Whole or Fragmentary Information on Parathyroid Hormone?

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More than a decade ago, Brossard *et al.* (1) drew attention to the fact that the so-called "intact," second-generation parathyroid hormone (PTH) assays measured not only the PTH-(1-84) molecule but also large PTH fragments in patients with chronic kidney disease (CKD). One of the major problems is that the proportion of PTH-(1-84) and its fragments in the circulation changes in response to the serum level of ionized calcium; therefore, in presence of hypercalcemia, the parathyroid gland releases less PTH-(1-84) but more PTH fragments. The reverse is true in the presence of hypocalcemia, where more active PTH-(1-84) is needed. The difference is particularly striking in patients with CKD. When considering the potential biologic relevance of this finding, it is even more disturbing that at least one of the fragments, namely PTH-(7-84), has been shown to act as a partial antagonist of PTH-(1-84), with opposite biologic activities (2–4). Progressive awareness of these methodologic problems and the underlying biologic complexity went along with the development of third-generation PTH assays that recognize only PTH-(1-84), also called "whole," "bio-intact," or "biologically active" PTH (5).

Theoretically, the assessment of second- and third-generation PTH assays combined should reflect parathyroid activity more adequately than second-generation assays alone, reflecting the sum of potentially opposing effects of PTH-(1-84) and its fragments. Several authors explored changes of serum PTH levels, as measured with various assays, with progression of CKD and in response to medical interventions. Reduction in GFR is accompanied by a higher increase in large PTH-related C-terminal fragments than in PTH-(1-84) in patients with CKD (6,7). The administration of cinacalcet to patients with stage 5 CKD and secondary hyperparathyroidism (8) or to patients with parathyroid cancer (9) did not change the ratio between intact PTH (iPTH) and PTH-(1-84). This is somewhat surprising because cinacalcet reduces serum calcium, and hypocalcemia is associated with changes in the PTH ratio. In contrast, surgical parathyroidectomy, which often leads to profound hypocalcemia, has been shown to normalize the ratio (10).

In an original article in this issue, Monier-Faugere *et al.* (11) report the effects of the administration to long-term hemodialysis patients of calcitriol, the most active metabolite of vitamin D, and its active derivative paricalcitol on circulating levels of PTH-(1-84), iPTH, large C-terminal PTH fragments (C-PTH), and the PTH-(1-84)/C-PTH fragment ratio, also called PTH-(1-84)/C-PTH- (7-84) ratio. They present results that were obtained first in a longitudinal, crossover design study that compared paricalcitol with calcitriol and second in a cross-sectional study that compared paricalcitol with no vitamin D treatment. In the longitudinal study, they observe a lower PTH ratio in response to calcitriol but a higher PTH ratio in response to paricalcitol, as compared with respective baseline values. In the cross-sectional study, they find identical iPTH levels in both groups, that is with paricalcitol or no vitamin D treatment, but higher PTH-(1-84) levels and thus higher PTH ratio values in the group that received paricalcitol. They conclude that calcitriol administration leads to lower bioactive PTH-(1-84) levels than paricalcitol in presence of similar iPTH levels. Whether this difference has clinical relevance is uncertain and cannot be answered in the absence of a confrontation with surrogate markers of outcome or hard end points. Unfortunately, there are no data on the effects of paricalcitol on bone in humans. From a more general point of view, it may be inappropriate to calculate the serum concentration of large C-PTH fragments simply as the difference between iPTH and PTH-(1-84) serum concentrations. Second-generation PTH assays recognize PTH fragments other than only large C-PTH fragments, and third-generation assays also seem to measure PTH moieties other than whole PTH-(1-84) alone. The occurrence of the latter, which is characterized by an abnormally high PTH-(1-84)/iPTH ratio (12), was recently demonstrated by Tanaka *et al.* (10) and Arakawa *et al.* (13) in association with severe secondary hyperparathyroidism and by Rubin *et al.* (9) in association with parathyroid cancer.

A more convincing answer to this issue could come from comparisons of the value of second- and third-generation PTH assays in confrontation with bone histomorphometric findings. In previous work, Monier-Faugere *et al.* (14) indeed showed improved assessment of bone turnover by the PTH-(1-84)/large C-PTH fragment ratio in patients with ESRD, in particular in vitamin D–naive patients; however, two subsequent bone histomorphometry studies in patients with ESRD failed to confirm the claimed superiority of third-generation assays or the PTH-(1-84)/large C-PTH fragments ratio in the distinction between low- and high-turnover bone disease or mixed renal osteodystrophy (15,16). Clearly, there is a need for multicenter studies that examine the value of measuring serum PTH-(1-84) and its

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fragments in large cohorts of patients with CKD and different types of CKD-related mineral and bone disorder.

We need to point out that for Monier-Faugere *et al.*, the term PTH ratio means PTH-(1-84)/PTH-(7-84) (*i.e.*, PTH-(1-84)/iPTH minus PTH-(1-84). In contrast, for others, (9,10,13) this ratio stays for whole PTH/iPTH. In the exceptional cases in which the PTH-(1-84) level is paradoxically higher than that of iPTH, it is obvious that one cannot calculate PTH-(7-84) as the difference between iPTH and PTH-(1-84), because this would yield a negative value. In addition to bone histology findings, a confrontation of the relative merits of second- and third-generation PTH assays could be made on the basis of other surrogate markers of importance for patient outcome, including morphologic and functional cardiovascular parameters, and possibly also inflammatory and nutritional status.

Finally, we mention two other issues. The first is a practical problem. To date, measurement of PTH with third-generation assays is not widely available because the only currently available kit for this measurement is an immunoradiometric assay that cannot be used in the majority of clinical laboratories. If it were to come available everywhere, then its usefulness in clinical practice would need to be ascertained. The second is a theoretical issue. In the future, we hopefully will be able to rely not only on serum PTH but also on circulating and other markers of bone structure and function for the assessment of renal osteodystrophy and on markers of cardiovascular disease related to secondary hyperparathyroidism (17).

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See related article, "Opposite Effects of Calcitriol and Paricalcitol on the Parathyroid Hormone-(1-84)/Large C-terminal Parathyroid Hormone Fragments Ratio in Patients with Stage 5 Chronic Kidney Disease," on pages 1255–1260.