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How to manage an isolated elevated PTH?

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Abstract

The aim of this article is to discuss the diagnostic approach of an increased serum PTH concentration in a normocalcemic, normophosphatemic patient. Detection of this biological presentation is frequent in routine practice all the more that PTH reference values established in vitamin D replete subjects with a normal renal function are used by the clinical laboratories. The first step in this diagnostic approach will be to rule out a cause of secondary hyperparathyroidism (SHPT). Among these, the most frequent are vitamin D deficiency, very low calcium intake, impaired renal function, malabsorptions, drugs interfering with calcium/bone metabolism, such as lithium salts and antiresorptive osteoporosis therapies, hypercalciuria due to a renal calcium leak. If no cause of SHPT are evidenced, the diagnosis of normocalcemic primary hyperparathyroidism (PHPT) should be considered. A calcium load test is a very useful tool for this diagnosis if it shows that serum PTH is not sufficiently decreased when calcemia rises frankly above the upper normal limit. In a normocalcemic patient with hypercalciuria and a high serum PTH concentration, a thiazide challenge test may help to differentiate SHPT due to a renal calcium leak from normocalcemic PHPT. Beyond the discussion of this diagnostic flowchart, we also discuss some points about the merits and the difficulties of measuring and interpreting ionized calcemia and 24-h calciuria.

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Keywords: Parathyroid hormone; Vitamin D; Primary hyperparathyroidism; Secondary hyperparathyroidism; Hypercalciuria

Résumé

Le but de cet article est de discuter la démarche diagnostique d'une élévation de la PTH chez un patient normocalcémique et normophosphatémique. Cette anomalie biologique est retrouvée fréquemment en pratique clinique, et cela d'autant plus fréquemment que les valeurs de référence de PTH utilisées par le laboratoire ont été établies chez des sujets non déficitaires en vitamine D et dont la fonction rénale est normale. En effet, la limite supérieure de la normale établie chez ces sujets est généralement plus basse que celle retrouvée dans des populations apparemment en bonne santé mais dont le statut vitaminiq ue D et le débit de filtration glomérulaire n'ont pas été préalablement évalués. La première étape de cette démarche diagnostique est d'éliminer les différentes causes d'hyperparathyroïdie secondaire. Parmi ces causes, les plus fréquentes sont un déficit en vitamine D, des apports calciques très faibles, une fonction rénale altérée, une malabsorption, la prise de médicament interférant avec le métabolisme phosphocalcique et osseux comme les sels de lithium, les diurétiques de l'anse, ou les traitements de l'ostéoporose inhibant la résorption osseuse, une hypercalciurie due à une fuite rénale de calcium. Si aucune cause d'hyperparathyroïdie secondaire n'est retrouvée, le diagnostic d'hyperparathyroïdie primitive normocalcémique peut être envisagé, en particulier lorsque la calcémie est dans la partie haute des valeurs de référence. Le test de charge calcique est un outil très important pour ce diagnostic lorsqu'il montre une PTH insuffisamment freinée lorsque la calcémie (si possible ionisée) s'est élevée très significativement au-dessus de la limite supérieure de la normale. Chez un patient normocalcémique et hypercalciurique avec une PTH élevée, le test au thiazidique est un autre outil intéressant pour différencier une hyperparathyroïdie primitive normocalcémique d'une hyperparathyroïdie secondaire due à une fuite rénale de calcium. Au-delà de la discussion sur cette démarche diagnostique, nous aborderons également les problèmes de dosage et d'interprétation des mesures de la calcémie ionisée et de la calciurie des 24 heures.

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Mots clés : Hormone parathyroïdienne ; Vitamine D ; Hyperparathyroïdie primitive ; Hyperparathyroïdie secondaire ; Hypercalciurie

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An isolated increase of serum parathyroid hormone (PTH) concentration (i.e. associated with a normal calcium and phosphate serum level) is a frequent finding in routine clinical practice. It most frequently reflects a situation of secondary hyperparathyroidism (SHPT), but may be caused by a so-called “normocalcemic” primary hyperparathyroidism (PHPT). Before going further and discussing the management of this biological situation, we believe that one important question needs to be addressed.

1. How the PTH reference values are (or should be) established, and are they comparable from one laboratory to another?

Assuming that “elevated PTH” means a serum PTH level above the upper limit of the reference values, this is indeed an important question in light of the present article.

The first step in establishing reference values for serum PTH is to recruit a healthy reference population. Exclusion criteria for this population can be defined as any situation possibly inducing an increase or a decrease in PTH concentration. Some of these conditions, such as the use of a treatment and/or the existence of a symptomatic disease are easily identified at inclusion, but others are often asymptomatic and may be ignored if not searched. Among these conditions, vitamin D insufficiency (low serum 25-hydroxyvitamin D [25OHD] concentration) is highly frequent in the general population [1] and should thus be prevalent in an otherwise apparently healthy group. If one admits that vitamin D insufficiency may induce an increase in PTH secretion, and that serum PTH concentration decreases (normalizes) when these patients are given vitamin D [2], it is then logical to exclude subjects with vitamin D insufficiency from a reference population recruited to establish normative data for serum PTH. This point has been strongly recommended in the two most recent guidelines on the diagnosis and management of asymptomatic primary hyperparathyroidism (PHPT) published in 2009 [3] and 2014 [4]. However, as vitamin D insufficiency is usually asymptomatic, excluding vitamin D insufficient subjects from the reference group requires measuring the 25OHD level beforehand in all subjects, a practice which greatly complicates the establishment of reference values and had not been taken into account in most previous studies which provided serum PTH reference values for different immunoassays [5–9]. By doing this, however, we have demonstrated in several studies that excluding subjects with a low serum 25OHD concentration from a reference population decreased the upper normal limit for serum PTH by 20–35% depending on the assay considered [1,10–13]. A point that deserves a consensus however is the 25OHD cut-off below which a 25OHD concentration may be considered “low”. Indeed, at least two 25OHD cut-offs, 20 and 30 ng/mL, are debated. The 20 ng/mL cut-off is supported by the Institute of Medicine (IOM) report which is targeted towards the general (healthy) population in order to define optimal vitamin D intake (which intake is necessary so that most individuals in the general population have a 25OHD concentration at or above 20 ng/mL?) [14]. The 30 ng/mL cut-off is supported by the Endocrine Society and is intended for the care

Table 1

Reference ranges (ng/L) proposed by kit manufacturers of 10 PTH kits compared with the reference ranges established in our laboratory with the same kits in the same group of 240 healthy subjects (120 women, 120 men) with a 25OHD concentration > 30 ng/mL and an eGFR (MDRD formula) > 60 mL/mn/1.73 m². For all these assays, our upper normal value is lower than those of the manufacturer. The difference is sometimes slight (Architect, or Vitros), but sometimes huge (access 2). It is most often of magnitude of 25–30%. The obvious conclusion is that, according to the normal range that is used, a given patient might be considered as having a normal (manufacturer normal range) or high (our normal range) PTH concentration, despite the fact that the same assay is used [10].

Assay (manufacturer)	Manufacturer normal range	Our normal range
<i>2nd generation assays</i>		
Architect (Abbott)	15–68	16–65
Immulite (Siemens)	12–65	0.5–50
Vitros (Ortho-clinical)	7.5v53	11–48
Liaison N-tact (DiaSorin)	17.3v73	21–68
TIPTH (Scantibodies)	14–66	8–50
Elecsys (Roche Diagnostics)	15–65	14–50
DiaSorin IRMA (DiaSorin)	13–54	7–36
Access 2 (Beckman-Coulter)	12–88	10–47
<i>3rd generation assays</i>		
CA-PTH (Scantibodies)	5–39	7–31
Liaison 3 ^o G (DiaSorin)	5.5–38	5–26

of the patients [15]. In our opinion, this 30 ng/mL cut-off value is the one that should be used when recruiting “vitamin D replete” subjects to establish PTH normal values. This is not because we think that everybody needs a 25OHD concentration above 30 ng/mL, but rather because many reports and meta-analyses have concluded that serum PTH concentration may still be elevated in some subjects if their 25OHD concentration is below 28–32 ng/mL [16], and decreases when these subjects are given vitamin D [2,17]. Another point which should be taken into account in the inclusion criteria for establishing PTH reference values is renal function. It is generally accepted that PTH may rise in some patients when estimated glomerular filtration rate (eGFR) is below 60 mL/mn/1.73 m² [18]. Such eGFR may be present but ignored in some apparently healthy subjects, especially in those aged more than 60 years. In a recent paper, we have compared the PTH reference range provided by the manufacturers of 10 commercial PTH kits to those obtained in an apparently healthy group of 240 adult subjects (120 women, 120 men) with a serum 25OHD concentration > 30 ng/mL and an eGFR > 60 mL/mn/1.73 m² (MDRD formula) [12]. As shown in Table 1 for each of the 10 PTH kits, the upper value of our reference range was lower than those of the manufacturer. It must be underlined that in this study, as well as in our previous studies on the same topic [1,10–13], blood samples were obtained in the morning (7:30–9:30 AM) after an overnight fast. This seems of importance as the upper limit of the PTH normal range derived from healthy persons in whom blood samples were obtained in a non-fasting state over a larger interval of time was higher than in our studies [19] (see discussion in [1]).

Another issue concerning PTH reference values is whether the reference population should be stratified according to various factors, such as age, gender, menopausal status, body mass index, and race. Indeed, it has been reported for example that

serum PTH is higher in black than white people [20], in overweight than in lean individuals [1], and in the elderly than the young [21]. However, 25OHD is also known to be usually lower in black than white people [20], in overweight than in lean persons [1], and in the elderly than in the young [21] and this can explain part of the higher PTH concentration found in blacks and elderly people. These differences in vitamin D status between young and old, whites and blacks, lean and overweight individuals should thus be reevaluated in vitamin D replete subjects. We found for example in [1] that the PTH concentration differed by weight status in the French general population (higher in overweight) but that this difference disappeared in subjects with higher vitamin D status ($25\text{OHD} \geq 30 \text{ ng/mL}$).

As stressed above, using PTH reference values which take vitamin D status into account will decrease the upper limit of normal when compared to what is generally obtained in an apparently healthy general population. The evident consequence is that above-normal concentrations will be found more often in clinical practice. On the one hand, this will improve the diagnostic sensitivity of PTH measurements as serum PTH will be more frequently elevated in patients with either true SHPT or PHPT, but, on the other hand, it must be evaluated whether this may reduce specificity (i.e. find a “high” PTH concentration in patients without any reason for an increased PTH secretion). In a study published more than 10 years ago, we have verified that PTH reference values established in vitamin D replete subjects do not induce a decrease in diagnostic specificity, by showing that there were no more than the expected 3% of above-normal PTH concentrations in 360 consecutive osteoporotic patients for whom no reasons for high PTH were found after examining their medical chart and extensive biological evaluation [22].

2. Which biological parameters should be included in an exploration of calcium/phosphorus metabolism?

The response to this question is not easy as disorders of calcium/phosphorus are potentially numerous. The challenge is to determine a panel of biological parameters that is able to detect a maximum of anomalies at a minimal cost. A first-line exploration may include serum calcium, phosphate, PTH, and 25OH, 24-h calciuria being added, specially in patients presenting with urolithiasis or nephrocalcinosis. Measurement of serum creatinine and report of eGFR should be included systematically. A “second-line” exploration which includes complementary measurements will be performed if an anomaly (including an isolated elevated PTH) is detected in the first-line exploration without the possibility to propose a definitive diagnosis. In this case, it is mandatory for an optimal interpretation of the results to measure again the parameters measured in the first-line exploration. The most frequent “second-line” parameters should be 24-h calciuria (if not included in the first-line exploration), phosphaturia and creatininuria (and calculation of TmP/GFR), serum alkaline phosphatase, TSH, and (sometimes) magnesium. Dietary and supplementary calcium intake should be recorded. Serum ionized calcium, FGF23, and calcitriol are important tools but their assays are difficult to perform and should be reserved to specialized laboratories. Clinical units specialized in bone and mineral

metabolism should be identified as they can perform dynamic tests or genetic research if needed. An exploration of phosphocalcic metabolism should always be done in the morning after an overnight fast, with the exception of an emergency situation (i.e. acute symptoms of hyper- or hypocalcemia). Indeed, ingestion of foods that contain significant amount of calcium will increase calcemia and decrease PTH. Salt, protein as well as glucids may increase calciuria. Furthermore, calcemia, PTH, and phosphatemia undergo marked circadian variations. The following paragraphs underline some points that should be taken into account when interpreting the most common biochemical parameters.

2.1. Calcemia

Serum total calcium concentration is the first-line parameter. It corresponds to the sum of ionized calcium (around 50%), calcium complexed to different anions (around 5%), and calcium bound to proteins, essentially albumin (around 45%). Only ionized calcemia, the “active” fraction, is tightly regulated. In case of hypo- or hyperalbuminemia, discrepancies between ionized and total calcemia may occur and it is frequent to use formula to correct total calcemia in function of albuminemia, especially in case of hypoalbuminemia. Ionized calcium concentration is however highly influenced by the pH as the affinity of albumin for calcium increases when the pH increases, and decreases when the pH decreases. Assuming the same serum albumin and total calcium concentration, ionized calcemia will be thus lower in case of alkalosis and higher in case of acidosis. Ionized calcemia at the patient’s pH is the « gold standard » but its measurement requires strict sample handling (avoiding tourniquet use) and preanalytical precautions, especially the respect for anaerobiosis. To compensate for a variation of pH due to (frequent) preanalytical problems, it is possible to obtain a pH-adjusted ionized calcemia for a theoretical pH of 7.40. However, this supposes that the patient’s pH is close to 7.40, and this correction is not valid in case of acido-basic disorder, such as found in patients with chronic kidney disease for example [23]. Although less relevant than the direct measurement at the patient’s pH, pH-adjusted ionized calcemia for a theoretical pH of 7.40 has been shown to detect mild hypercalcemia better than total calcemia, corrected or not for albuminemia [24]. Having said that, ionized calcemia remains the “gold standard” to evaluate disturbances of calcium metabolism. Assuming adequate preanalytical and analytical conditions, patients with either low or high (even mildly) ionized calcemia should be considered as being hypo- and hypercalcemic, respectively and, thus, do not correspond to the situation discussed in the present article (“isolated” PTH) even if their total albumin-corrected calcemia is normal.

2.2. Calciuria

Calciuria may be measured on 24-h urine collections (in this case, it represents intestinal absorption of calcium), or on the second morning void obtained after an overnight fast (in this case, it is expressed as a ratio to creatininuria and represents

an index of bone resorption as the measured calcium may only come from bone).

Twenty-four-hour calciuria is expressed in mg/24 h or, better, in mg/kg/24 h. Normal values for men and women are < 4 mg/kg/24 h. It must be underlined that this “norm” has been established in normal subjects whose calcium intake was close to 1000 mg/day [25] (in case of very low calcium intake, a 24-h calciuria of 4 mg/kg/24 h should be regarded as a frank hypercalciuria). It is thus important to evaluate the calcium intake the day of the 24-h collection, which is difficult in routine practice and seldom done. It is also interesting to measure urine sodium and urea as a high sodium or protein diet may increase calciuria. If one adds to these points the difficulty to obtain a true 24-h urine collection, it becomes obvious that interpreting calciuria is not so easy.

2.3. Phosphatemia and phosphaturia

Hemolyzed samples must be avoided for the measurement of phosphatemia due to the high phosphate content of red blood cells. Contrary to calcemia which is stable throughout life, reference values for phosphatemia vary with age (typically: 1.50–2.30 mmol/L in newborns less than one month; 1.50–2.00 mmol/L from one month to 2 years; 1.40–1.70 mmol/L from 2 to 12 years; 1.00–1.50 mmol/L from 12 to 16 years, and 0.80–1.40 in adults). Phosphaturia (not to be prescribed in the « first-line » evaluation) should be measured in case of hypophosphatemia to determine whether this anomaly is due to a renal leak or to another cause. In this situation, rather than phosphaturia alone, it is recommended to calculate the phosphate reabsorption rate or (better) the TmP/GFR. A low TmP/GFR in a hypophosphatemic patient signs the renal nature of the hypophosphatemia.

3. Diagnostic approach of an « isolated » elevated PTH

As indicated above, the upper limit of our proposed PTH reference values established in vitamin D replete subjects with a normal renal function is usually lower than what is proposed in most laboratories. Their use could thus induce an increase in the detection of high serum PTH in otherwise normocalcemic patients. In most cases, this will reflect SHPT and the first step will be to search for causes of SHPT. In fact, any reason for a trend toward a decrease in ionized calcium may be associated with an increase in PTH secretion. This does not mean that the PTH concentration is always above the upper normal value. Indeed, assuming a PTH concentration of (for example) 20 ng/L (normal values of 12–50 ng/L) in a patient with a normal calcium balance, and assuming that this patient becomes vitamin D deficient, its PTH level may rise to 30–40 ng/L, which, although being a “normal” value, may be considered as a secondary increase in PTH, and will return to 20 ng/L when the vitamin D stock will be replenished.

3.1. First step in the diagnostic approach of an isolated increased PTH: rule out causes of SHPT

There are many potential causes for a secondary increase of PTH (i.e. to compensate for a decrease in calcemia) allowing to keep a normal calcemia. The most common are listed below:

- vitamin D deficiency/insufficiency. In theory, 25OHD has been measured in the “first-line” exploration. If this was not the case, then it must be measured in the “second-line” exploration. To exclude vitamin D insufficiency to be responsible for the increase in PTH concentration, we usually require the 25OHD level to be above 30 ng/mL (or even more). In case of a 25OHD concentration lower than this threshold, it is advisable to refuel the patient with large amounts of vitamin D3 during a short period and retest vitamin D status after this repletion period. It should be understood that the present goal is to exclude SHPT due to vitamin D insufficiency, and not to consider that the patient needs absolutely a 25OHD level of more than 30 (or 40 ng/mL). We thus take into account the measurement uncertainty of 25OHD testing and we have previously shown that to be sure that a measured value corresponds really to a concentration above 30 ng/mL, one needs to obtain a measured concentration of 35–40 ng/mL depending on the 25OHD assay used [26]. We must underline that the decrease of the PTH concentration may take some time and that optimisation of calcium intake is also mandatory;
- very low calcium intake. It is important to evaluate calcium intake by means of a dietary questionnaire (many are available freely on internet) and try to modify calcium diet or prescribe calcium pills in case of insufficient intake;
- malabsorptions. This includes celiac disease (measure anti-transglutaminase antibodies), cystic fibrosis, inflammatory bowel disease, malabsorptive bariatric surgery (i.e. Roux-en-Y bypass) among other conditions;
- impaired renal function. As soon as the GFR decreases below 60 mL/mn/1.73 m², PTH may increase (far before an increase in phosphatemia or a decrease in calcemia) in some patients [27];
- hypomagnesemia. While hypomagnesemia may be responsible for a transient hypoparathyroidism, it is also able to induce resistance to PTH (phosphatemia is usually high-normal in this case) in some patients [28];
- pseudohypoparathyroidism. While calcemia is usually low and phosphatemia usually high in patients with pseudohypoparathyroidism, they may be normal (low-normal calcemia and high-normal phosphatemia) in some patients [29];
- “Hungry bone syndrome”. Frequent situation with a mild presentation after parathyroid- or thyroid surgery, which usually resolves with high doses of calcium and vitamin D prescribed for a short period;
- interacting drugs that may induce an increase in PTH. Besides lithium salts that may increase PTH through a switch in calcium-sensing, all antiresorptive drugs may also induce an increase in PTH secretion due to their effect on bone resorption, and, thus, a decrease of the calcium flux from bone to plasma. The most potent antiresorptive drugs (anti-RANKL

Mab, bisphosphonates) are more likely to do that, but less potent drugs, such as raloxifene might also candidate for this effect in rare patients. It is thus important, in patients with fractures and/or a low bone mineral density, to exclude a secondary cause of secondary osteoporosis, and thus to prescribe a biological exploration, before the initiation of an antiresorptive treatment. It is also important to underline that bisphosphonates have strong remanent effects that may last for a long time after completion of the treatment. In other words, a mildly increased PTH in a patient that has stopped a bisphosphonate treatment a few weeks (or even months) ago may be explained by the long-lasting effect of the drug;

- hypercalciuria due to a renal leak of calcium. Many tubular anomalies may cause hypercalciuria through a defect in renal calcium reabsorption and thus induce a trend toward hypocalcemia, which, invariably, will be compensated by an increase in PTH. This situation, initially named “renal” hypercalciuria, may be caused by drugs, such as loop diuretics or excessive salt intake (measure natriuria), excess tea or coffee consumption, by genetic defects (many mutations of genes, such as *paracellin 1*, *CLCN5*, *TRPV5*, *OCRL1*, *NPT2c*, *NKCC2*, *ROMK1*, have been identified as potential candidates for hypercalciuria often associated with complex sets of anomalies), or may be “idiopathic”. Thiazide diuretics are often effective in reducing or even normalizing calciuria if well tolerated;
- rare causes of (possible) SHPT, such as Paget disease of bone, severe hypothyroidism . . . should also be ruled out

3.2. Second step: only if no cause of SHPT are identified, and especially if calcemia is in the upper half of the normal values, the diagnosis of normocalcemic PHPT may be suspected

Besides the usual hypercalcemic presentation, normocalcemic PHPT (i.e. with both normal total and ionized calcemia) is now a recognized variant of PHPT [30]. Two different theories have been proposed to explain normocalcemia in this situation. Lowe et al. hypothesized that these patients represent a first phase of the disease in which patients have not yet become hypercalcemic [31]. Maruani et al., in an elegant study, demonstrated that a significant proportion of patients with normocalcemic PHPT presents an end-organ resistance to the hypercalcemic effects of PTH [32]. Since these pioneering papers, several reports have described this phenotype [33] and a recent population-based study concluded that it may be much more frequent than initially thought, even if not all causes of SHPT, such as described above, were ruled out [34]. It was thus recommended in the last guidelines on the diagnosis and management of asymptomatic PHPT to monitor patients with normocalcemic PHPT in the same way the hypercalcemic PHPT patients are monitored, and thus to propose parathyroid surgery to those who present one or several criteria for parathyroidectomy [4]. We agree with this recommendation all the more that we have recently shown that normocalcemic PHPT patients with osteoporosis increase their bone mineral density during the year

following parathyroidectomy to the same extent than hypercalcemic PHPT patients [35].

However, the definitive diagnosis of normocalcemic PHPT is challenging. Assessing ionized calcium is important as it is frequent to find a mildly high-ionized calcemia in a patient with a normal total calcemia and a high PTH level [24]. In this case, the patient may be categorized as having hypercalcemic PHPT, and thus does not correspond any more to the topic that is discussed in the present article. A special attention should be paid to patients with a normal calcemia, a high PTH, and an increased calciuria. In this situation, we usually propose a thiazide challenge test with the aim to differentiate normocalcemic PHPT and SHPT due to a renal calcium leak. This test is fully described in [36]. After two weeks of thiazide treatment (50 mg/day), a new set of laboratory tests is performed. If the initial hypercalciuria was due to a renal calcium leak, calciuria and PTH will be significantly reduced (and often normalized) without hypercalcemia. If the initial hypercalciuria was due to normocalcemic PHPT, then, hypercalcemia may be unmasked with only a moderate decrease in PTH concentration, which usually remains elevated. It must be noted that salt intake must be strictly limited during the thiazide treatment period for the test to be efficient. In the other situations of high PTH and normal calcemia, and after exclusion of causes for SHPT (or if the thiazide challenge did not allow a definitive conclusion), a calcium load test should be performed in our opinion. In the context of a differential diagnosis of PHPT, the aim of this test is to bring calcemia (preferably ionized calcemia) significantly above the upper normal limit, and evaluate how PTH secretion is blunted. In our practice, we perform an oral calcium load test with 1 g elemental calcium (several protocols have been published [32,37–41]) and measure serum ionized and total calcium and PTH 2 or 3 h later. If serum ionized calcium has not reached our target concentration (1.35–1.40 mmol/L at least), we perform a slow calcium infusion (2 mg/kg elemental calcium) and measure again calcium and PTH [35]. It should be recognized that, even in frank PHPT, PTH might significantly decrease during the calcium load test. However, in case of PHPT, serum PTH is not enough blunted (it remains above the median of the reference values), even when the ionized calcium concentration rises frankly above the normal values. A limit in the interpretation of the test is that a “grey zone” exists, in that some patients decrease their PTH quite much, but not enough to exclude definitely PHPT (i.e. between the lower normal value and the median). It must be noted that there is a lack of published PTH reference values adapted to different levels of hypercalcemia. Instead of using “static” reference values for serum PTH established as described in the first paragraph of the present article, another mode of calculation has been proposed by Lepage et al. [42]. These authors have determined “dynamic” PTH reference intervals obtained in normal subjects in whom serum calcium was acutely modified, either decreased (by infusion of Na₂-EDTA) or increased (by infusion of CaCl₂). These “dynamic” reference values may significantly improve the diagnostic sensitivity of PTH measurement by improving the evaluation of the adequacy between serum PTH and calcium concentrations. Another way to improve the diagnostic performance of the calcium load test would be to establish the

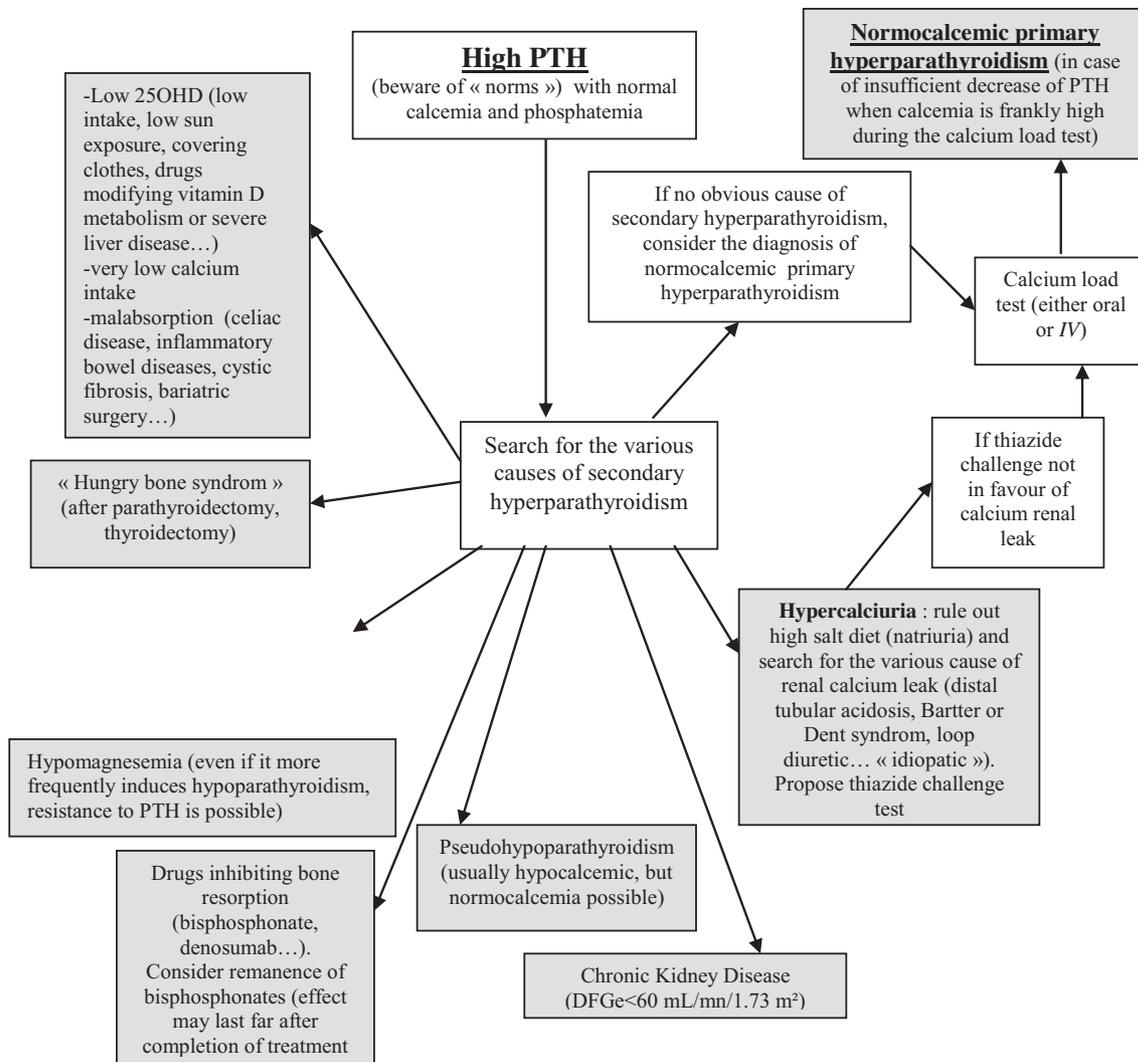


Fig. 1. Proposed diagnostic strategy for the exploration of an “isolated” elevated PTH concentration. Grey Blocks represent the possible diagnoses; white blocks are the intermediary steps.

variations of PTH in function of ionized calcemia in a large group of healthy subjects in whom a calcium load test, either oral and IV, is performed. Some previous studies have included a control group that received an oral calcium load but, unfortunately, these groups were small with ionized calcemia not always frankly high during the test [39–41]. Finally, it should be kept in mind that there is a huge inter-method variability in PTH results [12], so that such studies should be replicated by using various PTH kits.

4. Conclusion

In normocalcemic patients with fragility fractures, low bone mineral density, kidney stones, or nephrocalcinosis, searching an etiology for an increased PTH is worth to be done. It necessitates to rule out the various causes of SHPT and, if none are detected, to perform a calcium load test to diagnose normocalcemic PHPT. It is important to underline that, if a vitamin D deficiency is detected during the “first-line” biological evaluation in a normocalcemic patients with an

elevated PTH, calcemia, phosphatemia and PTH should be retested after vitamin D repletion as another cause of SHPT may be present (PTH remains high) or a PHPT may be unmasked (the patient becomes hypercalcemic). As many patients with a normocalcemic SHPT or PHPT may be hypophosphatemic, the diagnostic approach proposed above also applies to hypophosphatemic, normocalcemic patients with an elevated PTH before considering a diagnosis of primary renal phosphate leak.

Fig. 1 is a tentative diagnostic flowchart for the diagnostic approach of an isolated elevated PTH concentration.

Disclosure of interest

JCS reports lecture fees and/or travel/hotel expenses (DiaSorin, Roche Diagnostics, Abbott, Amgen, Shire, MSD, Lilly, Rottapharm).

EC is consultant for IDS and DiaSorin and has received lecture fees from IDS, DiaSorin, Roche, Abbott and Amgen.

CC has nothing to declare.

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