

## Diagnosis, Assessment, and Treatment of Bone Turnover Abnormalities in Renal Osteodystrophy

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**T**HE ABNORMALITIES of the skeleton in chronic kidney disease (CKD), collectively known as renal osteodystrophy, are an important cause of morbidity and decreased quality of life. In the management of patients with kidney disease, it is necessary to have a rational approach to the diagnosis and assessment of renal osteodystrophy in order to devise a treatment plan that hopefully will lead to an improved outcome. In the past, the term renal osteodystrophy was mainly equated only with abnormalities of bone turnover, but as described in the article by Cunningham and Sprague<sup>1</sup> in this same issue, renal osteodystrophy is a complex disorder of compromised bone strength in CKD patients. While osteoporosis is a term used to describe fragile bones prone to fracture in the general population and is most often assessed by dual x-ray absorptiometry (DEXA), renal osteodystrophy should be the principal term to describe fragile bones prone to fracture and other morbidities in CKD. Renal osteodystrophy is a function of bone turnover (assessed by bone biopsy), bone density (assessed by DEXA or quantitative CT [qCT]), and bone architecture, but the principal determinant of bone fragility in CKD is abnormal bone turnover. However, diagnosing and treating bone turnover abnormalities remains challenging.

Our discussion group met to assess the current state of knowledge, understand the basis of our current therapy, and identify the information that needs to be gathered to improve the therapy of bone turnover and thereby improve the disorder

of renal osteodystrophy. A number of important questions, listed in Table 1, were considered.

### BONE BIOPSY

The precise nature of abnormalities of bone turnover can be reliably determined with the use of bone biopsy, which remains the gold standard for diagnosis. Bone biopsy is the parameter to which all serum biochemistry and other noninvasive assessments of bone turnover in CKD must be compared.<sup>2</sup> A major disadvantage is the invasive nature of the procedure, the analysis of a single site and type of bone, as well as its overall complexity and cost. While the general statement that bone biopsy is the gold standard is beyond debate, there are many issues with the technique that need to be considered.<sup>2-4</sup> The principal site of biopsy is the iliac crest. Investigators use 1 of 2 techniques to obtain the bone sample—either a transiliac approach or vertical biopsy. The bone is then embedded in plastic, sectioned, stained, and analyzed using quantitative histomorphometry, a technique that requires considerable expertise and is only available at a few centers in the world. The standard assessment has been mainly of trabecular bone, and evaluation of cortical width or cellular activity in the cortex and endosteal envelope has not been well integrated into the evaluation of renal osteodystrophy. Additional difficulties with the biopsy procedures include the number and nature of the healthy bone samples used to define the normal ranges for the various cellular activities. Normal ranges are often based upon small numbers of patients and may not be truly representative of the patient groups for which they serve as controls.

Age, sex, race, and geographic area may be important in determining the normal ranges for the parameters measured, and appropriate normal ranges need to be developed and expanded using standardized techniques. There is a need for the biopsy technique to be standardized, not only in the approach, but also in the parameters

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**Table 1. Questions Considered by the Work Group on Diagnosis, Assessment, and Treatment of Renal Osteodystrophy**

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- Should bone biopsy remain the gold standard?
  - What is the current prevalence of the different types of bone turnover abnormalities in renal osteodystrophy (ROD)?
  - How and how often should PTH be measured?
  - What bone markers are useful?
  - In there a role for DEXA in assessing bone turnover?
  - How does bone turnover relate to vascular calcification?
  - What about CKD Stages 3 and 4?
  - What is the role of newer dialysis techniques?
  - What is the role of new therapeutic agents?
  - Where should we go from here?
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that are measured and their method of measurement. In general, histomorphometry follows the nomenclature established by the American Society of Bone and Mineral Research. However, standardization of sample processing, sample preservation, and analysis could be further improved by the use of quality control samples sent to the various laboratories making the measurements. Standardization of the histomorphometric analysis of uremic bone would help ensure the integrity and consistency of bone histology analysis regardless of the laboratory being used. Thus, while bone biopsy remains the gold standard for assessment of bone turnover, the work group identified a need for improved standardization of this assessment tool, and a need to increase the number of individuals who are trained in the technique.

#### EPIDEMIOLOGY OF RENAL OSTEODYSTROPHY

The prevalence of the different types of bone turnover observed in renal osteodystrophy appears to have changed within the past 2 decades. The predominance of hyperparathyroid bone disease (high-turnover disease) has diminished as more adynamic renal osteodystrophy (low-bone-turnover disease) has appeared, especially in the dialysis population.<sup>5-7</sup> The changing profile of the different types of bone turnover has likely occurred because of changes in the therapy of renal osteodystrophy, changes in dialysis techniques, and changes in patient populations. The current prevalence of the different types of bone turnover is uncertain, not only in patients on dialysis, but also throughout the course of CKD.

Prevalence may also vary according to differences in individual centers and geographic areas.

Abnormalities of bone turnover begin early in CKD.<sup>8</sup> Therefore, it would be highly desirable to begin therapy in CKD stages 3 and 4 (or earlier in children), rather than the current approach of deferring intervention until the patient reaches dialysis. Recent observations indicate that many variables in the pathogenesis of renal osteodystrophy have not been routinely considered in epidemiologic studies of its treatment. Thus, it is becoming increasingly important to consider race, sex, age, the type and chronicity of kidney disease, the effects of prior therapy including glucocorticoids and immunosuppressive agents, recombinant growth hormone in children, the effects of nutrition and malnutrition on the skeleton, menopausal status, and the differences between hemodialysis and peritoneal dialysis. It may also be necessary to consider the geographic location of the patients studied. All of these variables may lead to abnormal bone turnover and induce other abnormalities of bone strength.

Because of these multiple variables, the precise prevalence of the different types of renal bone disease is uncertain. Additional broad cross-sectional studies would be useful to form a basis for further evaluation of traditional and new therapies. Information on the state of the skeleton in CKD stages 3 and 4 is also needed so that adequate treatment strategies can be planned. The work group identified a need for large cross-sectional studies to better characterize bone across all stages of CKD.

#### BIOCHEMICAL MARKERS

##### *Parathyroid Hormone*

While bone histology is the gold standard for accurate assessment of bone turnover, the search for biochemical markers has been ongoing for a number of years. Measurement of parathyroid hormone (PTH) has been widely used since PTH is a major regulator of bone turnover and skeletal cellular activity.<sup>7,9-11</sup> Over the past 1 to 2 decades, the principal biochemical marker for diagnosis and classification and for monitoring the therapy of bone turnover has been measurements of PTH by a 2-site immunometric technique called "intact" PTH. While such assays have been extremely valuable, it is now known that these assays also measure a large PTH fragment

**Table 2. Glossary of PTH Terminology**

**Intact PTH**, usually refers to PTH measured by a 2-site immunometric assay. If radioactive reagents are used, the term immunoradiometric assay (**IRMA**) would apply, while if chemiluminescent reagents are used, the term immunochemiluminescence assay (**ICMA**) would apply. Initial assays were called “second-generation PTH assays” as a comparison to the older mid-region and n-terminal assays. However, the widely used intact assay is a first generation of *intact* assays whereby 2 antibodies are used to simultaneously detect the N-terminal and C-terminal. However, it is now known that many, if not all, such assays also measure C-terminal PTH fragments such as PTH 7-84, which are of unclear biologic significance. As a result, new “second-generation intact” assays such as the bio-intact and whole PTH assays have been developed.

**Bio-Intact PTH** is a 2-site chemiluminescence assay specific for PTH 1-84 developed by Nichols Institute Diagnostics.

**Whole PTH** is also a 2-site immunoradiometric assay specific for PTH 1-84 developed by Scantibodies, Inc. Since PTH 1-84 mediates its biological effects by increasing the activity of adenylate cyclase, this assay is also known as **CAP** (cyclase-activating PTH).

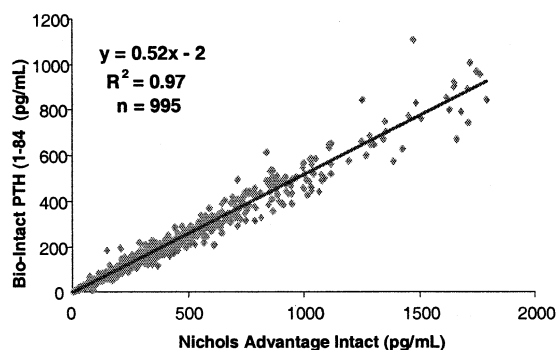
Since **PTH 7-84** does not stimulate adenylate cyclase, the measurement of PTH 7-84 is known as **CIP** (cyclase-inactive PTH). PTH 7-84 can be measured by subtracting values for PTH 1-84 from values obtained with the older “intact” PTH assays.

that is likely PTH 7-84. This has led to the development of PTH assays specific for PTH 1-84. Currently, there are 2 such assays available, Bio-Intact PTH from Nichols (Santee, CA) and Whole PTH (CAP) from Scantibodies (San Clemente, CA)<sup>11-14</sup> (Table 2). Much of the data with renal osteodystrophy and its correlation with PTH values, however, relate to data obtained with the original immunometric “intact” PTH assays from patients either untreated with vitamin D or who received small doses of oral calcitriol.

The recently published NKF K/DOQI guidelines (*Am J Kidney Dis* 42:S1-S202, 2003 [suppl 3]) provide guidance on the diagnosis and treatment of disorders of renal osteodystrophy using evidence-based guidelines constructed from literature with the intact assay, and the work group felt it was premature to utilize the new assays as bone biopsy data with the new specific PTH 1-84 immunometric assays are limited at the present time. Clearly, further definitive confirmatory data are necessary.

A comparison of PTH determinations in patients on hemodialysis using intact and whole/bioactive immunometric assays is shown in Fig 1. While the correlation between the 2 assays is excellent, the more specific PTH 1-84 assays will ultimately be useful, offering the potential for improved standardization of PTH measurements in every country. This will likely bring some homogeneity to the field, since many of the older assays measure these PTH fragments with varying efficacy, as illustrated in Fig 2. PTH values in these assays are not readily comparable to those

obtained by other investigators using different clinical laboratories. In contrast, as illustrated in Fig 3, results obtained with 2 different whole/bioactive PTH 1-84 immunometric assays appear to give comparable results. Thus, there is now the possibility of widespread standardization of PTH determinations. Some investigators have suggested that measurement of these N-terminally truncated PTH fragments, particularly when considered together with values for PTH 1-84, may offer some enhanced diagnostic potential by creating a ratio between the intact PTH 1-84 and PTH fragments.<sup>15</sup> Such conclusions remain controversial,<sup>13,16</sup> and much further work is required on the biology of such PTH fragments before reliable diagnostic or therapeutic decisions would be made from these values.



**Fig 1. A comparison of PTH determinations using a first-generation immunometric assay (Nichols Advantage Intact) to results obtained with a second-generation PTH 1-84 immunometric assay (Bio-Intact PTH 1-84) in patients on hemodialysis. (Dr K. Ramki, Nichols Diagnostic Institute, personal communication; cited in Martin et al.<sup>46</sup>)**

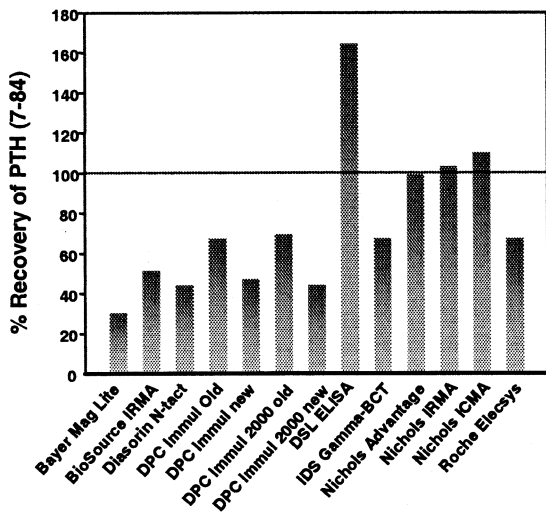


Fig 2. The ability of various commercial first-generation "intact" PTH immunometric assays to detect PTH 7-84. Considerable variability is apparent and may contribute to variations in PTH values between different laboratories. (Data from UK NEQAS, with permission.)

Research is currently ongoing to define the variables involved in such measurements, and with time, it is likely that the diagnostic correlates of PTH assays will improve. If measurements of PTH are the mainstay of categorizing, monitoring, and treating abnormal bone turnover, it is critical to handle the sample carefully, evaluate sample stability, and consider the timing of the blood draws in order to obtain reliable results. In general, more frequent measurements of PTH should be performed and consideration should be given to multiple results of PTH determinations for trend analysis. Ambient serum calcium also must be considered for diagnostic and therapeutic consideration. This is particularly important in the initial assessment of hyperparathyroidism and in the active phases of treatment. Measurements of PTH every 3 months are sufficient only in an otherwise stable patient who has reached the established bone management targets.

*Other Biochemical Markers*

While measurements of PTH are the mainstay of the assessment of bone turnover and thus the precise type of renal osteodystrophy, other biochemical markers may also be useful. Measurements of total alkaline phosphatase should be

considered in conjunction with determinations of PTH.<sup>17-20</sup> Measurements of total alkaline phosphatase are complicated by the measurement of nonskeletal enzyme and accordingly, in some cases, measurements of bone-specific alkaline phosphatase may be required. However, there are insufficient data available to recommend that bone-specific alkaline phosphatase concentrations be measured routinely.

The measurements of many other biochemical markers that may reflect skeletal activity, such as collagen breakdown products and osteocalcin, are complicated by the accumulation of these collagen breakdown products in serum, since they depend on the kidney for glomerular filtration and excretion. Thus, the measurement of these markers has limited utility in the setting of kidney failure. While it would be attractive to use such markers in the presence of less impaired renal function, particularly in stages 3 to 4 CKD, correlative data with bone histology are lacking at these stages of CKD. Much further work needs to be done to validate the use of these biochemical markers at the various stages of kidney disease. Recent studies have provided preliminary evidence that measurements of the isoenzyme acid phosphatase, TRAP-5b, may be useful as an index of osteoclast activity in the setting of

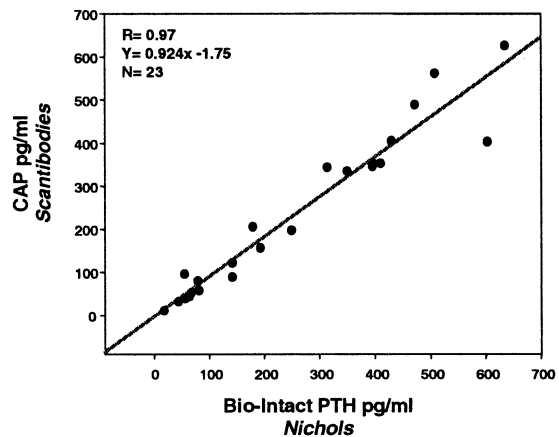


Fig 3. The correlation between 2 different second-generation PTH 1-84 immunometric assays in patients on hemodialysis. CAP refers to cyclase-activating PTH and is the PTH 1-84 assay from Scantibodies Inc. Bio-Intact PTH is the PTH 1-84 assay from the Nichols Diagnostic Institute. The correlation between the 2 assays is excellent. Comparable values are obtained with each assay, offering the potential for excellent standardization of PTH 1-84 results between different laboratories. (Data from Martin et al.<sup>46</sup>)

kidney disease. Similarly, emerging data suggest that measurements of osteoprotegerin (OPG) may also contribute useful information in the assessment of renal osteodystrophy. These observations stem from developments showing that the receptor activator of nuclear factor  $\kappa$ B [RANK]/RANK ligand [RANKL]/OPG system is a major regulator of bone metabolism,<sup>21</sup> and accordingly, measurements of the components of this system may provide useful information. The data available at the present time should be considered preliminary, and much further work needs to be done before such results can be interpreted in a definitive fashion. Indeed, such results will need to be compared with bone histology.

#### ROLE OF DEXA

DEXA is a widely used technique to measure bone mineral density; however, its role in the assessment and therapy of renal osteodystrophy is not well established.<sup>20</sup> In general, there is no role for the use of DEXA in the assessment of bone turnover. Its role is limited to providing information on overall bone mineral content/density, but not how that mineral is arranged. In the setting of kidney disease, measurements of bone mineral content do not give any indication of abnormalities in the cellular components of bone, and so cannot be used for classification of various forms of renal osteodystrophy (eg, high-turnover and low-turnover disease). While it is reasonable to assume that some useful information could be obtained with this technique on a longitudinal basis, precise data are not available to support this view. Theoretically, if bone mineral content is progressively decreasing, the skeleton is undergoing demineralization, a problem that ultimately will need to be addressed. Much of the current data on the use of bone mineral density relates to fracture risk in osteoporosis. No such data are available for the fracture risk in patients with renal osteodystrophy. Similarly, there is a lack of data to support the use of DEXA in CKD stages 2 to 4, since interpretation of results may be complicated by menopausal status, testosterone levels, or other concurrent therapy, eg, with glucocorticoids, which may contribute to decreased bone mineral content. In general, the correlations with bone histology and DEXA are poor. Overall, the role of DEXA in the assessment and management of renal osteodystro-

phy is uncertain at the present time, and much further work needs to be done to define the role of this technique.

#### VASCULAR CALCIFICATION AND ITS RELATION TO BONE TURNOVER

The relationship between vascular calcification and bone turnover is an active area of research. Existing data demonstrate an association between these parameters, but many details remain to be determined. This topic is explored in detail by the vascular calcification group and will not be considered further here.

#### RENAL OSTEODYSTROPHY IN CHILDREN

Renal osteodystrophy in children appears to differ from that seen in adults in that bony deformities and abnormal linear bone growth and abnormal growth velocity are significant problems. Associated abnormalities such as acidosis, vitamin D deficiency, protein-calorie malnutrition, and abnormal insulin-like growth factor (IGF-1) and growth hormone systems may play a role.<sup>22</sup> These factors may be operative through the course of CKD from CKD stages 2 to 5. The correction of acidosis as well as administration of calcitriol each can lead to improved growth velocity. In general, adynamic bone is not commonly seen in childhood but may develop as a result of treatment with large doses of calcitriol,<sup>23</sup> and may result in severe growth retardation.<sup>24</sup> In children, high-turnover bone disease secondary to hyperparathyroidism seems to predominate. Thus, broad generalizations between findings in adults and children should be considered with caution because of the different manifestations of skeletal abnormalities. The abnormalities of the growth plate merit detailed consideration.

#### ROLE OF NEWER DIALYSIS TECHNIQUES

Much of what we currently know about renal osteodystrophy in patients on dialysis applies to patients on hemodialysis 3 times a week or to patients who receive chronic ambulatory peritoneal dialysis. How newer dialysis techniques may impact bone and mineral metabolism is unknown. Long dialysis 6 days a week, eg, nocturnal dialysis, is often associated with phosphate depletion, and phosphate supplementation is required. Progressive decreases in bone min-

eral content occur in these patients, the significance of which is unclear at the present time. In such patients, this loss of bone mineral has been treated with increases in dialysate calcium, but the consequences of this treatment on bone or other extraskeletal calcification processes are unknown. Since long nocturnal dialysis is such a major difference from our current therapies, this approach needs detailed study in order to refine how the needs of the skeleton should be addressed. Similarly, whether short daily dialysis may be associated with a different spectrum of skeletal abnormalities remains to be determined.

#### THE ROLE OF NEW THERAPEUTIC AGENTS

##### *Vitamin D Analogs*

While the identification and therapy of renal osteodystrophy continues to evolve, new therapies are being brought to bear on this problem. Over the last several years, there has been an introduction of 4 vitamin D analogs designed to manipulate the activity of the parathyroid glands while minimizing the toxicities that may result from increased intestinal absorption of calcium and phosphorus produced by the native hormone, calcitriol. 19-nor-1,25-(OH)<sub>2</sub>D<sub>2</sub>, or paricalcitol, an analog based upon the vitamin D<sub>2</sub> structure with lesser toxicity than calcitriol, is the most widely used vitamin D sterol in the United States.<sup>25-29</sup> Also in the United States, a synthetic pro-hormone, 1- $\alpha$ -(OH)D<sub>2</sub>, or doxercalciferol, has been introduced that also has the potential for lesser toxicity than calcitriol because it too is based on the vitamin D<sub>2</sub> structure.<sup>30,31</sup> In Asia, 22-oxacalcitrol, or maxacalcitol, is widely used,<sup>32</sup> and falecalcitriol has also been introduced.<sup>33</sup> With paricalcitol, there is broad experimental evidence in animals of lesser toxicity than the native hormone.<sup>34-37</sup> These findings have been confirmed in patients, albeit to a more limited extent. The influence of this sterol on the histology of bone is not well understood at the present time. Recent retrospective data suggest that there may be a survival advantage in patients treated with paricalcitol compared to calcitriol, which cannot be accounted for by adjustments for known comorbidities.<sup>38</sup> Further studies in this regard are indicated. If this survival advantage can be confirmed, the strategy for the use of such vitamin D analogs with lesser toxicity than the parent compound would be validated.<sup>39</sup> Differences in the

actions of such analogs on the vasculature and vascular calcification processes need to be clarified. One area of therapy that has not been adequately addressed is the possibility that vitamin D sterols may affect the skeleton independent of PTH, and so reliance on the reduction in PTH measurements may be an oversimplification. The independent influences of vitamin D sterols on bone should be considered.

##### *Novel Phosphate Binders*

In recent years, as a result of the focus on calcification at extraskeletal sites, including the vasculature, non-calcium-containing phosphate binders have been developed. Sevelamer hydrochloride, a phosphate-binding, nonabsorbable polymer, is widely used.<sup>40</sup> One prospective randomized trial indicates that the progression of vascular calcification may be retarded with this agent,<sup>41</sup> and this observation needs to be confirmed. Other non-calcium-containing phosphate binders are in development or in clinical trial.<sup>42</sup>

##### *Calcimimetic Agents*

A novel class of agents, the calcimimetics, has been designed to target the calcium receptor in the parathyroid glands, thereby providing the means of controlling hyperparathyroidism independent of other approaches. Preliminary studies of 1 calcimimetic agent appear to show efficacy in the control of hyperparathyroidism. The mechanism of action of this agent is independent of traditional approaches to the control of hyperparathyroidism in that it offers the potential to lessen calcium toxicity and is likely to be useful to augment current therapeutic approaches.<sup>43-45</sup>

#### SUMMARY

Renal osteodystrophy, in which abnormalities of bone turnover predominate, continues to be a complication of CKD and is associated with morbidity and poor quality of life. There is a need to assess the current status and distribution of the types of renal osteodystrophy and to define appropriate therapeutic targets. Bone biopsy remains the gold standard in the diagnosis of the precise type of pathologic changes of bone turnover. There is also a need to standardize bone histology and biopsy techniques and to refine the targets for biochemical parameters that will al-

low more accurate noninvasive assessment of skeletal activity. Enhanced understanding of the differences in renal osteodystrophy in children compared to adults is needed. The use of newer vitamin D analogs such as paricalcitol may result in improved patient outcomes compared to therapy with the native hormone, calcitriol. Such studies need to be confirmed and extended. Novel compounds such as the calcimimetics may provide additional therapeutic approaches to control hyperparathyroidism with minimum calcium toxicity.

### REFERENCES

- Cunningham J, Sprague SM, on behalf of the Osteoporosis Work Group: Osteoporosis in chronic kidney disease. *Am J Kidney Dis* 43:566-571, 2004
- Trueba D, Sawaya BP, Mawad H, et al: Bone biopsy: Indications, techniques, and complications. *Semin Dial* 16: 341-345, 2003
- Coen G, Mazzaferro S, Ballanti P, et al: Renal bone disease in 76 patients with varying degrees of predialysis chronic renal failure: A cross-sectional study. *Nephrol Dial Transplant* 11:813-819, 1996
- Parfitt AM: Renal bone disease: A new conceptual framework for the interpretation of bone histomorphometry. *Curr Opin Nephrol Hypertens* 12:387-403, 2003
- Sherrard DJ: Aplastic bone: A nondisease of medical progress. *Adv Ren Replace Ther* 2:20-23, 1995
- Sherrard DJ, Hercz G, Pei Y, et al: The aplastic form of renal osteodystrophy. *Nephrol Dial Transplant* 11:29-31, 1996 (suppl 3)
- Pei Y, Hercz G, Greenwood C, et al: Risk factors for renal osteodystrophy: A multivariate analysis. *J Bone Miner Res* 10:149-156, 1995
- Coen G, Ballanti P, Bonucci E, et al: Renal osteodystrophy in predialysis and hemodialysis patients: Comparison of histologic patterns and diagnostic predictivity of intact PTH. *Nephron* 91:103-111, 2002
- Malluche HH, Mawad H, Trueba D, et al: Parathyroid hormone assays—Evolution and revolutions in the care of dialysis patients. *Clin Nephrol* 59:313-318, 2003
- Wang M, Hercz G, Sherrard DJ, et al: Relationship between intact 1-84 parathyroid hormone and bone histomorphometric parameters in dialysis patients without aluminum toxicity. *Am J Kidney Dis* 26:836-844, 1995
- Martin KJ, Gonzalez EA: The evolution of assays for parathyroid hormone. *Curr Opin Nephrol Hypertens* 10:569-574, 2001
- Malluche HH, Monier-Faugere MC: PTH 1-84, PTH fragments and bone turnover. *Am J Kidney Dis* 41:1127, 2003
- Coen G, Bonucci E, Ballanti P, et al: PTH 1-84 and PTH “7-84” in the noninvasive diagnosis of renal bone disease. *Am J Kidney Dis* 40:348-354, 2002
- Goodman WG, Juppner H, Salusky IB, et al: Parathyroid hormone (PTH), PTH-derived peptides, and new PTH assays in renal osteodystrophy. *Kidney Int* 63:1-11, 2003
- Monier-Faugere MC, Geng Z, Mawad H, et al: Improved assessment of bone turnover by the PTH-(1-84)/large C-PTH fragments ratio in ESRD patients. *Kidney Int* 60: 1460-1468, 2001
- Salusky IB, Goodman WG, Kuizon BD, et al: Similar predictive value of bone turnover using first- and second-generation immunometric PTH assays in pediatric patients treated with peritoneal dialysis. *Kidney Int* 63:1801-1808, 2003
- Urena P, De Vernejoul MC: Circulating biochemical markers of bone remodeling in uremic patients. *Kidney Int* 55:2141-2156, 1999
- Urena P, Hruby M, Ferreira A, et al: Plasma total versus bone alkaline phosphatase as markers of bone turnover in hemodialysis patients. *J Am Soc Nephrol* 7:506-512, 1996
- Coen G, Ballanti P, Bonucci E, et al: Bone markers in the diagnosis of low turnover osteodystrophy in haemodialysis patients. *Nephrol Dial Transplant* 13:2294-2302, 1998
- Rix M, Andreassen H, Eskildsen P, et al: Bone mineral density and biochemical markers of bone turnover in patients with predialysis chronic renal failure. *Kidney Int* 56:1084-1093, 1999
- Gonzalez EA: The role of cytokines in skeletal remodeling: Possible consequences for renal osteodystrophy. *Nephrol Dial Transplant* 15:945-950, 2000
- Kuizon BD, Salusky IB: Growth retardation in children with chronic renal failure. *J Bone Miner Res* 14:1680-1690, 1999
- Salusky IB, Kuizon BD, Belin TR, et al: Intermittent calcitriol therapy in secondary hyperparathyroidism: A comparison between oral and intraperitoneal administration. *Kidney Int* 54:907-914, 1998
- Kuizon BD, Goodman WG, Juppner H, et al: Diminished linear growth during intermittent calcitriol therapy in children undergoing CCPD. *Kidney Int* 53:205-211, 1998
- Slatopolsky E, Dusso A, Brown A: New analogs of vitamin D3. *Kidney Int Suppl* 73:S46-S51, 1999
- Slatopolsky E, Cozzolino M, Finch JL: Differential effects of 19-nor-1,25-(OH)(2)D(2) and 1 $\alpha$ -hydroxyvitamin D(2) on calcium and phosphorus in normal and uremic rats. *Kidney Int* 62:1277-1284, 2002
- Sprague SM, Lerma E, McCormick D, et al: Suppression of parathyroid hormone secretion in hemodialysis patients: Comparison of paricalcitol with calcitriol. *Am J Kidney Dis* 38:S51-S56, 2001 (suppl 5)
- Martin KJ, González EA, Gellens M, et al: 19-nor-1 $\alpha$ -25-dihydroxyvitamin D<sub>2</sub> (Paricalcitol) safely and effectively reduces the levels of intact PTH in patients on hemodialysis. *J Am Soc Nephrol* 9:1427-1432, 1998
- Martin KJ, Gonzalez EA, Gellens ME, et al: Therapy of secondary hyperparathyroidism with 19-nor-1 $\alpha$ ,25-dihydroxyvitamin D<sub>2</sub>. *Am J Kidney Dis* 32:S61-S66, 1998 (suppl 2)
- Frazao JM, Elangovan L, Maung HM, et al: Intermittent doxercalciferol (1 $\alpha$ -hydroxyvitamin D(2)) therapy for secondary hyperparathyroidism. *Am J Kidney Dis* 36:550-561, 2000
- Maung HM, Elangovan L, Frazao JM, et al: Efficacy and side effects of intermittent intravenous and oral doxercalciferol (1 $\alpha$ -hydroxyvitamin D(2)) in dialysis patients with

secondary hyperparathyroidism: A sequential comparison. *Am J Kidney Dis* 37:532-543, 2001

32. Akizawa T, Suzuki M, Akiba T, et al: Long-term effect of 1,25-dihydroxy-22-oxavitamin D(3) on secondary hyperparathyroidism in haemodialysis patients. One-year administration study. *Nephrol Dial Transplant* 17:28-36, 2002 (suppl 10)

33. Akiba T, Marumo F, Owada A, et al: Controlled trial of falecalcitriol versus alfalcidol in suppression of parathyroid hormone in hemodialysis patients with secondary hyperparathyroidism. *Am J Kidney Dis* 32:238-246, 1998

34. Martin KJ, Gonzalez EA: Strategies to minimize bone disease in renal failure. *Am J Kidney Dis* 38:1430-1436, 2001

35. Slatopolsky E, Brown AJ: Vitamin D analogs for the treatment of secondary hyperparathyroidism. *Blood Purif* 20:109-112, 2002

36. Brown AJ, Slatopolsky E: Vitamin D analogs: Perspectives for treatment. *Miner Electrolyte Metab* 25:337-341, 1999

37. Martin KJ, Gonzalez E, Lindberg JS, et al: Paricalcitol dosing according to body weight or severity of hyperparathyroidism: A double-blind, multicenter, randomized study. *Am J Kidney Dis* 38:S57-S63, 2001 (suppl 5)

38. Teng M, Wolf M, Lowrie E, et al: Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. *N Engl J Med* 349:446-456, 2003

39. Drueke TB, McCarron DA: Paricalcitol as compared with calcitriol in patients undergoing hemodialysis. *N Engl J Med* 349:496-499, 2003

40. Chertow GM, Burke SK, Dillon MA, et al: Long-term effects of sevelamer hydrochloride on the calcium  $\times$  phosphate product and lipid profile of haemodialysis patients. *Nephrol Dial Transplant* 14:2907-2914, 1999

41. Chertow GM, Burke SK, Raggi P: Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. *Kidney Int* 62:245-252, 2002

42. Hutchison AJ: Calcitriol, lanthanum carbonate, and other new phosphate binders in the management of renal osteodystrophy. *Perit Dial Int* 19:S408-S412, 1999 (suppl 2)

43. Coburn JW, Maung HM: Calcimimetic agents and the calcium-sensing receptor. *Curr Opin Nephrol Hypertens* 9:123-132, 2000

44. Olgaard K, Lewin E: Prevention of uremic bone disease using calcimimetic compounds. *Annu Rev Med* 52:203-220, 2001

45. Quarles LD, Sherrard DJ, Adler S, et al: The calcimimetic AMG 073 as a potential treatment for secondary hyperparathyroidism of end-stage renal disease. *J Am Soc Nephrol* 14:575-583, 2003

46. Martin KJ, Gonzalez EA: Parathyroid hormone: New assays, new receptors. *Semin Nephrol* 24:3-4, 2004