiency should be corrected. Treatment with calcium supplements seems to be clearly beneficial.

Conclusion The prevalence of NCePTH is high. The causes of secondary hyperparathyroidism should be investigated carefully. Patients require treatment and long-term follow-up.

Keywords Parathyroid hormone · Hyperparathyroidism, Primary · Parathyroidectomy · Post-operative period · Post-operative hyperparathyroidism · Review

Introduction

Success in surgery for primary hyperparathyroidism (PHPT) is traditionally defined as the return to normal serum calcium levels 6-month post-parathyroidectomy. In patients who are hypercalcemic post-surgery, the presence of elevated parathyroid hormone (ePTH) is taken to indicate persistent or recurrent disease.

However, the regular monitoring of serum calcium and PTH in the follow-up of patients undergoing parathyroidectomy for primary HPT has drawn attention to a group of patients with post-operative normocalcemic ePTH (NCePTH). The incidence and/or prevalence of post-operative normocalcemic hyperparathyroidism varies from study to study, due to the differences in the surgical techniques used and in the timepoints when the measurements were made.

Several etiological factors and mechanisms have been proposed for NCePTH. The long-term consequences for health of this ePTH are unclear: it is not known whether treatment may reduce or eliminate this condition [1], which has been described up to 14 years after parathyroidectomy [2].

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In this paper, we present a literature review in an attempt to answer these questions.

Materials and methods

We conducted an unlimited PubMed search updated on March 31, 2017, with the following search strategy: [(elevated) or (elevation) or (high) or (upper) or (raised)] and (parathyroid hormone) and [(post-operative) or (after parathyroidectomy) or (after surgery)]. We obtained 1628 results. After analyzing the abstracts for relevance, we selected a total of 37 articles which included cases of post-operative NCePTH or analyzed factors associated with the condition, along with their references.

Thirty-three articles presented series which included cases of post-operative NCePTH, and 23 conducted statistical studies to assess factors associated with the condition.

Results

Prevalence of post-operative normocalcemic PTH elevation

We analyzed 33 series [2–34] which reported the prevalence of ePTH at one or more timepoints during the post-operative period following parathyroidectomy (Table 1).

Elevated PTH and elevated serum calcium were taken as indicating failure or recurrence of HPT, and patients presenting these criteria were excluded from the analysis.

In the series with more than one PTH measurement during follow-up, taking the minimum and maximum values of each study, the prevalence of NCePTH ranged from 3% in measurements made between 3 and 12 months [8] and 1 year [15] to 46% in a measurement made between 7 and 12 months [21].

Dividing the time interval between parathyroidectomy and NCePTH assessment into three periods, the minimum and maximum prevalences of NCePTH were:

1. At less than 3 months: between 12 [8] and 43% [17, 19].
2. Between 3 and 6 months: in Beyer's group, the frequency of ePTH was 13% in patients treated with calcium carbonate and calcitriol compared with 43% in patients who were treated with calcium carbonate alone [21].
3. At more than 6 months: 3 [8] to 46% [21].

In all, 6699 patients were included in the studies (Table 1). In reports in which PTH was measured on more than one occasion during follow-up, the prevalence of ePTH was taken to be the highest value resulting from dividing the number of patients with NCePTH by the total number of patients analyzed at the time of the study, since patients with ePTH in the early post-operative period were not necessarily the same as the ones with ePTH at a later date [6, 8, 10, 14, 18, 20–23, 26]. Thus, considering the maximum prevalence of each series, 1498 out of 6365 patients (23.5%) had NCePTH.

In most studies, the prevalence of NCePTH declined over time. In the studies that measured PTH at least twice, the prevalence was lower in the second (or last) measurement: at 6 months [24–32], at 12 months [6, 10, 18, 23, 29], at a mean of 16 months [14], at 18 months [23], at 2 years [7], or at 5 years [15].

In four series, however, the prevalence of ePTH increased over time:

- Yamashita et al.'s study of 90 patients, with a prevalence of 26% at 1 week and 43% at 1 month [19].
- Yen et al.'s study of 290 patients, with prevalences at 1 week, 3 and 6 months of 15.9, 25, and 25.2%, respectively [20].
- Beyer et al.'s study of 86 patients, with prevalences of 11% at < 30 days, 31% at 1–3 months, 28% at 4–6 months, and 46% at 7–12 months [21].
- Rianon et al.'s study of 112 patients, with prevalences of 12% at 6 months and 13% at 12 months [30].

Although the possible explanations for the decrease in the prevalence of NCePTH were not discussed in the studies, it may be due to the progressive correction over time of factors such as the bone mineralization deficit, vitamin D deficit, and the administration of calcium supplements. Prospective studies assessing this behavior are now needed.

Predictors of post-operative normocalcemic PTH elevation

Twenty-three studies included statistical analyses to evaluate pre- and post-operative factors associated with NCePTH (Table 2). In this section, we analyze the predictors of post-operative NCePTH that reached statistical significance in the univariate and multivariate analyses (Table 2).

In the univariate analyses, 18 of 23 studies showed a higher pre-operative PTH concentration in NCePTH patients [6–8, 10, 11, 13, 17–19, 21–24, 26, 27, 29, 32, 33]. Other factors associated with NCePTH in comparison with patients with normal PTH in several studies were:

- Higher pre-operative serum calcium [6, 7, 19, 26, 32].
- Lower pre-operative 25(OH)D3 [6, 18, 19, 29].
- Higher alkaline phosphatase level [3, 6, 8, 10, 11, 19, 24].
- Higher osteocalcin [6, 10, 11, 18, 30].
- Greater adenoma weight [6, 10, 11, 21, 29, 31].

Table 1 Prevalence in the literature of normocalcemic elevation of PTH after successful parathyroidectomy for primary hyperparathyroidism

References	Total no. patients	Study design/level of evidence[a]	No. patients with normocalcemic elevated PTH/total patients (%)
Duh et al. [3]	141	–/4	First week: 24/94 (26) 2 weeks to 6 months: 33/84 (40)
Irving et al. [4]	77	–/4	5–16 years: 28/75 (37)
Mulder et al. [5]	48	R/4	Not specified: 20/48 (42)
Bergenfelz et al. [6]	82	P/3	8 weeks 20/82 (24) 1 year: 13/78 (17)
Tisell et al. [7]	51	P/3	10 days and 3 months: 16/51 (31) 12 years 24 months: 4/51 (8)
Mandal et al. [8]	78	P/3	1 week: 9/78 (12) 3–12 months: 2/78 (3)
Carneiro et al. [9]	320	R/4	Not specified: 31/320 (9.7)
Westerdahl et al. [10]	17	P/3	8 weeks: 6/17 (35) 1 year 17% (3)
Denizot et al. [11]	97	P/3	At least once in 6 months: 30/97 (30)
Vestergaard et al. [12]	83	R/4	Early post-operative phase: 23/83 (28)
Carty et al. [13]	380	P/4	> 5 months: 105/374 (28.3)
Mittendorf et al. [14]	85	P/3	10–14 days: 23/85 (27) Average 16 months: 7/20 (8)
Westerdahl et al. [15]	102	P/3	1 year: 16/97 (16) 5 years: 9/80 (11)
Ferrer et al. [16]	57	P/3	4–12 weeks: 18/57 (31.6)
Dhillon et al. [17]	49	R/4	1 week–13 months: 21/49 (43)
Nordenström et al. [18]	99	R/4	8 weeks: 28/99 (28) 1 year: 19/99 (19) 5 years: 11/83 (13)
Yamashita et al. [19]	90	P/3	1 week: 23/90 (26) 1 month: 39/90 (43)
Yen et al. [20]	290	R/4	44/276 (15.9) 3 months: 36/144 (25) 6 months: 37/147 (25.2)
Beyer et al. [21]	86	R/4	< 30 days: 8/75 (10.6) 1–3 months: 20/65 (30.8) 4–6 months: 8/29 (27.6) 7–12 months: 7/15 (46) Total?: 25/85 (29.4)
Wang et al. [22]	768	R/4	Within several weeks of surgery: 114/768 (15)
Mizrachi et al. [23]	76	R/4	1 months: 19/76 (25) 12 months: 16/76 (21) 18 months: 13/76 (17)
Ning et al. [24]	611	P/3	1 week: 105/611 (17.2) 6 months: 57/611 (9.3)
Heller et al. [25]	194	R/4	At the last follow-up (1 to 24 months -median, 5 months-): 23/194 (12)
Solorzano et al. [26]	505	R/4	Any time during follow-up (> 6 months): 160/505 (31.7) At the last follow-up (6–165 months): 108/505 (21)
Mazzaglia et al. [27]	678	R/4	At 2 weeks: 201/678 (30)
Goldfarb et al. [28]	96	P/3	Follow-up ≥ 119.5 months: 38/96 (40)
Carsello et al. [29]	300	R/3	6 months: 62/300 (21) ≥ 1 year: 29/300 (9.7)
Rianon et al. [30]	112	R/3	6 months: 13/112 (12) 12 months: 9/71 (13)
Lang et al. [31]	161	–/3	6 months: 63/161 (39)
Pathak et al. [32]	129	P/3	2 weeks: 20/129 (16) 6 months: 16/113 (14)

Table 1 (continued)

References	Total no. patients	Study design/level of evidence[a]	No. patients with normocalcemic elevated PTH/total patients (%)
Stuart et al. [2]	171	R/4	< 2 years: 16/171 (9.3) > 2 years: 14/171 (8.2)
Duke et al. [33]	119	R/3	1 month or more: 30/119 (25)
Lavryk et al. [33]	547	R/3	6 months: 128/538 (23.8) 12 months: 65/276 (23.6)
Total	6699		Maximum prevalence: 1498/6365 (23.5%)

R retrospective, *P* prospective

[a]Level of evidence: OCEBM Levels of Evidence Working Group. "The Oxford 2011 Levels of Evidence". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

Table 2 Predictors of post-operative normocalcemic PTH elevation

Univariate analysis	Multivariate analysis
Higher pre-operative PTH [6–8, 10, 11, 13, 17–19, 21–24, 26, 27, 29, 32, 33]	Higher pre-operative PTH [19]
Lower pre-operative 25(OH)D3 [6, 18, 19, 29]	Lower pre-operative 25(OH)D3 [19, 31]
Higher serum calcium [6, 7, 19, 26, 32]	
Higher pre-operative BUN [3]	
Lower glomerular filtration [33]	
Higher creatinine [3, 11, 30, 31, 33]	
Higher alkaline phosphatase level [3, 6, 8, 10, 11, 19, 24]	
Higher osteocalcin [6, 10, 11, 18, 30]	
Large tumors [3]	
Greater adenoma weight [6, 10, 11, 21, 29, 31]	Greater adenoma weight [21]
Lower phosphorus [8, 19]	
Older age [8, 21, 22, 24, 26, 30, 32]	Older age [31]
Propeptide of type I collagen [10]	
Lower bone mineral content [10, 11]	
Higher urinary calcium [10]	
Higher Z score [11]	
Double adenoma [14]	
Lower post-operative 1,25 (OH)2D3 [17]	
Black race [14, 29]	
Musculoskeletal symptoms [14]	
Lower creatinine clearance [19]	Lower creatinine clearance [19]
Prevalence of vitamin D deficiency [19]	
Vitamin D supplementation [21]	Vitamin D supplementation [21]
Bilateral explorations [22]	
Multiple hypercellular parathyroids [22]	
Lesser median percent decrease in IOPTH [22, 23, 32]	
Higher median final IOPTH [22, 23]	
High 10-min IOPTH [31]	High 10-minute IOPTH [31]
Lower median initial post-operative calcium [22]	
Lower median post-operative Vit D-25 [22]	
Higher recurrent primary HPT [24]	
Higher post-operative creatinine [26]	
Routine four-gland exploration [27]	
Male gender [28]	
Higher BMI [29]	

Normocalcemic patients with elevated PTH vs normal PTH

- Older age [8, 21, 22, 24, 26, 30, 32].

Three studies [19, 21, 31] performed multivariate analyses, which revealed significant differences in patients with NCePTH in relation with those who had normal PTH, as follows:

- Lower 25OHD [19, 31].
- Higher pre-operative PTH [19].
- Lower creatinine clearance [19].
- Vitamin D supplementation [21].
- Greater adenoma weight [21].
- Older age [31].
- Higher 10-min IOPTH [31].

Most studies found that renal function was normal and did not differ significantly between groups, though there were a number of exceptions [6, 18, 19, 21, 26, 33, 35].

Patients assigned to minimally invasive surgery were more likely to present ePTH than those who underwent bilateral neck exploration [2]. In Mazzaglia`s series of NCePTH [27], however, there was no significant difference in ePTH incidence between patients who received focused-approach surgery and those who underwent a routine four-gland exploration.

Post-operative PTH kinetics

Mandal et al.'s study of immediate post-operative calcium and PTH observed that 9 (12%) of the 78 patients presented NCePTH. On the night of the operation, intact PTH levels were significantly higher in the group with secondary hyperparathyroidism (20 ± 6 vs 10 ± 2 pg/mL). One-week post-surgery, intact PTH levels rose in both groups. Total calcium concentration remained stable in patients without secondary hyperparathyroidism (9.1 ± 0.1 mg/dL), but fell significantly in patients with this condition (8.7 ± 0.2 mg/dL) [8].

Several authors have assessed the intraoperative dynamics of PTH in patients with post-operative NCePTH. Mizrachi et al. observed that PTH levels fell less during surgery in the patients who would present NCePTH post-operatively than in those who would later present normal PTH (87.8 vs 83.7%, $p = 0.044$). PTH values were also higher in patients with post-operative NCePTH 20 min after adenoma excision (21.51 vs 30.16 pg/mL, $p = 0.037$) [23].

The evolution of post-operative NCePTH varied according to the studies analyzed. Lang et al. found that ePTH peaked at a time between 3 and 6 months [31]. Another study found a peak of ePTH after 2 months [11]. In general, as noted in the section on prevalence, ePTH tended to normalize over time [6, 7, 10, 14, 15, 18, 23, 24, 29, 32]. In Beyer et al.'s series, however, there was clearly an upward trend over time [21].

In most patients with elevated PTH, levels fluctuate over an extended period [26]. Nordenström et al. identified four subgroups of patients during a 5-year follow-up period in whom PTH levels were: (1) consistently normal; (2) initially elevated normalizing during follow-up; (3) variable, fluctuating between normal and elevated; and (4) consistently elevated. Patients with fluctuating PTH levels presented serum increased calcium and phosphate levels [18]. In the first 2-year post-surgery, Lang et al. found that more than half of patients had at least one increased PTH measurement and that PTH levels were persistently elevated in 5% of their sample [31].

Etiology

The etiology is a matter for debate, but it is probably multifactorial.

Among the etiologies proposed for the phenomenon of NCePTH are physiological variation in PTH due to relative post-operative hypocalcemia, vitamin D deficiency, fall in the glomerular filtration rate (GFR), altered calcium-sensing receptors in the remaining glands leading to a higher set-point for PTH secretion, reduced peripheral sensitivity to PTH, and renal calcium leak. We will now look at some of them in detail (Table 3).

Physiological variation in PTH

PTH may rise in response to changes in serum calcium. A reduction in ionized calcium activates the calcium receptor of the parathyroid cell, increasing PTH production.

Westerdahl et al. showed that patients with NCePTH responded to an oral calcium load 8-week post-surgery, thus demonstrating that the fall in PTH was not due to decreased calcium sensitivity [10].

Nordenström et al. reported that patients with sustained post-operative NCePTH levels in a PTH infusion test showed signs of decreased peripheral sensitivity to PTH due to PTH receptor dysfunction or down-regulation [35].

Taken together, these results suggest a possible relation between NCePTH and reduced calcium absorption at a specific point in time, and also that this phenomenon is reversible and transient [28].

Hungry bone

The presence of hyperparathyroidism reduces bone mass and may thus cause hungry bone syndrome. Patients with a higher pre-operative incidence of musculoskeletal symptoms have a higher incidence of post-operative NCePTH [14].

As noted above, univariate analyses in many studies have shown a significant association between post-operative

Table 3 Etiological factors of normocalcemic elevated PTH

Physiological variation in PTH due to reduced calcium absorption at a specific point in time [28, 35]
Hungry bone
Higher pre-operative incidence of musculoskeletal symptoms [14]
Pre-operative bone turnover and formation markers
Higher alkaline phosphatase level [3, 6, 8, 10, 11, 19, 24], osteocalcin [6, 10, 11, 18, 30], *Z* score and propeptide of type I collagen [10]
Lower phosphorus [8, 19], bone mineral content [10, 11]
Pre-operative or post-operative vitamin D deficiency [6, 18, 19, 29]
Fall in the glomerular filtration rate:
Reduced creatinine clearance [19]
Increased creatinine both pre-operatively [3, 11, 30, 31, 33] and post-operatively [26]
Other possible causes:
Impaired renal responsiveness to PTH
Renal leak of calcium

NCePTH and the following pre-operative bone turnover and formation markers (Table 2):

- Higher alkaline phosphatase level [3, 6, 8, 10, 11, 19, 24].
- Lower phosphorus [8, 19].
- Lower bone mineral content [10, 11].
- Higher osteocalcin [6, 10, 11, 18, 30].
- Higher Z score [11].
- Propeptide of type I collagen [10].

Patients with elevated levels of alkaline phosphatase presented improvements in bone mineral content at 1 year, but no improvements were seen in patients with normal post-operative PTH levels [10].

Rianon et al. observed a significant positive association between pre-surgery levels of serum osteocalcin and post-operative NCePTH, both 6 and 12 months after surgery. These results corroborate the hypothesis that persistent NCePTH despite calcium normalization after parathyroidectomy for primary HPT is the result of bone remineralization [30], which is known to cause hypocalcemia and raise PTH levels in the first years after parathyroidectomy. Silverberg et al. reported that the increase persists for 4 years at least [36]. The reduced serum calcium concentration is caused by the increase in calcium deposition in the bone. The presence of a hungry bone syndrome may lead to post-operative ePTH to maintain normal extracellular calcium levels [7].

Vitamin D deficiency

Vitamin D deficiency (serum 25(OH)D < 25 nmol/L) and insufficiency (serum 25(OH)D between 25 and 50 nmol/L) are highly prevalent all over the world [37].

The increased catabolism of vitamin D in hyperparathyroidism contributes to reducing vitamin D levels [38]. Several studies have demonstrated that patients with pre-operative NCePTH have lower 25 (OH) D3, suggesting the coexistence of secondary hyperparathyroidism [6, 18, 19, 29] and a higher prevalence of vitamin D deficiency [19]. Reductions in vitamin D-level post-surgery have also been recorded in patients with post-operative NCePTH and in patients, whose ePTH did not eventually return to normal. These findings corroborate the notion that at least some patients with NCePTH present a mild form of secondary hyperparathyroidism and hypocalcemia, due to low vitamin D levels and possibly also to bone remineralization [22].

A significantly lower incidence of NCePTH was also found in patients treated post-operatively with calcitriol [21].

Lewin et al. reported that most patients with vitamin D deficiency present resistance to the action of PTH and that treatment with vitamin D compounds can correct this resistance [39].

Fall in the glomerular filtration rate

Levin et al. suggested that serum PTH may surpass 65 mg/dL in patients with estimated GFR below 45 mL/min, but that there was no substantial effect on serum calcium and phosphate levels until estimated GFR fell below 20 mL/min. Interestingly, secondary HPT was observed in around 12% of patients with GFR > 80 mL/min/1.73 m^2, in 17% of patients with GFR of 70–79 mL/min/1.73 m^2, in 21% of those with GFR between 60 and 69 mL/min/1.73 m^2, and in 56% of those with GFR < 60 mL/min/1.73 m^2 [40].

NCePTH presented significant associations with reduced creatinine clearance [19] and increased creatinine both pre-operatively [3, 11, 30, 31, 33] and post-operatively [26].

Other possible causes

Several authors have attributed persistent NCePTH to impaired renal responsiveness to PTH [10, 17, 19, 35]. This

impairment may be due to PTH receptor down-regulation in patients with higher PTH concentrations prior to surgery [1].

Another factor to be considered is the renal leak of calcium, which may produce secondary HPT [1, 38].

Long-term implications

Recurrence

The first point at issue is to establish whether NCePTH leads to a recurrence of PHPT.

Most studies suggest that NCePTH after parathyroidectomy does not increase the risk of recurrence, since rates of recurrent PHPT are similar in patients with or without ePTH [3, 20, 28, 29, 31]. It has been suggested that post-operative NCePTH may be a dynamic, reversible, and transient clinical entity that does not predict recurrence [28].

However, other authors suggest that NCePTH may be the result of an incomplete parathyroidectomy or may signal a recurrence of PHPT [13, 18, 22, 24, 32]. Some authors have reported a statistically significant difference (4.8 vs 0%) [26]. Recurrent PHPT is reported in 1.6–7% of patients with persistent elevation of PTH after parathyroidectomy [13, 14, 18, 26, 31].

Specifically, patients with serum calcium levels ≥ 9.7 mg/dL 1 week after surgery [24] or ≥ 9.6 mg/dL at the first post-operative evaluation [22], together with a persistent ePTH, may have a significantly increased risk of recurrent disease. For example, Ning et al. found a recurrence rate of 16% in ePTH patients with post-operative calcium ≥ 9.7 mg/dL compared with 0% in those with calcium < 9.7 mg/dL [24]. Recurrent HPT was significantly higher in patients with ePTH (5.4%), than in patients with normal calcium and PTH levels (1.2%) [24]. In Wang et al.'s series, Three out of 38 patients with ePTH and calcium levels of 9.6 mg/dL or more developed recurrent HPT after 1 year, but none of the patients with ePTH and lower calcium levels did so [22].

As noted above, Solorzano et al. observed that patients with recurrent hyperparathyroidism had persistently increased PTH levels which did not fall below 70 pg/mL at any time in the post-operative period [26].

In the case of patients undergoing parathyroidectomy following PHPT, the differentiation between NCeHPT and recurrent HPT can only be confirmed when the patient presents both high serum calcium and PTH. Radiological localization can aid diagnosis.

It is increasingly common to operate on patients with normocalcemic PHPT. In the post-operative period, it may be impossible to distinguish between patients with persistent disease and those with NCePTH. This point was not raised in the articles reviewed. Performing radiological examinations might help to identify a parathyroid gland that is enlarged or presents increased uptake, but the definitive differentiation depends on the evolution of calcium over time, which is increased in the case of persistent or recurrent disease.

Other consequences

Like untreated patients with PHPT, patients with persistent post-operative NCePTH may have an increased risk of cardiovascular disease [6], ischemic heart disease and hypertension [12] compared with their normal PTH peers. However, Mandal et al. found no significant differences in heart disease between NCePTH and normal PTH groups [8]. The long-term impact of persistent NCePTH on bone health and renal function is unknown [38].

Pathak et al. found that NCePTH after curative parathyroidectomy may slow symptom improvement. At 6-week post-surgery, the proportion of patients who presented improvements was higher in the normal PTH group with respect to 14 out of 18 symptoms. The difference was statistically significant for four of the symptoms (anxiety, thirst, constipation, and polyuria). The difference for joint pain and irritability almost attained statistical significance ($p = 0.06$), but resolved at 6 months [32].

Follow-up

The literature review does not allow any general conclusions to be drawn about post-parathyroidectomy evaluation and follow-up. Usually, calcium and PTH levels at least are evaluated in the first post-operative visit. However, the scheduling of the subsequent controls varies considerably, and there is no consensus regarding the laboratory parameters that should be assessed.

In our view, post-operative evaluation of patients with NCePTH should include screening for factors that have been associated with ePTH, namely, kidney function, vitamin D levels, and bone mineral density. In addition, to assess the impact and prevalence of this phenomenon, patients should be followed up at least once a year for a minimum of 10 years [2].

It remains to be established whether post-operative ePTH is an early sign of recurrence, with a similar effect on the target organs (bone and kidney) as normocalcemic primary hyperparathyroidism, or a mere biochemical abnormality of no clinical significance. Until this matter is clarified, serum calcium, phosphorus, albumin, 25-OH vitamin D, creatinine, and PTH should be monitored at least once a year.

Oltman et al. propose a post-operative follow-up regime for PHPT involving determination of calcium, PTH, phosphorus, and creatinine levels 2 weeks post-operatively. Laboratory measurements are repeated at 6 months in patients with normal initial post-operative calcium and PTH levels, followed by a yearly calcium measurement thereafter. In patients with NCePTH, laboratory measurements are

repeated at 3 months. If the PTH elevation has resolved or is attenuated, levels are re-assessed at 6 months and calcium is measured yearly thereafter. If the PTH elevation presents an upward trend in the setting of eucalcemia, additional workup includes 24-h urine calcium and creatinine, serum creatinine, ionized calcium, magnesium, and 1,25-dihydroxyvitamin D measurements and another 25-hydroxyvitamin D measurement [38].

Prevention or treatment

Some authors have reported improvements in NCePTH with the use of oral calcium and vitamin D supplements.

Carty et al. prospectively followed the clinical development of 380 patients after parathyroidectomy [13]. Patients with elevated PTH at 5 months were assigned calcium supplements (calcium carbonate, 1 g twice daily). The authors reported a longer time to normalization of PTH in patients who did not take post-operative calcium supplementation than in those who started this treatment either 5 months or more post-surgery or immediately after the operation (781, 484, and 347 days, respectively). Although delaying treatment with calcium and vitamin supplements did not produce a clear benefit, patients who began taking these supplements immediately after surgery were far less likely to present increased serum PTH more than 5 months post-operatively. NCePTH was recorded in 15.1% of 126 patients taking long-term use of calcium supplements post-surgery, compared to 36.3% of patients who did not report receiving this treatment ($p = 0.0005$) [13].

In Beyer et al.'s study, the authors found that in cases of vitamin D deficiency, routine supplementation of vitamin D reduced the incidence of elevated PTH from 37 to 12% [21]. The problem with this retrospective study is that the variable calcium supplementation was not controlled. Nonetheless these findings corroborate those of earlier studies and favor the administration of aggressive vitamin D supplements in patients who have low 25-OH vitamin D levels [11, 22, 31, 41].

Vitamin D substitution was found to be beneficial in patients with persistently elevated post-operative PTH, who also improved BMD (both 33% radius and radius ultradistal) ($p < 0.05$) [42].

Yamashita et al. recommended pre-operative vitamin D treatment in cases of vitamin D deficiency, and calcium and vitamin D in patients with persistent NCePTH to limit the risk of osteoporotic bone fracture [19].

However, in Press et al.'s series of 1785 patients, the incidence of NCePTH after surgery for primary HPT was below 7%. This low percentage was related to the intense calcium supplementation, and no correlations were observed with pre-operative vitamin D levels. By protocol, all cases

Table 4 Analytical determinations in the follow-up of successful parathyroidectomy for primary hyperparathyroidism with elevated PTH

	1 week	1 month	6 months	1 year	Yearly[a]
Normal PTH	Calcium Albumin Phosphorus PTH Creatinine Glomerular filtration rate	Calcium Albumin Phosphorus PTH Creatinine Glomerular filtration rate Vitamin D	Calcium Albumin Phosphorus PTH Creatinine Glomerular filtration rate	Calcium Albumin Phosphorus PTH Creatinine Glomerular filtration rate Vitamin D	Calcium Albumin Phosphorus PTH Creatinine Glomerular filtration rate Vitamin D
	1 week	**1 month**	**Every 3 months**		
Elevated PTH[b]	Calcium Albumin Phosphorus PTH Creatinine Glomerular filtration rate	Calcium Albumin Phosphorus Magnesium PTH Creatinine Glomerular filtration rate 24-h urine calcium and creatinine Vitamin D Alkaline phosphatase	Calcium Albumin Phosphorus Magnesium PTH Creatinine Glomerular filtration rate 24-h urine calcium and creatinine Vitamin D Alkaline phosphatase		

[a]If bone densitometry was altered pre-operatively, it should be repeated annually

[b]When PTH normalizes, continue with follow-up: PTH normal

of NCePTH after surgery were treated with calcium supplements. No patient had a post-operative PTH > 91 pg/mL [43].

Grubbs et al. showed that administering ergocalciferol a mean of 28 days before parathyroidectomy to patients with vitamin D deficiency did not correlate with post-operative NCePTH. NCePTH did not differ between the three study groups (normal vitamin D, treated vitamin D deficiency and untreated vitamin D deficiency) [41].

Our study was based on a literature review, in which the predictive factors, etiological factors and the consequences of NCePTH were analyzed by the authors in a group of patients. This approach has obvious drawbacks such as the fact that it is impossible to identify single patients in the longitudinal analysis, their specific analytical data during their evolution, or the final prognosis.

Proposals

Our proposal for the follow-up and treatment of patients with elevated PTH in the post-operative period following parathyroidectomy for primary hyperparathyroidism is presented in Table 4 and Fig. 1.

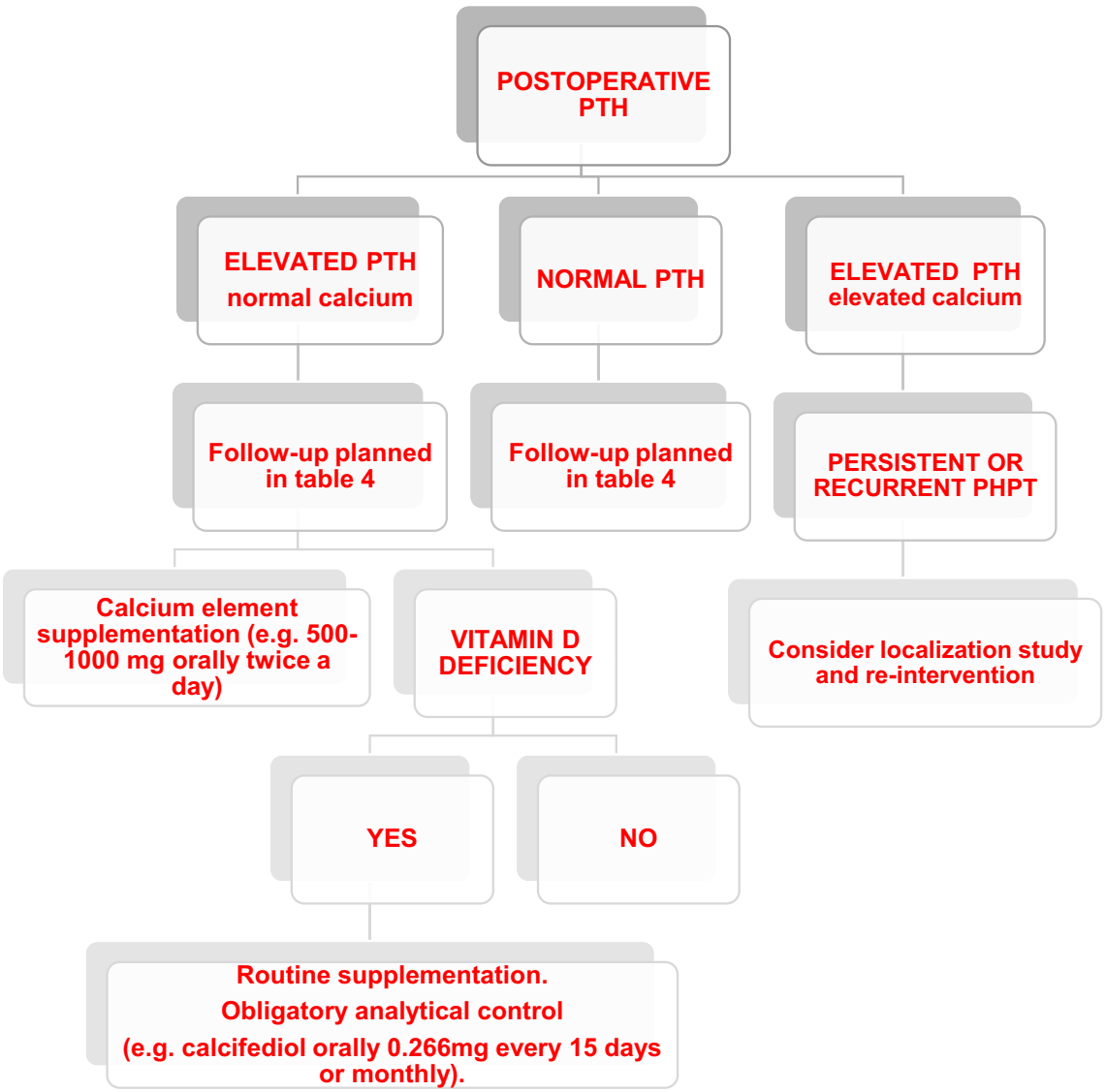

Fig. 1 Proposed treatment in patients with elevated PTH in the post-operative period after parathyroidectomy for primary hyperparathyroidism

Conclusions

The maximum mean prevalence of NCePTH following surgery for primary HPT was 23.5%, ranging from 3 to 46% in the series reviewed. Numerous pre- and post-operative factors have been associated with NCePTH, the most important being higher pre-operative PTH level, lower pre-operative 25(OH) D3, lower pre-operative creatinine clearance, and greater adenoma weight.

Several factors have been implicated in the etiology of NCePTH, and it seems that the condition may have a multifactorial origin. Particularly important are the physiological variation in PTH, bone hunger, vitamin D deficiency and decreased glomerular filtration rate.

NCePTH does not seem to be associated with increased recurrence of PHPT, although this possibility should be borne in mind. NCePTH appears to be associated with a higher incidence of cardiovascular disease.

After parathyroidectomy, all patients with NCePTH should be followed up and causes of secondary HPT should be ruled out. Although vitamin D treatment for these patients is not supported by all studies, vitamin D deficiency must be corrected. Calcium supplementation seems to be clearly beneficial in patients with NCePTH.

Compliance with ethical standards

Conflict of interest Authors declare that we have no conflict of interest.

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Ethical approval This article does not contain any studies with human participants or animals performed by any of the authors.

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