The Case for Routine Parathyroid Hormone Monitoring

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Summary
Parathyroid hormone (PTH) is a uremic toxin with multiple systemic effects including bone disorders (renal osteodystrophy), myopathy, neurologic abnormalities, anemia, pruritus, and cardiomyopathy. Hyperparathyroidism is common in CKD and results in significant morbidity and mortality if left untreated. Clinical practice guidelines from the Kidney Disease Improving Global Outcomes initiative broadened the optimal PTH range to >2 and <9 times the upper limit of normal for the assay measured. Furthermore, the guidelines recommend following trends in PTH to determine the appropriate therapy. These guidelines overcome issues with the assay variability and help clinicians make judgments when treating individual patients. They also require frequent measurement in order to determine trends and implement appropriate treatments.

Bone remodeling is a complex process involving multiple cell types. At any one moment in time, <20% of the adult skeleton is undergoing remodeling. The signal that tells the bone at a particular site to initiate a bone remodeling unit is not clear but likely involves the osteocytes: the mechano-, osmo-, and chemo-receptors of bone. The next phase involves activation of quiescent osteoblasts. These cells then signal circulating mononuclear cells to migrate to that area of bone and fuse together to become a multinuclear osteoclast via the osteoprotererin-receptor activated nuclear factor κ ligand (OPG-RANKL) signaling pathway. These osteoclasts then resorb bone, the osteoblasts fill in the resorption lacunae with unmineralized collagen and noncollagenous proteins, and mineralization subsequently occurs completing the remodeling cycle. The osteoclasts undergo apoptosis, and the osteoblasts become either apoptotic, lining cells, or osteocytes. This entire remodeling cycle takes 3–6 months for an area of bone. The role of PTH in this remodeling cycle includes direct activation of osteoblasts, stimulation of the OPG-RANKL signaling pathway, and likely a role in cellular apoptosis. However, many other factors are similarly involved in a remodeling cycle.

The use of bone biopsy as the gold standard for the diagnosis of renal osteodystrophy predates much of the knowledge about the biologic functions of the osteocytes, OPG-RANKL, and cellular apoptosis. In addition, for convenience purposes, we utilize the iliac crest as the location of the biopsy but it may not be the site that is actively remodeling at the time of the biopsy and is not reflective of weight-bearing bones. Thus, the expectation that a single time point PTH concentration would accurately predict bone remodeling when the biopsy is from one site and a remodeling cycle is up to 6 months long is grandiose indeed. However, so is the expectation that other markers such as alkaline phosphatase, an enzyme of nonbone
and bone etiology, are adequate for assessing bone. In the largest series to date, the Kidney Disease Improving Global Outcomes (KDIGO) initiative analyzed 590 bone biopsies that were performed worldwide with simultaneously drawn blood samples. The blood was then analyzed at a central laboratory for several bone biomarkers to determine the positive and negative predictive values of individual and combinations of bone biomarkers. PTH, measured by the intact assay (Elecsys PTH 1–84 Assay; Roche Diagnostics Corporation, Indianapolis, IN), was equally predictive to bone-specific alkaline phosphatase of underlying bone turnover with a sensitivity of 0.580 versus 0.403, a positive predictive value of 0.373 versus 0.287, and a negative predictive value of 0.903 versus 0.877 (PTH versus bone-specific alkaline phosphatase, respectively) for the detection of increased bone formation rates. The two together did not improve the sensitivity or specificity (4). Furthermore, PTH and other biochemical parameters would respond immediately to therapies, whereas the results on a specific bone biopsy are reflective of a complex process that could take up to 6 months to achieve. Thus, it is not surprising that a single biomarker measured at a single time point is reflective of bone histology. These findings of good negative predictive value, but a poor positive predictive value or sensitivity, are in fact a testament to the role of PTH given the complexities described above.

Despite this less than ideal ability of PTH to predict underlying bone histology, the role of PTH in renal osteodystrophy cannot be disputed. The rapid improvement in bone remodeling, bone pain, and mineral metabolism after parathyroidectomy is indeed proof of the role of PTH. Studies in humans with hyperparathyroidism demonstrated improvement in bone histology after parathyroidectomy (5,6). There is a marked decrease in active bone resorption and a sharp rise in osteoblast bone formation just 1 week after parathyroidectomy in dialysis patients. These findings indicate how critical PTH is for the major cells involved in bone remodeling and that the biochemical manifestations of hungry bone syndrome are definitively due to the rapid decrease in PTH concentrations and their effect on bone immediately after parathyroidectomy (7). Furthermore, bone density increases in both the axial and appendicular skeletons after parathyroidectomy in dialysis patients (8). In US Renal Data Service data, the risk of fracture after parathyroidectomy was reduced by 32% compared with matched patients and adjusted for multiple factors (9). In addition to bone biopsy changes and fractures, specific radiographic findings have been associated with hyperparathyroidism. Radiographs showing thinning bones, periosteal resorption, especially noted in fingers, distal scapula, sacroiliac joint, and the skull, can be described as “ground glass” or “salt and pepper.” Furthermore, cystic lesions, brown tumors, are known to develop with severe disease and could be misdiagnosed as cancerous. Finally, in observational studies, patients who underwent a parathyroidectomy have improved survival compared with those who do not (10). Thus, the role that PTH plays in patient morbidity or mortality cannot be disputed, at least when markedly elevated and rapidly decreased by a parathyroidectomy.

In clinical practice, only a small portion of patients with elevated PTH undergo parathyroidectomy. Instead, as internists, we prefer to prevent morbidity and the need for a surgical procedure. It is this basic concept that requires us to monitor PTH and utilize calcitriol and its analogs and/or calcimimetics to lower PTH. The use of calcitriol to improve bone histology was demonstrated in humans in 1989 (11), followed by data supporting regression of parathyroid hyperplasia by ultrasonography (12). Animal studies demonstrate improved histology with the use of calcitriol analogs and less hypercalcemia. Unfortunately, there are limited data demonstrating improved bone histology in response to analogs of calcitriol in human studies (13). For calcimimetics, bone is improved with its use in animal studies (14,15) but again human data are thus far lacking although small studies demonstrated efficacy (16). However, a randomized controlled trial comparing the bone histology effects of 1 year of therapy with cinacalcet versus placebo is completed, with results due later in 2012 (17).

Clinically, renal osteodystrophy manifests principally as impaired growth in children and bone pain and radiologic abnormalities in adults; the aggressive approach to treat hyperparathyroidism has lessened the prevalence of these abnormalities. Delayed growth is common in children with CKD and has been associated with chronic acidosis, malnutrition, secondary hyperparathyroidism, and low levels of somatomedin (18). Similarly, multiple bone deformities are common in children and appear to be related to the high rates of bone remodeling associated with hyperparathyroidism. The radiologic features of rickets-like lesions observed in uremic children have histologic features consistent with hyperparathyroidism-induced osteitis fibrosa cystica rather than vitamin D deficiency or osteomalacia (19). In adults, bony deformities arise predominantly from fractures or increased remodeling, with the axial skeleton most commonly affected. Thus, rib deformities and kyphoscoliosis commonly produce a “funnel chest” abnormality. Enlargement of the distal tufts of the fingers due to increased bone resorption produces distal acro-osteolysis also referred to as pseudo-clubbing (20). Before the current practice of treating hyperparathyroidism, bone pain in the lower back, hips, and legs was a common manifestation of severe hyperparathyroidism. The improvement or disappearance of the pain after calcitriol therapy or parathyroidectomy confirmed that the pain arose from severe secondary hyperparathyroidism. Severe joint pain and even acute peri-arthritis were also common in long-term dialysis patients. The treatment of hyperparathyroidism has made many of these findings rare.

Progressive muscle weakness is also common in patients with long-term CKD. The weakness tends to be more pronounced in the proximal muscles and resembles that observed in both nutritional vitamin D deficiency and primary hyperparathyroidism. Although the pathogenesis of the myopathy is not known, improvement has been reported after parathyroidectomy (21). Spontaneous tendon rupture, although rare, has been reported to occur in dialysis patients and is almost always associated with severe secondary hyperparathyroidism (22). Fortunately, over the last 20 years with the routine measurement of PTH assays, there has been more aggressive diagnosis and treatment for hyperparathyroidism; thus, most
patients no longer present with clinically significant bone and muscle disease.

In addition to the role of PTH as a surrogate marker for bone turnover and a cause of bone disease, it is important to point out that it is truly a uremic toxin with multiple other clinical manifestations. The European Uremic Toxin Work Group notes that a significant uremic toxin must fulfill the following criteria (23):

A substance that accumulates in kidney disease that: (1) In vitro causes toxicity at physiologic levels, (2) In vivo is elevated in the blood of CKD patients, (3) In vivo is associated with some organ impairment in CKD, and the risk increases with duration and/or severity of CKD, (4) Lowering levels of this substance improves organ dysfunction, (5) Lowering levels of this substance improves hard clinical endpoints—reduced time to dialysis or survival.

Compared with most of the 90 or so “approved” uremic toxins, the evidence supporting that PTH is indeed a toxin is strong. Table 1 examines some of the data supporting that PTH is a uremic toxin with systemic effects that reach far beyond the bones.

The systemic manifestations of hyperparathyroidism are not surprising given the in vitro data that demonstrate that the PTH receptor is ubiquitously located in multiple tissues. The PTH1R receptor is specific for intact or N-terminus PTH only, and signals through the cAMP pathway and protein kinase C pathways, ultimately increasing intracellular calcium levels. Data in the 1970s and 1980s demonstrated that incubating multiple cells with PTH can adversely affect cell signaling (24). In 1981, Bogin incubated rat myocytes with PTH and found an increase in cAMP and intracellular calcium within minutes, leading to increased beats per minutes and cell death at an earlier time point than controls. This could be reversed if the PTH was removed from the culture or its activity blocked. Furthermore, incubation of the cells with uremic serum from animals reproduced these findings but not if the serum was from an animal that had undergone parathyroidectomy (25). In uremic dogs, electroencephalogram slowing was from an animal that had undergone parathyroidectomy (26). Other animal data support that parathyroidectomy in uremic dogs could also improve glucose intolerance (27), and reverse increased pulmonary calcification and hypertension with right ventricular hypertrophy (28).

In humans with hyperparathyroidism, studies have shown that abnormal electroencephalogram findings in patients with secondary hyperparathyroidism are correlated with elevated levels of PTH (29) and improve after parathyroidectomy (29,30). In addition, abnormal nerve conduction velocity is also worse with elevated levels of PTH and improves after parathyroidectomy (31,32). Hyperparathyroidism also leads to increased marrow fibrosis and diminished response to erythropoietin stimulating agents (33), and PTH has a direct effect to reduce bone marrow erythroid colony forming units (34). Parathyroidectomy increased blood reticulocytes and serum erythropoietin levels in dialysis patients (35). Other clinical manifestations include pruritus, a relatively common symptom associated with progressive and long-standing renal failure that frequently improves or disappears once chronic hemodialysis is initiated. However, it is especially common in patients with severe secondary hyperparathyroidism and often vanishes after parathyroidectomy (36).

Elevated PTH is also associated with cardiomyopathy, and parathyroidectomy lowers BP (37) and improves left ventricular function (38), albeit not in every study (39). In the Chronic Renal Insufficiency Cohort, PTH is a major risk factor for elevated pulse pressure; however, PTH was not associated with patient outcomes (40). Another study in predialysis CKD patients showed that PTH was associated with a history of heart failure and myocardial infarction, even after adjustment for age and diabetes (41). Calcitriol therapy has been shown to improve left ventricular hypertrophy with a strong correlation between the reduction in PTH and the improvement in left ventricular mass index (42). However, in a large randomized trial, paricalcitol significantly decreased PTH concentrations and was associated with decreased cardiovascular hospitalizations, although there was no change in left ventricular mass (43). Finally, lowering of PTH with cinacalcet improves coronary artery and valvular calcification (44). Critics of the role of PTH on cardiac disease may argue that the effects are due to the treatment itself, or to improvements in phosphorus when the PTH is lowered. However, Neves et al. performed parathyroidectomies in 5/6th nephrectomized rats and infused PTH to achieve a constant rate unresponsive to the normal homeostasis, and then fed the animals a low or high phosphorus diet to discriminate the effects of PTH and phosphorus. They found that arterial calcification occurred with elevated PTH, regardless of the phosphorus concentration (45). Furthermore, it has long been recognized that primary hyperparathyroidism has been associated with a high incidence of left ventricular hypertrophy, cardiac calcific deposits, and/or aortic and mitral valve calcification (46). Thus, PTH is a uremic toxin with major cardiovascular effects.

Extraskletal deposition of calcium also commonly occurs in patients with long-standing CKD and severe hyperparathyroidism. This may involve peri-articular, visceral, or subcutaneous deposition of calcium. Vascular calcification is almost a universal complication of long-standing CKD and the degree to which PTH plays a role is

| Table 1. Clinical manifestations associated with hyperparathyroidism in CKD |
|-----------------------------|-----------------------------|
| Bone and/or joint pain      | Fractures                   |
| Proximal myopathy           | Spontaneous tendon rupture  |
| Growth retardation in children | Extraskeletal calcifications |
| Calciphylaxis               | Anemia                      |
| Neurotoxicity               | Pruritus                    |
| Cardiomyopathy              |                             |
unclear. However, calciphylaxis was a significant and relatively common occurrence in patients with secondary hyperparathyroidism before more aggressive control of PTH and phosphorus. Calciphylaxis is characterized by spontaneous ischemic necrosis of the skin, muscles, and/or subcutaneous fat (47). This classic presentation of calciphylaxis was universally associated with marked hyperphosphatemia and hyperparathyroidism and demonstrated marked clinical improvement within days of parathyroidectomy (47). This presentation continues to occur, although much more rarely since the introduction of aggressive management of hyperparathyroidism. Unlike the earlier presentation of calciphylaxis, current presentation is not necessarily associated with very high PTH concentrations or improves with parathyroidectomy (48). The ability to recognize disorders of PTH and to direct therapy to prevent or treat many of these complications continues to require the measurement of PTH. To not measure PTH would negate all of the above knowledge and place our patients at significant risk.

Part of the problem with the use of PTH measurements has been confusion concerning the interpretation of the assays utilized. The measurement of PTH in blood has evolved since the early 1960s when RIAs were first developed for measurement of PTH. However, these first-generation assays proved not to be reliable owing to different characteristics of the antisera used and the realization that PTH circulates not only in the form of the intact 84-amino-acid peptide but also as multiple fragments of the hormone, particularly from the mid and carboxy (C)-terminal regions of the PTH molecule (45). These PTH fragments arise from direct secretion from the parathyroid gland as well as from peripheral metabolism of PTH (1–84). In the 1980s, second-generation immunometric assays (IMA) were developed and termed “intact” PTH assays, because in these assays one antibody is directed to the C-terminal region and the second to the N-terminal region (amino acids 1–34) (49). This configuration was thought to confer specificity for the 1–84 PTH (1–84), but it was subsequently learned that these assays also recognize other circulating fragments such as PTH (7–84), which may actually be inhibitory (49,50). More recently, third-generation IMAs become available, which are thought to be specific for the 1–84 PTH because the second antibody is directed to amino acids 1–4 (51,52). However, improved clinical specificity of the third-generation assays (compared with second-generation assays) in the management of CKD–mineral bone disorder has not yet been established.

A major contributing factor to this variability in PTH measurements is the lack of an international PTH standard and that the standard is usually recombinant PTH and thus does not contain circulating fragments. Furthermore, each company uses its own standard. Despite these limitations, the coefficient of variation of individual assays is very reasonable (10%–15%) (52) for a circulating biomarker. These observations resulted in KDIGO guideline recommendations, which state the following: “In patients with CKD stage 5D, we suggest maintaining intact PTH levels in the range of approximately two to nine times the upper normal limit for the assay” (guideline 4.2.3). Unfortunately, that guideline is often only partially quoted, without the second part: “We suggest that marked changes in PTH levels in either direction within this range prompt an initiation or change in therapy to avoid progression to levels outside of this range” (guideline 4.2.3 part 2) (53). This does not mean that we should not measure PTH, but in fact supports that it should be measured more often so that trends can be truly assessed. A study evaluating two different PTH assays in 12 normal volunteers and 22 hemodialysis patients revealed that even in normal volunteers multiple PTH determinations are required to assess an individual’s PTH status or change with treatment (54). Further supporting multiple PTH determinations is a study that measured PTH using six different assays in specimens obtained from 98 patients with CKD, the difference in results between the lowest and highest reading methods ranged from 1.2- to 2.7-fold. Fifty-two patients (53%) would have been treated differently according to the highest or lowest reading assay if the manufacturer’s reference interval data were used. These differences in classification could be decreased to 12% by applying assay-specific targets as recommended by the KDIGO guidelines (55).

With all of this evidence of the importance of PTH, why did the recent KDIGO guidelines (53) not assign a specific and narrower range for PTH targets? It is important to realize that clinical practice guidelines are meant to inform practice and policy, and thus only human studies, and ideally randomized controlled trials, are required as “evidence.” Evidence-based clinical practice guidelines require patient-level outcome studies to strongly support a specific therapy. Unfortunately, there are no data in human CKD patients demonstrating that these medical interventions to lower PTH prevent fracture or cardiovascular end points. But one should not confuse the absence of data with negative data. As is the case for all therapeutics, we should strive to determine their efficacy and safety in prospective randomized clinical trials. Clearly, the data above strongly support the role of PTH in the assessment of bone in patients with CKD. In addition, the results of the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events study (56) should be available in late 2012. This study randomized 3883 dialysis patients worldwide to cinacalcet or placebo, on top of standard therapies for secondary hyperparathyroidism to a target intact PTH of 300 pg/ml. The primary end point is time to the composite event comprising all-cause mortality or non-fatal cardiovascular events (myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event). This study will be the first to directly test if lowering PTH with a calcimimetics to a predetermined value will affect patient-level end points. Whether all interventions that lower PTH to this value have similar efficacy would need to be further tested in clinical trials.

In summary, PTH is clearly a uremic toxin with systemic manifestations that result in patient morbidity and mortality. The only way to assess the presence or degree of hyperparathyroidism is to measure PTH. The use of PTH as a biomarker of bone remodeling is by no means perfect, but hyperparathyroidism has effects far beyond bone and should be treated. Given the costs of therapies used to treat hyperparathyroidism, more frequent assessment is likely to
be cost-effective so that true trends, rather than isolated values, are utilized in clinical decision making.

Acknowledgments
S.M.S. is supported by grants from the National Institutes of Health. S.M.S. is supported by grants from the National Institutes of Health and Veterans Administration.

Disclosures
S.M.S. is a consultant and has received honoraria from Amgen, Genzyme/Sanoﬁ, KAI, Litholink, and Novartis and has received grant support from Amgen, Genzyme, Shire, and Novartis. S.M.S. is a consultant and received honoraria from Amgen, Cytochrome, KAI, Litholink, and Roche, and has received grant support from Amgen, Abbott, Cytochrome, Shire, and Vifor.

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Published online ahead of print. Publication date available at www.cjasn.org.