Role of Bone Biopsy in Stages 3 to 4 Chronic Kidney Disease

Anca Gal-Moscovici*† and Stuart M. Sprague*

*Division of Nephrology and Hypertension and Department of Medicine, Evanston Northwestern Healthcare, Northwestern University Feinberg School of Medicine, Evanston, Illinois; and †Nephrology and Hypertension Services, Hadassah Medical Center, Hebrew University, Ein-Karem, Jerusalem, Israel

Secondary hyperparathyroidism develops relatively early in chronic kidney disease as a consequence of impaired phosphate, calcium, and vitamin D homeostasis. The disease state in chronic kidney disease, which includes the histologic features of bone disease, defined as renal osteodystrophy, and the hormonal and biochemical disturbances, have recently been redefined as a disease syndrome and is referred to as "chronic kidney disease–mineral and bone disorder." As chronic kidney disease progresses, specific histologic disturbances in the bone develop, which may or may not be predictable from the biochemical and hormonal changes that are associated with chronic kidney disease. In addition, patients may have had underlying bone disease before developing kidney failure or may have been treated with agents that will alter the classical pathologic findings of the bones in chronic kidney disease and their relation to parathyroid hormone. Thus, in stage 5 chronic kidney disease, bone biopsy with quantitative histomorphometric analysis is considered the gold standard in the diagnosis of renal osteodystrophy. In contrast to stage 5 chronic kidney disease, there are very few data on the histologic changes in bone in earlier stages of chronic kidney disease. There also is no adequate information on the etiopathogenesis of bone disease in stages 3 and 4 chronic kidney disease. Thus, because biochemical data cannot predict bone pathology in stages 3 and 4 chronic kidney disease, bone biopsy should be used to define these bone changes and to allow appropriate therapeutic approaches.

Clin J Am Soc Nephrol 3: S170–S174, 2008. doi: 10.2215/CJN.01100307

Patients with chronic kidney disease (CKD) have complex abnormalities in bone and mineral metabolism (1–4). In addition, patients may have other bone diseases before developing kidney failure (*e.g.*, osteoporosis, vitamin D deficiency, steroid-bone disease), which may respond differently to the abnormalities of mineral metabolism that are associated with CKD. Thus, the pathologic findings in bone may not be predicted by routine biochemical testing or bone densitometry. Bone biopsies are performed to understand the pathophysiology of bone disease and to relate histologic findings to the clinical symptoms and biochemical disorders that are associated with CKD. In addition, bone biopsies have been helpful in determining the clinical course and response to treatment. In stage 5 CKD, bone biopsy with quantitative histomorphometric analysis has become the gold standard in the diagnosis of renal osteodystrophy. In contrast to stage 5 CKD, the role of bone biopsy in earlier stages of CKD, in particular stage 3 or 4, is not well defined. This article focuses on the role of the bone biopsy in stages 3 and 4 CKD.

Role of Bone Biopsy in Stage 5 CKD

In stage 5 CKD, the established positive correlation between bone turnover determined by histomorphometric analysis as a function of bone formation rate or activation frequency (5) and serum parathyroid hormone (PTH) concentration has enabled the use of PTH as a marker of bone turnover for diagnosing and monitoring therapy of hyperparathyroid bone disease; however, the implementation of various treatment strategies directed to reducing PTH concentrations has resulted in disruption of the relationship between bone turnover and PTH (6), such as aluminum hydroxide, which directly suppresses bone metabolism by three major mechanisms: (*1*) Inhibition of hydroxyapatite formation and growth, (*2*) inhibition of bone cell proliferation, and (*3*) suppression of bone cell activity. These deleterious effects lead to inhibition of bone mineralization, resulting in osteoid accumulation (osteomalacia), decreased bone formation, and bone turnover independent of its effect on PTH (7–10). Similarly, the use of calcium-based phosphate binders may affect bone metabolism. They adversely affect the osteoblastic and osteoclastic number and activity by a mechanism that is independent of the PTH concentrations, leading to low-turnover bone that differs from that caused by aluminum by the absence of osteomalacia (11,12). The use of active vitamin D compounds, particularly the intermittent administration of relatively high dosages of calcitriol, corrects some of the histologic features of hyperparathyroid bone disease, but a substantial proportion of these patients may also develop adynamic bone disease despite persistently elevated PTH levels (13,14). This loss of correlation between PTH concentrations and bone turnover has rendered the use of PTH as a definitive marker for the determination and monitoring of renal bone disease less than ideal.

The spectrum of bone disease observed in CKD–mineral and bone disorder ranges from high-turnover bone disease, classically represented by increased bone formation rate (BFR), increased osteoblastic/osteoclastic activity and number, reduced

Correspondence: Dr. Anca Gal-Moscovici, Nephrology and Hypertension Services, Hadassah Medical Organization, Jerusalem 91120, POB 12000, Israel. Phone: 972-2-6776881; Fax: 972-2-6446335; E-mail: galanca@hadassah.org.il

ISSN: 1555-9041/301–0170

osteoid volume, and high peritrabecular fibrosis surface area, to low turnover lesions, whereby low BFR is generally defined as being equal to or below the lower value observed in normal individuals. The most representative forms of low-turnover bone disease are osteomalacia, defined as markedly increased osteoid volume and thickness with decreased fibrosis, and adynamic or aplastic bone disorder, characterized by paucity of bone cells with severely reduced osteoid seams and absence of fibrosis. Between these extremities is the so-called mixed uremic osteodystrophy, which includes findings of increased osteoid volume and fibrosis surfaces and may present with different degrees of BFR that vary from high to normal and low (4). Specifying the BFR value is of extreme importance when authors report on mixed uremic osteodystrophy, because this disorder may belong to low or high bone turnover depending on the value of BFR. This also creates difficulties in interpreting the correlation of the different forms of renal bone disease with the PTH levels (6). Consequently, histomorphometric analyses have become indispensable in many patients with stage 5 CKD in which the bone status is affected by different treatment modalities and no longer correlates with the circulating PTH levels.

Pathogenesis of Bone Disease in Early Stages of CKD

In the earlier stages of CKD, little is known about changes in bone metabolism and the effect of disturbed mineral metabolism on bone histology. In the incipient stages of CKD, normal or mildly elevated PTH concentrations have until recently seldom resulted in therapy and thus may have mitigated the demand for bone biopsy; however, it has become evident that disturbances in bone metabolism presents very early in CKD. Humoral factors that usually are involved in the maintenance of normal bone homeostasis are perturbed as soon as the GFR drops below 60 to 70 ml/min (15). An increase in the fractional excretion of phosphate is the first disorder to develop to maintain normal serum phosphorus concentrations. Phosphorus regulation is mediated by increased secretion of phosphaturic hormones such as PTH and fibroblast growth factor 23 (FGF-23) and decreased production of calcitriol (16,17). Serum FGF-23 levels increase as soon as the GFR decreases below 60 ml/min, before the development of hyperphosphatemia and hyperparathyroidism (18). Additional studies have shown that the maximal tubular reabsorption of phosphate negatively correlates with serum concentrations of FGF-23 in stage 3 CKD, whereas in advanced CKD, this correlation is mitigated (18,19). Nevertheless, the increased FGF-23 further aggravates calcitriol deficiency by directly inhibiting the renal 1α-hydroxylase activity (19).

Both FGF-23 and calcitriol are important regulators of bone homeostasis. Calcitriol and its receptor, the vitamin D receptor (VDR), are critical for normal bone metabolism, because appropriate activation of the VDR is necessary for normal osteoblastic bone formation and osteoclastic bone resorption, as well as for the coupling of osteoblastic and osteoclastic activity (20). FGF-23 overexpression is associated with severe skeletal phenotype characterized by disturbed mineralization process and growth plate architecture; however, they could not differentiate between local skeletal action and systemic effects of FGF-23 (21). In addition, recently published data suggested that FGF-23 is a negative regulator of PTH mRNA expression and secretion *in vitro* (22). Thus, a possible association of high FGF-23 with low PTH and calcitriol concentrations coupled with downregulation of the VDR may adversely affect bone metabolism, resulting in impaired bone turnover in the early CKD stages. This speculation requires further validation.

Bone Histology in Early CKD

The available data on bone histology in patients with stages 3 and 4 CKD are summarized in Table 1. The lesions reported include a wide spectrum of histologic combinations characterized by low, normal, or high bone turnover. A substantial number of patients with increased bone turnover featuring hyperparathyroid bone lesions have been reported during the 1980s and early 1990s. In contrast, the limited data that have become available in the past decade suggest that low-turnover bone disease seems to be increasing (23–32). Most of the studies that reported on predominantly high-turnover bone included predialysis patients with advance renal failure, shortly before the initiation of dialysis, whereas studies that reported on the prevalence of low-turnover bone included patients predominantly with mild to moderate kidney disease, and those with severe kidney disease were in the minority (5,28,29,31,32). Apparently, this shift does not seem to be the consequence of treatment differences, because most of the patients received calcium-based phosphate binders and did not receive vitamin D compounds. Unfortunately, the studies are not comparable, because there was great variability with regard to genetic, dietary, and ethnic factors, as well as with regard to criteria used to recruit patients and with underlying disease. Coen *et al.* (29) looked for the correlation between the degrees of GFR impairment, as estimated from the serum creatinine, and the bone turnover rate and revealed that low-turnover bone (mainly aplastic bone disorder) was observed predominantly in patients with higher GFR and lower PTH levels, whereas high-turnover lesions became evident as the GFR dropped and PTH levels increased significantly. Most of these studies showed that PTH was a poor predictor of bone turnover (29–32).

These findings suggest that low-turnover bone might represent the early presentation of renal osteodystrophy in incipient stages of CKD. This increased prevalence of low-turnover bone disease could result from an unbalanced effect between bone anabolic and suppressive agents. Mostly low calcitriol/VDR and normal PTH concentrations but also gonadal hormone deficiency, presence of diabetes, and aging could account for the missing bone anabolic agents in early CKD that leave the effect of suppressive agents unopposed. Whether increased FGF-23 level plays a role in this metabolic unbalance has to be verified. In advanced CKD, as kidney function continues to deteriorate, both the calcitriol/VDR deficiency and the development of hyperphosphatemia contribute to the development of hyperparathyroidism and high-turnover bone lesion.

Standardized evaluation of biochemical data and characterization of the bone histology by bone biopsy with histomor-

Table 1. Bone biopsies results in predialysis patients[a]

Reference	No. of Patients	SHPTH (%)	MHPTH (%)	OM (%)	MBD (%)	AMBD (%)	ABD (%)	Normal Bone (%)	Treatment
Eastwood *et al.*, 1982 (23)	38	86.8		44.7[b]			NA	10.2	No vitamin D
Mora Palma *et al.*, 1983 (24)	327	54.0		34.0			NA	12.0	NA
Dahl *et al.*, 1988 (25)	60	80.0		1.6			NA	11.0	NA
Hutchinson *et al.*, 1993 (26)	30	27.0	23.0	7.0	13.0		27.0		$CaCO_3$ 2 to 10 g/d
Hernandez *et al.*, 1994 (27)	92	57.4	23.0	11.0					No vitamin D $CaCO_3$
Torres *et al.*, 1995 (28)	38	30.0	10.0	2.0		10.0	48.0		No vitamin D $CaCO_3$
Hamdy *et al.*, 1995 (15)	87 placebo	71.0		1.0	20.0		3.0		
	89 vitamin D	75.0		0.0	18.0		7.0		$CaCO_3$ 3 to 8 g/d
Coen *et al.*, 1996 (29)	76	2.7		9.0	34.2	28.0	11.8	13.0	No vitamin D No $CaCO_3$
Shin *et al.*, 1999 (30)	58	8.6	36.2	10.0	12.0		24.1	8.6	NA
Ballanti *et al.*, 2001 (5)	27	8.0		11.0	34.0	26.0	26.0		No vitamin D No $CaCO_3$
Spasovski *et al.*, 2003 (31)	84	9.0		12.0		18.0	23.0	38.0	$CaCO_3$ 0.5 g/d No vitamin D

[a]ABD, adynamic bone disease; AMBD, advanced mixed bone disease; MBD, mixed bone disease; MHPTH, mild hyperparathyroidism; NA, not available; OM, osteomalacia; SHPTH, severe hyperparathyroidism.
[b]Percentage of patients with SHPTH also had OM.

phometric analysis would enable a better understanding of the bone and mineral pathophysiology that develops in the earlier stages of CKD. Furthermore, this information would be critical in determining appropriate treatment protocols. Considering the possible pathophysiologic process described, in the earlier stages of CKD, administration of vitamin D or other VDR activators may exert a beneficial anabolic effect on bone by increasing the expression of the VDR on bone cells and anabolic activity of these cells (33,34). As such, administration of calcitriol in low dosages to predialysis patients was demonstrated to ameliorate not only the renal bone lesions of high-turnover osteodystrophy but also lesions of low-turnover disease (15,35–38). Thus, vitamin D replacement at this stage might act as an anabolic agent and improve bone metabolism when administered at physiologic dosages. Furthermore, early treatment with VDR activators could prevent parathyroid hyperplasia and the development of skeletal resistance (39–41). Whether the low-turnover bone lesion in the early stages of CKD differs from its counterpart in the dialysis patient is an issue that has to be clarified because different pathophysiologic mechanisms may suggest that different therapeutic considerations are required. Apparently, in incipient CKD, there might be a deficiency in anabolic factors such as calcitriol/VDR and PTH supporting low-turnover bone, whereas in advanced stages of CKD, low-turnover bone is mostly iatrogenic, as the result of pharmacologic dosages of calcitriol or other VDR agonists and the use of high dosages of calcium-based phosphate binders and possibly calcimimetics (2,40). Thus, patients with incipient kidney disease may benefit from small, physiologic dosages of vitamin D compounds that could potentially prevent skeletal resistance to PTH in the advance stages of CKD. This supposition requires further study but would support the importance of performing bone biopsies in patients with earlier stages of CKD.

In summarizing the existing data, it seems that 70 to 90% of patients with stages 3 to 4 CKD present with bone lesions. Hyperparathyroid bone disease is predominant in patients with advanced CKD, whereas patients with incipient kidney disease may present with low bone turnover; however, the data are extremely limited, and there is great overlap between the various forms of bone lesions at the different stages of CKD. Because the early initiation of appropriate therapy may prevent or ameliorate the bone disturbances that develop in late CKD, the ability to define better the histologic abnormalities and the pathophysiologic process underlying these bone abnormalities would facilitate appropriate treatment decisions. Bone biopsies with histomorphometric analysis should be performed using standardized criteria as proposed by Kidney Disease: Improving Global Outcomes (KDIGO) (43). The data must be collected and reported in relation to previous therapy; to the duration of treatment; and to the biochemical changes in calcium, phosphorus, and PTH during the previous 6 to 12 mo. These therapies include calcium and noncalcium binders, phosphorus restriction, vitamin D supplementation, calcitriol and other VDR agonists, bisphosphonates, steroids, and any other factor that is known to affect the bone activity. Multicenter clinical trials conducted in a unified program would provide a realistic answer to the definition of the bone abnormalities in these patients as well as to the appropriate therapeutic regimen.

Disclosures

None.

References

1. Sherrard DJ, Hercz G, Pei Y, Maloney NA, Greenwood C, Manuel A, Saiphoo C, Fenton SS, Segre GV: The spectrum of bone disease in chronic renal failure: An evolving disorder. *Kidney Int* 43: 436–442, 1993

2. Malluche HH, Monier-Faugere MC: Renal bone disease 1990: An unmet challenge for the nephrologist. *Kidney Int* 38: 193–211, 1990
3. Hruska KA, Teitelbaum SL: Renal osteodystrophy. *N Engl J Med* 333: 166–174, 1995
5. Ballanti P, Coen G, Mazzaferro S, Taggi F, Giustini M, Calabria S, Ferrannini M, Bonucci E: Histomorphometric assessment of bone turnover in uraemic patients: Comparison between activation frequency and bone formation rate. *Histopathology* 38: 571–583, 2001
6. Qi Q, Monier-Faugere MC, Geng Z, Malluche HH: Predictive value of serum parathyroid hormone levels for bone turnover in patients on chronic maintenance dialysis. *Am J Kidney Dis* 26: 622–631, 1995
7. Malluche HH, Faugere MC: Aluminum-related bone disease. *Blood Purif* 6: 1–15, 1988
8. Sedman AB, Alfrey AC, Miller NL, Goodman WG: Tissue and cellular basis for impaired bone formation in aluminum related osteomalacia in pig. *J Clin Invest* 79: 86–92, 1987
9. Quarles LD, Dennis VW, Gitelman GJ, Harrelson JM, Drezner MK: Aluminum deposition at the osteoid-bone interface: An epiphenomenon of the osteomalacic state in vitamin-D deficient dogs. *J Clin Invest* 75: 1441–1447, 1985
10. Goodman WG, Leite Duarte ME: Aluminum: Effects on bone and role in the pathogenesis of renal osteodystrophy. *Miner Electrolyte Metab* 17: 221–232, 1991
11. Hercz G, Pei Y, Greenwood C, Manuel A, Saiphoo C, Goodman WG, Segre GV, Fenton S, Sherrard DJ: Aplastic osteodystrophy without aluminum: The role of "suppressed" parathyroid function. *Kidney Int* 44: 860–866, 1993
12. Kurz P, Mauniere-Faugere MC, Bognar B, Werner E, Roth P, Vlachojannis J, Malluche HH: Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. *Kidney Int* 46: 855–861, 1994
13. Salusky IB, Kuizon BD, Belin TR, Ramirez JA, Gales B, Segre GV, Goodman WG: Intermittent calcitriol therapy in secondary hyperparathyroidism: A comparison between oral and intraperitoneal administration. *Kidney Int* 54: 907–914, 1998
14. Goodman WG, Ramirez JA, Belin TR, Chon Y, Gales B, Segre GV, Salusky IB: Development of adynamic bone in patients with secondary hyperparathyroidism after intermittent calcitriol therapy. *Kidney Int* 46: 1160–1166, 1994
15. Hamdy NA, Kanis JA, Beneton MN, Brown CB, Juttmann JR, Jordans JG, Josse S, Meyrier A, Lins RL, Fairey IT: Effect of alfacalcidol on natural course of renal bone disease in mild to moderate renal failure. *BMJ* 310: 358–363, 1995
16. Levin A, Bakris GL, Molitch M, Smulders M, Tian J, Williams LA, Andress DL: Prevalence of abnormal serum vitamin D, PTH, calcium, and phosphorus in patients with chronic kidney disease: results of the study to evaluate early kidney disease. *Kidney Int* 71: 31–38, 2007
17. Shimada T, Hasegawa H, Yamazaki Y, Muto T, Hino R, Takeuchi Y, Fujita T, Nakahara K, Fukumoto S, Yamashita T: FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Miner Res* 19: 429–435, 2004
18. Shigematsu T, Kazama JJ, Yamashita T, Fukumoto S, Hosoya T, Gejyo F, Fukagawa M: Possible involvement of circulating fibroblast growth factor 23 in the development of secondary hyperparathyroidism associated with renal insufficiency. *Am J Kidney Dis* 44: 250–256, 2004
19. Gutierrez O, Isakova T, Rhee E, Shah A, Holmes J, Collerone G, Juppner H, Wolf M: Fibroblast growth factor-23 mitigates hyperphosphatemia but accentuates calcitriol deficiency in chronic kidney disease. *J Am Soc Nephrol* 16: 2205–2215, 2005
20. Panda DK, Miao D, Bolivar I, Li J, Huo R, Hendy GN, Goltzman D: Inactivation of the 25-hydroxyvitamin D 1alpha-hydroxylase and vitamin D receptor demonstrates independent and interdependent effects of calcium and vitamin D on skeletal and mineral homeostasis. *J Biol Chem* 279: 16754–16766, 2004
21. Larsson T, Marsell R, Schipani E, Ohlsson C, Ljunggren O, Tenenhouse HS, Juppner H, Jonsson KB: Transgenic mice expressing fibroblast growth factor 23 under the control of the alpha1(I) collagen promoter exhibit growth retardation, osteomalacia, and disturbed phosphate homeostasis. *Endocrinology* 145: 3087–3094, 2004
22. Krajisnik T, Björklund P, Marsell R, Ljunggren O, Akerström G, Jonsson KB, Westin G, Larsson TE: Fibroblast growth factor-23 regulates parathyroid hormone and 1alpha-hydroxylase expression in cultured bovine parathyroid cells. *J Endocrinol* 195: 125–131, 2007
23. Eastwood JB: Quantitative bone histology in 38 patients with advanced renal failure. *J Clin Pathol* 35: 125–134, 1982
24. Mora Palma FJ, Ellis HA, Cook DB, Dewar JH, Ward MK, Wilkinson R, Kerr DN: Osteomalacia in patients with chronic renal failure before dialysis or transplantation. *Q J Med* 52: 332–348, 1983
25. Dahl E, Nordal KP, Attramadal A, Halse J, Flatmark A: Renal osteodystrophy in predialysis patients without stainable bone aluminum: A cross-sectional bone-histomorphometric study. *Acta Med Scand* 224: 157–164, 1988
26. Hutchison AJ, Whitehouse RW, Boulton HF, Adams JE, Mawer EB, Freemont TJ, Gokal R: Correlation of bone histology with parathyroid hormone, vitamin D3, and radiology in end-stage renal disease. *Kidney Int* 44: 1071–1077, 1993
27. Hernandez D, Concepcion MT, Lorenzo V, Martinez ME, Rodriguez A, De Bonis E, Gonzalez-Posada JM, Felsenfeld AJ, Rodriguez M, Torres A: Adynamic bone disease with negative aluminium staining in predialysis patients: Prevalence and evolution after maintenance dialysis. *Nephrol Dial Transplant* 9: 517–523, 1994
28. Torres A, Lorenzo V, Hernandez D, Rodriguez JC, Concepcion MT, Rodriguez AP, Hernandez A, de Bonis E, Darias E, Gonzalez-Posada JM, *et al*.: Bone disease in predialysis, hemodialysis, and CAPD patients: Evidence of a better bone response to PTH. *Kidney Int* 47: 1434–1442, 1995
29. Coen G, Mazzaferro S, Ballanti P, Sardella D, Chicca S, Manni M, Bonucci E, Taggi F: 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
30. Shin SK, Kim DH, Kim HS, Shin KT, Ma KA, Kim SJ, Kwak YS, Ha SK, Sherrard DJ: Renal osteodystrophy in predialysis patients: Ethnic difference? *Perit Dial Int* 19[Suppl 2]: S402–S407, 1999
31. Spasovski GB, Bervoets AR, Behets GJ, Ivanovski N, Sikole A, Dams G, Couttenye MM, De Broe ME, D'Haese PC:

Spectrum of renal bone disease in end-stage renal failure patients not yet on dialysis. *Nephrol Dial Transplant* 18: 1159–1166, 2003
32. Coen G, Ballanti P, Bonucci E, Calabria S, Costantini S, Ferrannini M, Giustini M, Giordano R, Nicolai G, Manni M, Sardella D, Taggi F: Renal osteodystrophy in predialysis and hemodialysis patients: Comparison of histologic patterns and diagnostic predictivity of intact PTH. *Nephron* 91: 103–111, 2002
33. Van Driel M, Pols HA, van Leeuwen JP: Osteoblast differentiation and control by vitamin D and vitamin D metabolites. *Curr Pharm Des* 10: 2535–2555, 2004
34. van Leeuwen JP, van Driel M, van den Bemd GJ, Pols HA: Vitamin D control of osteoblast function and bone extracellular matrix mineralization. *Crit Rev Eukaryot Gene Expr* 11: 199–226, 2001
35. Healy MD, Malluche HH, Goldstein DA, Singer FR, Massry SG: Effects of long-term therapy with calcitriol in patients with moderate renal failure. *Arch Intern Med* 140: 1030–1033, 1980
36. Goodman WG, Coburn JW: The use of 1,25-dihydroxyvitamin D3 in early renal failure. *Annu Rev Med* 43: 227–237, 1992
37. Coen G, Mazzaferro S, Bonucci E, Ballanti P, Massimetti C, Donato G, Landi A, Smacchi A, Della Rocca C, Cinotti GA, *et al.*: Treatment of secondary hyperparathyroidism of predialysis chronic renal failure with low doses of 1,25(OH)2D3: Humoral and histomorphometric results. *Miner Electrolyte Metab* 12: 375–382, 1986
38. Malluche HH, Ritz E, Werner E, Meyer-Sabellek WA: Long-term administration of vitamin D sterols in incipient and advanced renal failure: Effect on bone histology. *Clin Nephrol* 10: 219–228, 1978
39. Fukuda N, Tanaka H, Tominaga Y, Fukagawa M, Kurokawa K, Seino Y: Decreased 1,25-dihydroxyvitamin D3 receptor density is associated with a more severe form of parathyroid hyperplasia in chronic uremic patients. *J Clin Invest* 92: 1436–1443, 1993
40. Goodman WG, Salusky IB: Evolution of secondary hyperparathyroidism during oral calcitriol therapy in pediatric renal osteodystrophy. *Contrib Nephrol* 90: 189–195, 1991
41. Dusso AS: Vitamin D receptor: Mechanisms for vitamin D resistance in renal failure. *Kidney Int Suppl* (85): S6–S9, 2003
42. Andress DL, Norris KC, Coburn JW, Slatopolsky EA, Sherrard DJ: Intravenous calcitriol in the treatment of refractory osteitis fibrosa of chronic renal failure. *N Engl J Med* 321: 274–279, 1989
43. Moe S, Drueke T, Cunningham J, Goodman W, Martin K, Olgaard K, Ott S, Sprague SM, Lameire N, Eknoyan G: Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 69: 1945–1953, 2006