editorial

Differences in the function of parathyroid peptides. What are we measuring?

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A century went by since the anatomical discovery of the parathyroid gland in 1825 until Collip demonstrated that the administration of the parathyroid hormone (PTH) prevented tetany and normalized plasma calcium levels.[1,2] In a more rapid way, within the last two decades the molecular mechanisms have been known as well as many other factors that act in a coordinated way at the parathyroid gland in order to regulate serum calcium levels. The identification and cloning of receptors for PTH, calcium and vitamin D, as well as the knowledge on the related hereditary disorders have allowed advancing in the knowledge on this complicated network. Is has also become evident that phosphorus plays a key role in PTH regulation, although we still do not know the existence of specific receptors for it at the thyroid gland.[3] Recently, the studies carried out in knockout mice have allowed knowing the connections between the fibroblast growth factor (FGF 23) and phosphorus, vitamin D, and PTH.[4] Finally, as another piece in this complex puzzle, there are recent evidences pointing out that PTH fragments may play an antagonistic role of the intact molecule, exerting thus a hypocalcaemic function.

There are several circulating parathyroid peptides with different functions and they even act through different receptors. Figure 1a shows a scheme of the different circulating PTH fragments known so far:

- *Intact PTH (PTH 1-84)* is compounded by a peptide of 84 amino acids (AA), obtained by consecutive proteolysis of two larger peptides of 115 AA and 90 AA, respectively.
- All carboxi-terminal fragments bear the C-terminal portion and lack a series of AA at the N-terminal position. They are categorized into two groups:
  1. The larger ones, «N-truncated», have lost a series of AA at any place of the segment comprised between AA 1 to 34. Their existence has been discovered within the last 5 years[5] and have been named *«PTH not 1-84»* (fig. 1a).
  2. There is another group of C-terminal fragments: these are lacking a segment beyond AA 34 and their N structure begins at positions 34, 37, 41, and 43. These fragments are classically named *«C-terminal»* (fig. 1a).
- Another recently discovered fragment is termed *«amino PTH»* and has got an AA sequence similar to that of the intact molecule (1-84), although it presents a phosphorylation at AA 17.[6] Its function is unknown. It has recently been observed that it is present in higher proportions among patients with parathyroid carcinoma and among patients with primary and secondary severe hyperparathyroidism.[7]

Given that the C-terminal fragments are biologically active and act through different receptors, some authors have proposed the term «parathyroid polyhormone».[8] These parathyroid peptides have different actions and regulation mechanisms and metabolism.

Intact PTH or the 1-84 fragment account for the classical functions on the bone and kidney and on the «vitamin D-1-alpha-hydroxilase» enzyme, inducing the synthesis of calcitriol. All of these actions share a common objective: to raise plasma calcium levels. Within the parathyroid gland, the Calcium-sensing receptor (CaSR)[9] is directly implicated in the mechanism responsible for the modulation of parathyroid hormone release depending on the extracellular calcium level. Thus, during hypocalcaemic conditions, PTH synthesis and release are stimulated. Hyperphosphatemia is another potent stimulating factor for PTH synthesis and release. By contrast, calcitriol, through its receptor (VDR), has an inhibitory effect. The classical actions of PTH 1-84 are mediated through a common PTH receptor (PTHR1) and PTH-related protein (PTH rP), which is present in many tissues. The amino-terminal sequence, constituted by the first 34 AA (N-terminal structure), is necessary for its action. The interaction between the amino terminal portion with the PTHR1 receptor activates the protein kinase A and C pathways at target tissues.

In experimental studies, it has been observed that the fragments termed «no-1-84», among which the most abundant one is fragment 7-84, have antagonistic biological effects to those of the intact molecule. Indeed, they have hypocalcaemic, hyperphosphatemic, and hypophosphaturic effects. On the other hand, they counteract the hypercalcaemic effect of PTH (1-34) and of PTH (1-84). Besides, they inhibit vitamin

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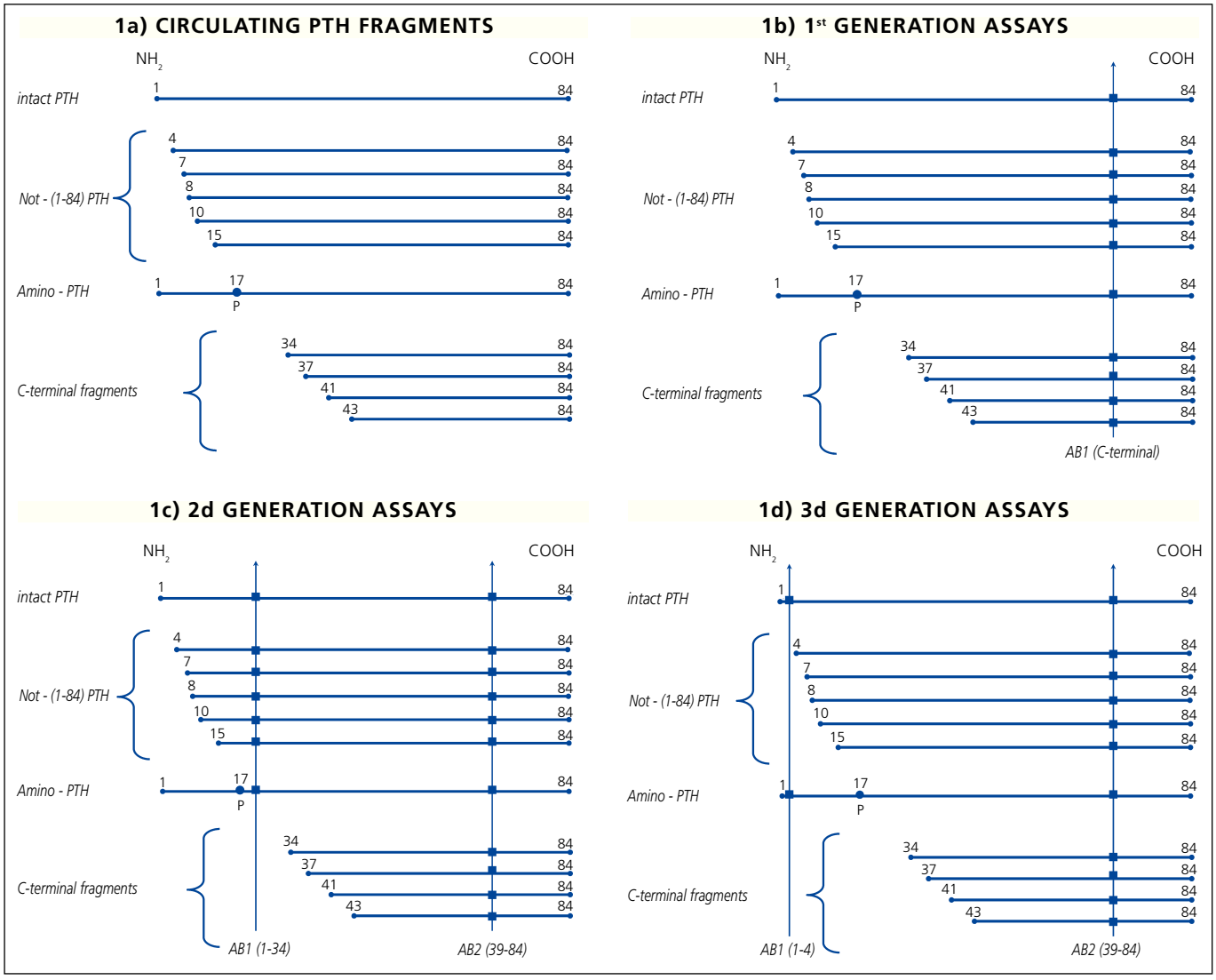

Figure 1. *Parathyroid peptides and their quantitative determination according to the method used.* 1a) It shows the parathyroid peptides. The *parathyroid hormone (PTH 1-84)* is compounded by an 84-AA long peptide. It has an N-terminal region of 34 AA that is necessary to bind to the PTH1R receptor and exert its classical hypercalcaemic actions. The opposite end is termed the C-terminal region. «PTH Not (1-84)» has lost a series of AA at any place of the segment comprised between AA 1 to 34. Of them the most abundant and studied one is 7-84; and the *C-terminal fragments*, which they lack a segment beyond AA 34 and their N-structure begins at position 34, 37, 41, and 43. The *amino PTH* has an AA sequence similar to the intact molecule (1-84) but it has got a phosphorylation at AA 17. 1b) First generation assay using an antibody directed against the C-terminal region of the PTH molecule (AB1 C-terminal). The arrowed line indicates the site of binding of the PTH fragments with the antibody. All fragments binding to this antibody are detected. As it may by observed, in addition to 1-84 all other circulating PTH fragments are also determined, so that the intact PTH level is well overestimated. 1c) Second generation assay using 2 antibodies, one directed against the amino-terminal region of the molecule (AB1 anti the wide 1-34 region) and another one against the C-terminal region of the PTH molecule (AB2, 39-84). The arrowed lines indicate the binging site of PTH fragments to the antibodies. The assay only quantifies the fragments binging to both antibodies. As it may be observed, in addition to PTH 1-84, the assay detects all other «not 1-84» fragments and the «amino PTH». Only the C-terminal fragments are left out from the quantification. 1d) Third generation assay using 2 antibodies, one directed against the amino-terminal region of the molecule (AB1, in this case directed against only the first 4-5 amino acids of the PTH molecule) and another one directed against the C-terminal region of the PTH molecule (AB2, 39-84). The arrowed lines indicate the binding site of the PTH fragments to the antibodies. The assay only quantifies the fragments binding to both antibodies. As it may be observed, in this case only PTH 1-84 and «amino-PTH» are detected.

D-induced osteoclastogenesis.[10] All the carboxi-terminal-type fragments of the PTH molecule bind to a new type of receptor of the hormone in bone cells (CPTHR), which is different from the PTHR1 receptor that requires the 1-34 amino terminal portion of intact PTH to get activated.[11]

In vivo studies have been carried out in parathyroidectomized rats. The administration of PTH 7-84 decreases serum calcium and phosphate levels and inhibits PTH 1-84-induced phosphaturia, suggesting that it promotes calcium and phosphate entry into the bone.[11] Slatopolsky et al.[12] showed that

thyro-parathyroidectomized rats become hypercalcaemic when they are administered PTH 1-84 and the 1-34 fragment (Teriparatide), and that simultaneous administration of PTH 7-84 blocks this effect and induces hypocalcaemia. They also showed that the administration of PTH 7-84 is accompanied by a decrease in the number of osteoclasts and osteoblasts and that *PTH 1-84*-induced bone formation is abrogated when *PTH 7-84* is administered simultaneously, thus seeming that the differences induced in serum calcium levels are due to a direct effect on the bone. The authors propose the interesting hypothesis that accumulation of these fragments during uremia may be responsible in part of skeletal resistance to PTH.[12]

The actions of the carboxi-terminal fragments (including the «not 1-84») have not yet been identified under physiological or pathological conditions. It is likely that the biological effect may be more relevant during renal failure since they might reach higher circulating levels. It has experimentally been shown that under acute hypocalcaemic conditions, PTH 1-84 excretion is favored over that of carboxi-terminal fragments, and that the induction of acute hypercalcaemia reverses the ratio. Under chronic hypocalcaemia conditions, the higher the amount of PTH needed to maintain the calcium level (for instance, in chronic renal failure with vitamin D deficiency), the higher the amount of PTH 1-84 is secreted at any calcium level and the lower the carboxi-terminal fragments are. It happens the same way in the opposite situation. The lower the amount of PTH needed (for instance, in vitamin D-induced hypercalcaemia), the lower the amount of PTH 1-84 is secreted and the higher the carboxi-terminal fragments are.[10] Therefore, given that the changes in serum calcium levels regulate the PTH 1-84/C-PTH ratio, secreted at the parathyroid glands, it seems logical to deduce that the carboxi-terminal fragments must have some physiological role.[13,14]

Carboxi-terminal fragments act through a receptor (*CPTHR*) other than *PTHR1,* which has not being well defined or cloned yet. It has been shown to be present on the cytoplasmic membrane of chicken renal cells, rat osteosarcoma cells, and *osteocyte-like cells* of mouse bone. These PTH R1-deficient cells have been used to show the affinity of carboxi-terminal fragments for this receptor. To date, there are no data *in vivo* showing the existence of such receptor.[15,16]

The regulation and metabolism of the different fragments condition their plasma levels. In healthy individuals, the amount of circulating C-PTH is very much higher (80%) than that of the intact molecule (20%). This disproportion is likely justified by the shorter half-life of the latter (5-8 minutes). The carboxi-terminal fragments are cleared by the kidney and accumulate when there is a decreased in glomerular filtration rate. So that in renal failure this type of fragments, which proportion is of 95%, accumulates.[14] Figure 2 shows the different proportions of circulating PTH fragments in healthy individuals and in renal failure.

The release and metabolism of the different PTH fragments is illustrated in an integrated way in figure 3**.** The parathyroid gland releases PTH 1-84 and C-PTH fragments in amounts proportional to serum calcium levels. Under hypocalcaemia the proportion of PTH 1-84 released is higher, and by contrast hypocalcaemia increases the amount of released C-PTH fragments. All of them exert their effect on the bone by interac-

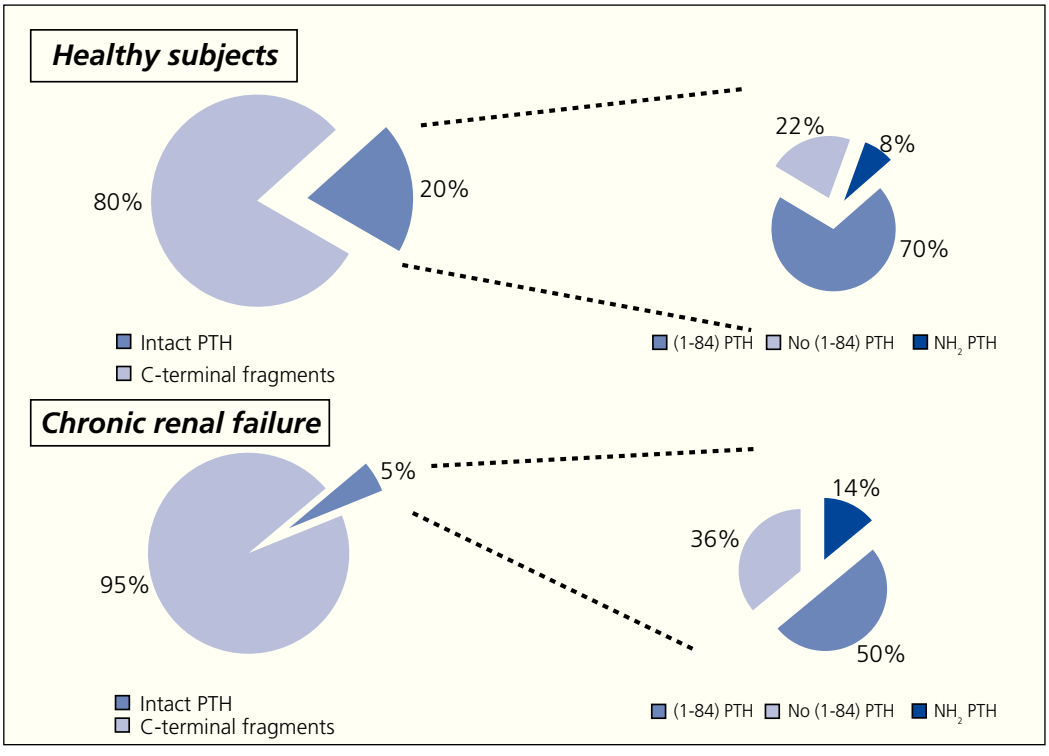

Figure 2. *Circulating parathyroid peptides.* In healthy individuals, the amount of circulating C-PTH is very much higher (80%) than that of the intact molecule (20%) due to the shorter half-life of the latter (5-8 minutes). The C-PTH fragments are cleared by the kidney and that is way C-PTH fragments are in a 95% proportion in renal failure. As shown in the Figure, what is being detected as «Intact PTH» with current *second generation* methods comprises a series of different peptides (PTH 1-84, PTH Not 1-84, and amino PTH), the proportion of which is also different in renal failure.

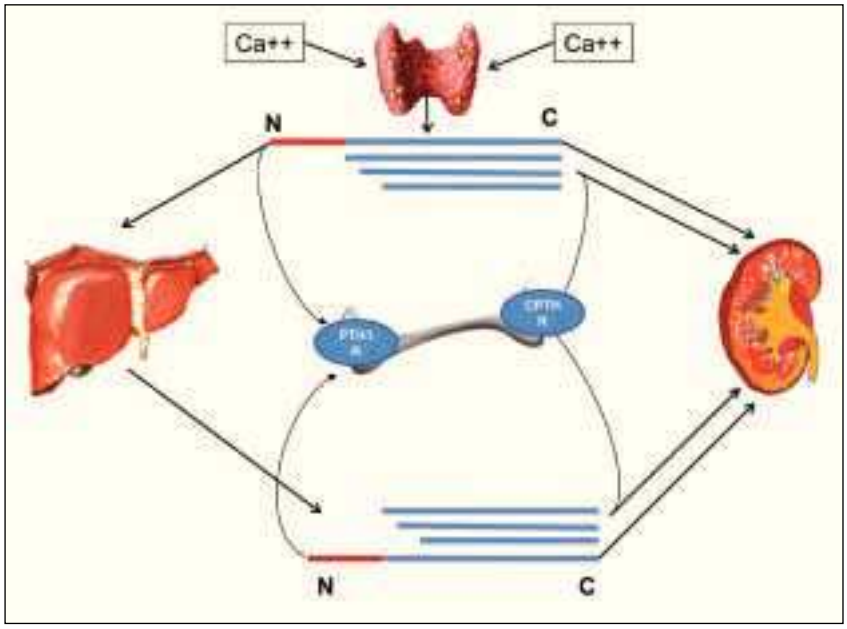

Figure 3. *Regulation of parathyroid peptides secretion and metabolism.* The figure illustrates in an integrated manner the secretion and metabolism of the different PTH fragments**.** The parathyroid gland releases PTH 1-84 and C-PTH fragments in amounts proportional to serum calcium levels. Under hypocalcaemic conditions, the proportion of PTH 1-84 released is higher and, by contrast, hypocalcaemic conditions increase the amount of C-PTH fragments released. All of them exert their effect on the bone by interacting with their specific receptors (PTHR1 o CPTHR), or are cleared by the kidney and the liver. PTH 1-84 is rapidly degraded within the liver Kupffer cells into a series of C-terminal fragments identical to those secreted by the parathyroid gland, which re-enter into the blood stream.[8]

ting with their specific receptors (PTHR1 o CPTHR) or are cleared by the kidney or the liver. PTH 1-84 is rapidly degraded by liver Kupffer cells into a series of carboxi-terminal fragments identical to those secreted by the parathyroid gland, which re-enter into the bloodstream.[13]

Given that the existence of many of these PTH fragments was unknown until relatively recent dates, the available assays for quantifying PTH 1-84 presented, and still present, crossed values with other parathyroid peptides. This fact may represent an important clinical problem when assessing the situation of the levels of this hormone for establishing a therapy, especially in the case of patients with chronic renal disease.

The first determinations of serum PTH levels were carried out by radio-immune analysis (RIA) around the year 1980. These assays were mounted at the same laboratories where the antibodies were generated and the hormone was labeled with ^{125}I.

In the assay an anti-PTH antibody was used detecting different fragments of the hormone depending on the site of it being recognized. Thus, there were radio-immune analyses for amino-terminal, intermediate, and carboxi-terminal PTH fragments. The carboxi-terminal fragments were the ones most commonly used, although as shown in figure 1b, all circulating PTH fragments besides PTH 1-84 were assessed, so that the true value of physiologically active («intact») PTH were highly overestimated, especially in patients with renal failure in whom the proportion of circulating C-terminal fragments was much higher than in subjects with normal renal function.

This situation was improved at the laboratories because kits for PTH determination started to be commercially available, so that there was no need for labeling the hormone or creating the antibodies to carry out the determination, although the problem of levels overestimation still was the same. These assays have been called *first generation assays* (fig. 1b).

An important change occurred in 1987[17] when the *Nichols Institute Diagnostic Inc* developed an immune-radiometric assay (IRMA) to detect PTH, the first of the so-called analysis of «intact PTH». The assay used two antibodies: one directed against the amino-terminal region (1-34 epitope) and the other one against the carboxi-terminal region (39-84). In order to be determined, a fragment has to simultaneously bind to both antibodies. Since at that time the existence of the «not 1-84» PTH fragments was unknown, which have been discovered more recently,[5] as well as of the «amino-PTH» fragment, [6] the general believe was that only intact PTH 1-84 values were being determined, and thus of the physiologically active hormone.

In theory, the assay was so perfect that from the several studies performed comparing histomorphometry with PTH levels determined by means of Nichols' IRMA[18-20] the «National Kidney Foundation/Kidney-Dialysis Outcomes Quality Initiative (NKF/K-DOQI)» guidelines were elaborated[21] recommending to maintain PTH levels in patients with renal osteodystrophy between 150 and 300 ng/L.

Figure 1c shows all the PTH fragments detected by IRMAs called «intact PTH». As it may be observed, in addition to PTH 1-84 the «not 1-84» fragments and «amino-PTH» are also detected, excluding only from the determination the C-terminal PTH fragments.

Several commercial firms developed their own IRMA-type or electrochemiluminescent kits of the so-called «intact-PTH». Generally all of them use antibodies directed against the same epitopes as the one used by Nichols, with the exception of the assay by Roche called Elecsys, which uses antibodies against the PTH regions 26-32 and 55-64 and which is the only one not detecting the amino-PTH fragment but yes all the «not 1-84» fragments, similar to the other assays of the

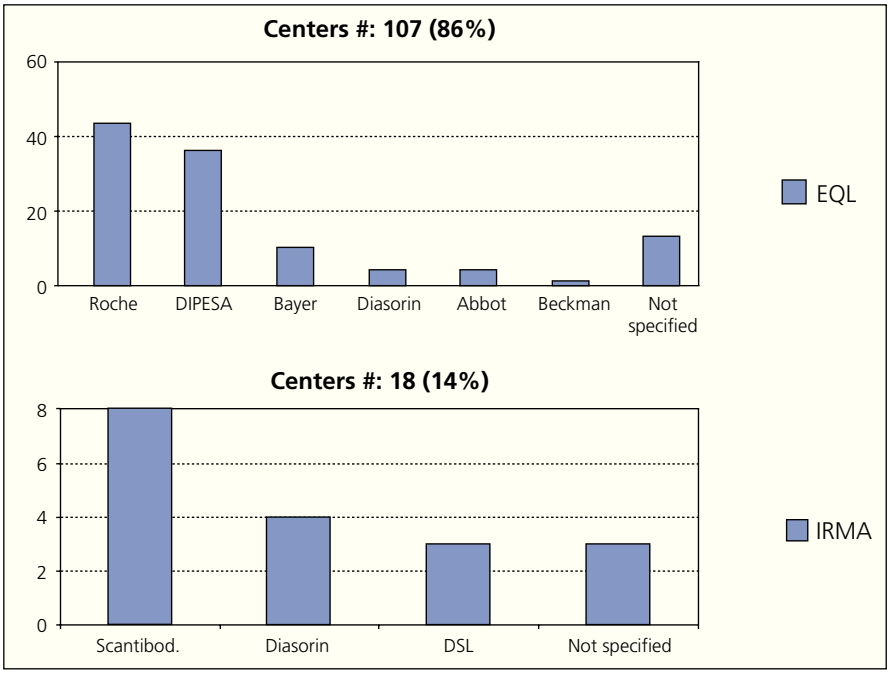

Figure 4. *Results from the spanish survey on the methods used to determined PTH levels.* Of the 125 surveys received, EQLM methods are used in 107 centers (86%), and isotopic methods (IRMA) are used in 18 centers (14%). EQLM: Eletrochemiluminescence. IRMA: Radio-immune analysis.

like from other commercial firms. These assays have been termed *2d generation assays* (fig. 1c).

Since the discovery of «not 1-84» PTH fragments, the manufacturer Nichols (that is no longer in the market) and other manufacturers such as Scantibodies, developed new methods with two antibodies in which they still used the antibody directed against the classical carboxi-terminal region and a new one directed against the 4-5 first AA within the amino-terminal region of the PTH molecule, so that most of «not 1-84» fragments were no longer detected, although the «amino-terminal» fragment was still recognized. Figure 1d shows the fragments detected by this type of assays, which have been termed *third generation assays,* or of *«bio-PTH»* detection or *«whole PTH»* detection. As it may be easily deduced, the sample analysis by means of a third generation assay offers much lower values than the use of a second generation assay since not all «not 1-84» fragments are being detected. Its determination has not become generalized in clinical practice because it is a technically demanding method. Another limitation to translate it into the clinical practice is that there are no studies correlating its values with bone histopathology in chronic renal disease, by contrast with «intact PTH».[22,23] On the other hand, the fact that «bio-PTH» and «Intact PTH» levels closely correlate has prevented the widespread use of the former. Some authors proposed that the PTH 1-84/»whole» PTH ratio could be useful in the differential diagnosis between low and high bone turnover, although the studies carried out in short patient series have not met the expectancies.[24,25]

In this way, in the case that quantification of bio-PTH or whole PTH is not feasible in routine clinical practice, we should be aware that the PTH levels provided by the laboratory have been quantified by means of a second generation assay and thus it corresponds to the sum of PTH 1-84 and «not 1-84» PTH (and in some cases also of amino-PTH, which is the minority), which are parathyroid peptides with antagonistic effects.

In addition to this serious problem of overestimation of the true PTH 1-84 value, there is another problem further complicating the use of the results from these assays by the clinicians: the lack of homogeneous calibration of the determinations between the different manufacturers. Since they do not use the same PTH standards, the numerical results with the same sample may significantly vary with the different techniques used, so that the reference interval of «150-300 ng/L» proposed by the K/DOQI guidelines is no longer valid. JC Souberbielle et al.[22] have confirmed this in an excellent work published in 2006.

This inter-method variability makes that, depending on the method used, there is a different percentage of patients requiring pharmacological treatment or even parathyroidectomy, provided that we assume that the values from our laboratory correspond to those used in the K/DOQI guidelines. This methodological error implies inappropriate clinical decision-making, which entails repercussions on health and a considerable financial impact due to the excessive prices of the drugs used for treating hyperparathyroidism.[26]

Given all this, under the auspices of the Spanish Society of Nephrology, the PTH Measurement Working Group comprised by experts on mineral metabolism and on clinical analyses, has carried out a survey among the Spanish Nephrology Departments in order to know the methods used in our country. Given the existence of high variability (fig. 4), this Group also considered calculating the inter-method variability in order to provide nephrologists with the appropriate correction factors that should be applied to obtain the same values as with the use of Allegro intact PTH by Nichols (that is

Table I. Equivalences between the PTH measuring methods most commonly used in Spain: the Nichols method (DOQI guidelines), and the «bio-PTH» measuring method by Scantibodies. The work has been carried out by the «PTH Measuring Techniques Study Group», under the auspice of the Spanish Society of Nephrology, and will be published in full in the near future

	PTH pg/mL	PTH pg/mL	PTH pg/mL
IRMA NICHOLS	150	300	1,000
EQL Elecsys (Roche)	185	338	1,033
EQL Immulite (DPC)	191	342	1,048
EQL Advia Centaur (Bayer)	206	385	1,221
EQL Abbott	249	441	1,337
IRMA PTH intacta (Scantibodies)	142	264	833
IRMA bio-PTH (Scantibodies)	84	165	543

☐ 3d Generation ■ 2d Generation

the one used for the K/DOQI reference ranges) and with the «bio PTH» by Scantibodies. Although this work is still on going, we already have available the preliminary results that we present since they may be useful in clinical practice. Table 1 shows the results obtained when analyzing PTH levels in 150 hemodialysis patients in whom PTH was simultaneously determined at the laboratories of the Fundación Jiménez Díaz Hospital, La Paz Hospital, and Gómez Ulla Hospital, by means of the six most commonly used methods in our country. It is striking the high inter-method variability that makes K/DOQI references invalid. We, the nephrologists, should from now on be informed of the method applied by our reference laboratory in order to apply the corresponding correction factors. This will allow the clinicians to keep on using the same references and guidelines until there will exist other valid alternatives.

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