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Annales d'Endocrinologie 76 (2015) 134–141

Annales d'Endocrinologie
Annals of Endocrinology

Journées Klotz 2015

# How to manage an isolated elevated PTH?

Jean-Claude Souberbielle [a,*], Etienne Cavalier [b], Catherine Cormier [c]

[a] *Physiology Department, Necker–Enfants-Malades university hospital, 75015 Paris, France*
[b] *Clinical Chemistry department, Sart Tilman university hospital, Liège, Belgium*
[c] *Rheumatology Department, Cochin University Hospital, 75015 Paris, France*

**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.


*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 vitaminique 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.


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

* Corresponding author. Service de physiologie explorations fonctionnelles, hôpital Necker–Enfants-Malades, 149, rue de Sèvres, 75015 Paris, France.
*E-mail address:* Jean-claude.souberbielle@nck.aphp.fr (J.-C. Souberbielle).

http://dx.doi.org/10.1016/j.ando.2015.03.005
0003-4266/

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 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 $m^2$ [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 $m^2$ (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

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 $m^2$. 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 |
|---|---|---|
| *2nd generation assays* | | |
| 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 |
| *3rd generationassays* | | |
| CA-PTH (Scantibodies) | 5–39 | 7–31 |
| Liaison 3e G (DiaSorin) | 5.5–38 | 5–26 |