Special Aspects of Renal Osteodystrophy in Children

By Isidro B. Salusky, Beatriz G. Kuizon, and Harald Jüppner

Renal osteodystrophy represents a spectrum of skeletal lesions that range from high-turnover to low-turnover bone disease. Similar factors are involved in the pathogenesis of renal osteodystrophy in adult and pediatric patients with chronic kidney disease (CKD). However, growth retardation and the development of bone deformities are specific complications that occurred in pediatric patients with CKD. Metabolic acidosis, renal osteodystrophy, malnutrition, and disturbances in the insulin growth factor (IGF)/growth hormone (GH) are among the main factors involved and they are discussed briefly in this article. In addition to disturbances in bone remodeling, longitudinal bone growth occurs at the growth plate cartilage by endochondral ossification. Although young rats with experimental CKD have growth retardation, the characteristics of the growth plate are markedly different between animals with severe secondary hyperparathyroidism and those with calcium-induced adynamic osteodystrophy. These disturbances may suggest potential molecular mechanisms by which endochondral bone formation may be altered in renal failure, consequently leading to growth retardation.

RENAL OSTEODYSTROPHY represents a spectrum of skeletal lesions that range from high-turnover disorders (osteitis fibrosa and mild lesions of secondary hyperparathyroidism) to low-turnover bone diseases (osteomalacia and adynamic lesions).[1] Mixed lesions of renal osteodystrophy have histologic evidence of both osteomalacia and hyperparathyroidism; the rate of bone formation in mixed lesions depends on the predominant lesion. A number of factors play a critical role in the pathogenesis of the different types of renal bone diseases and among those are disturbances in calcium and phosphorus homeostasis, reduced synthesis of 1,25-dihydroxyvitamin D_3, altered metabolism of parathyroid hormone (PTH), and impaired renal clearance of PTH fragments and accumulation of substances such as aluminum and β_2-microglobulin.

Although the type of renal bone disease is determined primarily by serum PTH levels, additional factors that modify bone formation and turnover include calcium, phosphorus, vitamin D, growth hormone (GH), and aluminum.[1] Similar factors are involved in the pathogenesis of renal osteodystrophy in adults and pediatric patients with chronic kidney disease (CKD).[2] However, there are specific manifestations of renal osteodystrophy in children characterized mainly by the presence of bone deformities and growth retardation. In the current article, the specific consequences of renal osteodystrophy on the growing skeleton are discussed.

GROWTH RETARDATION AND RENAL OSTEODYSTROPHY

A substantial proportion of children with CKD develop significant growth impairment assessed as failure to achieve or delayed normal linear growth, and/or abnormal growth velocity. Based on the North American Pediatric Renal Transplant Cooperative Study, the mean height standard deviation scores were 1.64 below the appropriate age- and sex-adjusted height levels at the start of dialysis in more than 3,000 patients studied; of these, men and younger patients were more growth impaired.[3] At the time of transplant, the mean height standard deviation scores were −1.91 in more than 6,600 patients studied, with greater height deficits in men, younger patients, and in those with previous renal transplants.[3] Multiple factors may be responsible for growth retardation in children with CKD including persistent metabolic acidosis, calcitriol deficiency and renal osteodystrophy, inadequate protein and caloric intake, and disturbances in the insulin growth factor (IGF)/growth hormone (GH) system.

Acidosis

Acidosis has been linked to delayed linear growth in patients with renal tubular acidosis and normal renal function, and correction of metabolic acidosis often leads to acceleration in growth velocity in such patients.[4] Acidotic rats have been

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found to have decreased GH secretion, serum IGF-1, and hepatic IGF-1 messenger RNA (mRNA) expression. Moreover, metabolic acidosis has been shown to inhibit the effects of GH in rats with normal and decreased renal function.[5-7] In the growth plate, incubation of murine mandibular condyles in acidic medium diminished the expressions of the GH receptor, IGF-I receptor, and IGF-I (both with and without GH treatment), and upregulated the expressions of IGF binding proteins 2 and 4, which are negative modulators of IGF-1.[6] Although metabolic acidosis is an important modifier of growth velocity in humans and experimental animals, whether correction of acidosis can prevent growth retardation in children with CKD remains to be determined. However, despite this uncertainty, it is recommended to maintain serum bicarbonate levels above 22 mEq/L.

Calcitriol Deficiency

Calcitriol deficiency also may contribute to growth retardation and bone disease in children with CKD. Indeed, treatment with daily doses of calcitriol (1,25-dihydroxyvitamin D_3) has been reported to improve linear growth in small numbers of children with stable CKD and in those receiving regular dialysis.[8-10] Such findings provide the rationale for the routine administration of calcitriol to nearly all children with CKD. However, in other studies, enhanced growth velocity was not shown on long-term follow-up evaluation and further studies have not shown that calcitriol consistently improves linear growth in children with CKD 3-5.[11-13]

Secondary Hyperparathyroidism

Secondary hyperparathyroidism remains prevalent in children with advanced renal disease, and osteitis fibrosa continues to be the most common skeletal lesion of renal osteodystrophy in those patients undergoing regular hemodialysis and peritoneal dialysis despite regular treatment with daily doses of oral calcitriol.[14-16] Delayed diagnosis of secondary hyperparathyroidism is most likely one of the potential factors involved in the persistence of osteitis fibrosa in patients treated with dialysis. It has not yet been widely appreciated that PTH concentrations reflect different states of bone formation and turnover with progression of CKD. Over the past decade, the availability of first-generation immunometric PTH assays allowed with reasonable accuracy the distinction between the spectrum of renal osteodystrophy in adult and pediatric patients treated with dialysis.[16-19] Accordingly, serum PTH levels above 300 pg/mL strongly suggest the presence of high-turnover skeletal lesions of renal osteodystrophy whereas values below 150 pg/mL were consistent with adynamic osteodystrophy.[17-19] However, it remained largely unexplained why the concentrations of intact PTH had to remain well above the normal range for healthy individuals (10-65 pg/mL) to maintain normal bone turnover and to prevent the development of adynamic bone disease in adult and pediatric patients treated with dialysis.[20] It is important to take into consideration that in such studies, at bone biopsy examination, patients were either not treated with 1,25$(OH)_2$D or received only small doses of daily calcitriol therapy.[17-19] Indeed, the relationship between PTH and bone formation is disrupted during intermittent calcitriol therapy (Fig 1).[21]

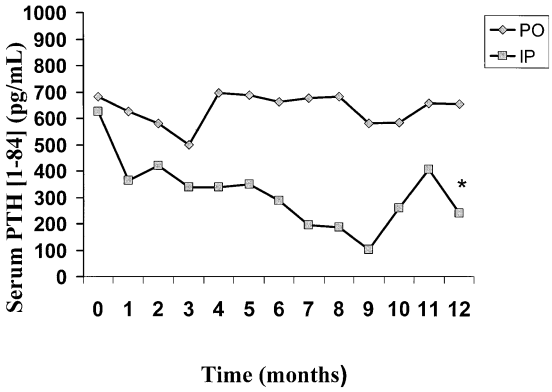

Fig 1. Serum PTH (first-generation PTH immunometric assay) during 12 months of treatment with intermittent doses of intraperitoneal (□) or oral (■) administration of calcitriol. *P < .001 versus pretreatment values. Reprinted from Salusky et al.[21]

In contrast to these recently developed data in CKD stage 5, the spectrum of the different forms of renal osteodystrophy in children with CKD stages 3 and 4 was first characterized more than 2 decades ago.[10,22-25] During this period, osteomalacia was one of the most predominant skeletal lesions of renal osteodystrophy owing to the widespread use of aluminum binders.[24] Moreover, such previous reports have not consistently used double tetracycline labeling of bone or histochemical assessments of bone aluminum content.[10,22-25] In addition, determinations of PTH levels were

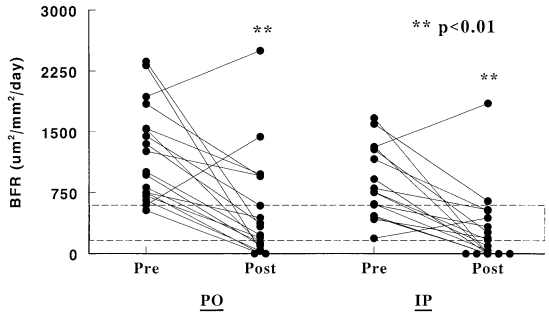

Fig 2. Individual rates of bone formation before and after 12 months of treatment with intermittent doses of intraperitoneal (IP) or oral (PO) administration of calcitriol. Modified from Salusky et al.[21]

performed by using radioimmunoassays that recognized different fragments of the PTH molecule.[15,23,24,26] Given the limitations, the relationship between serum PTH determined by current immunometric assays[27] and indices of bone remodeling has not yet been systematically established in children with CKD stages 3 and 4.

Large intermittent doses of calcitriol thus have been used to treat secondary hyperparathyroidism.[28-32] In children treated with peritoneal dialysis with bone biopsy–proven secondary hyperparathyroidism, therapy with intermittent calcitriol therapy was associated with marked reductions in bone formation rate despite increased PTH levels and a substantial proportion of patients developed adynamic osteodystrophy (Fig 2).[21] These findings are consistent with those initially reported by Andress et al[28] in 11 adult patients undergoing hemodialysis and receiving intravenous calcitriol. Thus, the frequency and dosage of calcitriol also may play an important role as a modifier of the relationship between PTH levels and indices of bone formation and turnover.[21,28] The finding that 1,25$(OH)_2$D treatment leads to reduced bone formation may reflect direct inhibitory actions of calcitriol on differentiated osteoblastic function that are not mediated by PTH and/or that calcitriol reduced the effects of PTH on this target tissue. Indeed, Gonzalez and Martin[33] showed that PTH or calcitriol exposure in vitro, both in a time- and dose-dependent manner, decrease PTH/parathyroid hormone–related protein (PTHrP) receptor mRNA in UMR 106-01 osteoblast-like cells. Moreover, Coen et al[34] showed that bone parameters changed more dramatically than did PTH during the daily administration of small doses of oral calcitriol in adult patients with CKD 3 and 4.

An alternative explanation for the discrepancy between PTH levels and bone turnover may be owing to an overestimation of PTH levels by first-generation PTH immunometric assays. Such assays use 2 antibodies, one directed against amino-terminal and one against carboxyl-terminal epitopes and, therefore, they were predicted to measure only full-length PTH(1-84).[27] As described in the article by Martin et al in this issue of *Seminars in Nephrology*, recent observations showed that first-generation PTH immunometric assays detected not only the intact hormone, but also additional PTH fragments truncated at the aminoterminus.[35,36] Unlike first-generation PTH immunometric assays, more recently developed second-generation assays do not detect these PTH fragments, which appear to circulate at much more elevated concentrations in patients undergoing dialysis. Unfortunately, the data to date do not show that these assays provide a more accurate assessment of bone turnover.[37,38]

Treatment with calcitriol was reported to improve linear growth and to prevent skeletal deformities more than 2 decades ago,[9,39] and, thus provided the rationale for the routine administration of calcitriol to nearly all children with CKD. However, diminished linear growth has been reported in prepubertal children with secondary hyperparathyroidism who developed adynamic renal osteodystrophy after treatment with large intermittent doses of calcitriol (Fig 3).[40] It is not known whether impaired growth resulted from a direct inhibitory effect of either high doses or intermittent dosing of

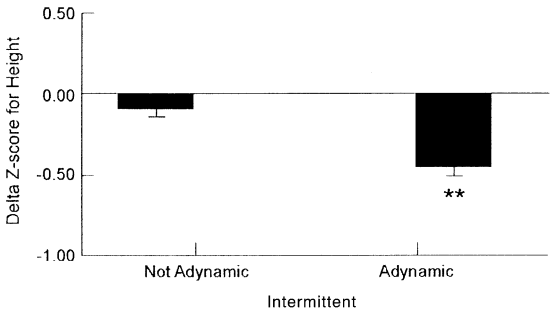

Fig 3. Delta z-score for height in patients who developed adynamic lesions of bone and in those with normal or persistently high bone formation rates **$P <$ .001. Reprinted from Kuizon et al.[40]

calcitriol on chondrocyte activity or whether it was a consequence of oversuppression of PTH. In a recent study, serum PTH levels determined by first-generation immunometric PTH assays correlated with growth velocity during daily or intermittent calcitriol therapy in children with CKD before dialysis.[41] Such findings are consistent with those previously reported in children treated with dialysis and suggest that the relationship between PTH levels and therapy with calcitriol may act as an additional modulator of growth in renal failure.[41,42] Studies in experimental animals in renal failure and with different subtypes of renal bone diseases tend support this hypothesis (vide infra).[43,44]

Disturbances in IGF/GH

Although the mechanisms responsible for the inhibitory actions of calcitriol on epiphyseal growth plate cartilage remain poorly understood, it is well known that calcitriol exerts dose-dependent inhibitory effects on cell proliferation in vitro both in chondrocytes and in osteoblast-like cells, and neither GH nor IGF-I can overcome these inhibitory effects.[45,46] In addition, recent studies show that vitamin D sterols increase the expression of a number of insulin-like growth factor binding proteins (IGFBPs) -2, -3, -4, and -5, which indirectly may suppress proliferation by sequestering IGF-I, and/or may exert IGF-I independent antiproliferative effects through its own receptors.[46-48] IGF binding proteins also may inhibit IGF-1 receptor signaling, block the cell cycle in the G1/G0 phase, or promote apoptosis.[49]

Growth hormone resistance has been described as one of the factors responsible for impaired linear growth in renal failure.[50] Poor growth develops despite normal or increased serum GH levels owing to enhanced pituitary GH secretion and decreased renal clearance of GH.[51] There is limited information, however, regarding the underlying molecular mechanisms for GH insensitivity in CKD. Animals with renal failure have been found to have diminished expression of the hepatic GH receptor and IGF-1 mRNA, and postreceptor defects in GH-mediated signal transduction in the liver.[52,53] Moreover, reductions in serum GH binding protein levels (derived from the extracellular domain of the GH receptor) have been described in children and adults with CKD. In addition, increased synthesis and reduced clearance of IGFBP-1, -2, -4, -6, and low molecular weight fragments of IGFBP-3 are found in uremic serum, and levels of IGFBP-1, -2, and -4 inversely correlate with height.[52] These excess IGFBPs, which have high affinity for IGF-1, may decrease the bioavailability of IGF-1 and also may exert direct, IGF receptor–independent actions on cell proliferation via their own receptors.[52] As such, improved growth velocity during recombinant human GH therapy has been ascribed to increased bioavailability of IGF-1 to target tissues because GH stimulates each component of the 150-kd serum ternary complex (acid-labile subunit, IGFBP-3, IGF-I, and IGF-II) and reduces serum IGFBP-1 level. However, children who are undergoing regular dialysis respond less well to recombinant human GH therapy than children with stable CKD.[54] The mechanisms for the differences in response to growth hormone therapy remain to be determined, but the potential interaction between calcitriol and recombinant human GH in the growth plate cartilage should be considered.[1]

GROWTH PLATE DISTURBANCES IN RENAL FAILURE

In adults, the skeletal lesions of renal osteodystrophy represent disturbances in bone remodeling, a continuous process throughout life by which old bone is reabsorbed and replaced by new bone at localized sites within the skeleton. In addition to disturbances in bone remodeling, renal bone disease in pediatric patients is associated with alterations in the 2 types of bone growth (ie, longitudinal bone growth and appositional modeling). Longitudinal growth occurs at the growth plate cartilage by endochondral ossification. Several hormones, including GH, IGF-I, thyroid hormone, glucocorticoids, and autocrine/paracrine factors (GH, IGF-I, PTHrP, and its receptor, Indian hedgehog, fibroblast growth factor receptor type 3, transcription factors, and other local factors) are integrally involved in the coordination of bone growth and development.[55-57] Our understanding of the complex autocrine/paracrine mechanisms within the growth plate has advanced considerably through extensive research in humans with skeletal abnormalities and in genetically altered animals with ablation or overexpression of several selected genes.[58] The demonstration of the expression of these genes in human growth plate chondrocytes suggests their possible role in normal human skeletal growth and in disease states. As such, further

analysis of these gene products may provide insights into the mechanisms responsible for poor linear growth in various metabolic bone diseases associated with CKD.

Marked chondroclastic erosion and abnormal vascularization of the growth plate cartilage was shown on autopsy material of long bones obtained from children with severe osteitis fibrosa more than 2 decades ago.[59] Although radiographically such lesions are defined as ricket-like lesions, Mehls et al[59] showed that secondary hyperparathyroidism was the primary factor involved in the pathogenesis of such lesions. In addition, Mehls et al[59] suggested that such growth plate abnormalities might have a role in the pathogenesis of growth retardation and epiphyseal slipping.[59] To our knowledge, since these initial observations, no further studies have been performed in human growth plates from children with renal failure. On the other hand, a number of studies have defined the growth plate in experimental animals.[60-63] Such studies in rodent models of renal failure have shown abnormalities in growth plate morphology, although the findings regarding the width of the growth plate have been inconsistent. Indeed, the growth plate width has been described as either increased, reduced, or unaltered compared with rats with intact renal function.[62,64,65] Such divergent findings may be attributable to differences in the severity and duration of renal failure, and the methodology used in measuring the width of the growth plate. More recently, Cobo et al[66] found increased growth plate width and abnormalities at the interface between the hypertrophic zone and metaphysis in rats with renal failure. Cell proliferation, as assessed by bromodeoxyuridine labeling, did not differ between control animals and those with renal failure but cell turnover and ossification were less in the latter, resulting in widening of the hypertrophic zone.[66] Further studies showed reduced mRNA expression of collagen types II and X, suggesting that disturbances in collagen metabolism may contribute to poor growth in renal failure.[60]

There has been limited information, however, regarding the role of the underlying bone disease and the key regulators of endochondral bone growth in CKD. In the past few years, we have initiated a series of experimental studies in CKD to understand the role of the various subtypes of renal osteodystrophy and their treatment on growth plate morphology and on the expression of key regulators of chondrocyte proliferation and/or differentiation. Indeed, we have described diminished growth velocity and reduction in the growth plate width and disorganization of the growth plate cartilage of uremic animals with severe secondary hyperparathyroidism.[60] On the other hand, in an experimental model of adynamic bone (induced by calcium supplementation fed to rats with renal failure) there was impaired linear growth associated with marked widening of the growth plate width, and disturbances in chondrocyte apoptosis, matrix degradation, and angiogenesis.[43] Thus, both models of high- and low-turnover lesions are associated with growth retardation but the growth plate abnormalities are markedly different (Fig 4). These disturbances may represent potential mechanisms to explain why growth failure is common in children with all forms of renal osteodystrophy.

To determine whether widening of the growth plate in uremic animals with adynamic bone induced by a calcium diet was caused by increased chondrogenesis or by diminished osteoclastic or chondroclastic activity within the primary spongiosa, mRNA expression for osteocalcin, collagen types II and X, and PTH/PTHrP receptor were assessed.[43] Osteocalcin mRNA expression was substantially less in uremic animals with adynamic bone, but increased as expected in uremic rats with severe secondary hyperparathyroidism, changes consistent with the prevailing serum PTH levels in these 2 groups. Transcripts for collagen types II or X did not differ among groups. The lack of change in markers of chondrocyte proliferation and differentiation in calcium-supplemented rats strongly suggest that widening of the growth plate in this rodent model of adynamic bone is not caused by enhanced chondrogenesis. In contrast to these findings, the expression of markers of osteoclastic/chondroclastic activity such as tartrate-resistant acid phosphatase staining and matrix metalloproteinase 9/gelatinase B mRNA expression, was reduced markedly in uremic animals with adynamic bone. Similar morphologic changes in the growth plate in mice with targeted deletions of both alleles for matrix metalloproteinase 9/gelatinase B also are associated with diminished bone growth.[67] Thus, calcium-mediated changes in matrix metalloproteinase 9/gelatinase B expression may contribute to alterations in linear growth in certain types of renal bone diseases.

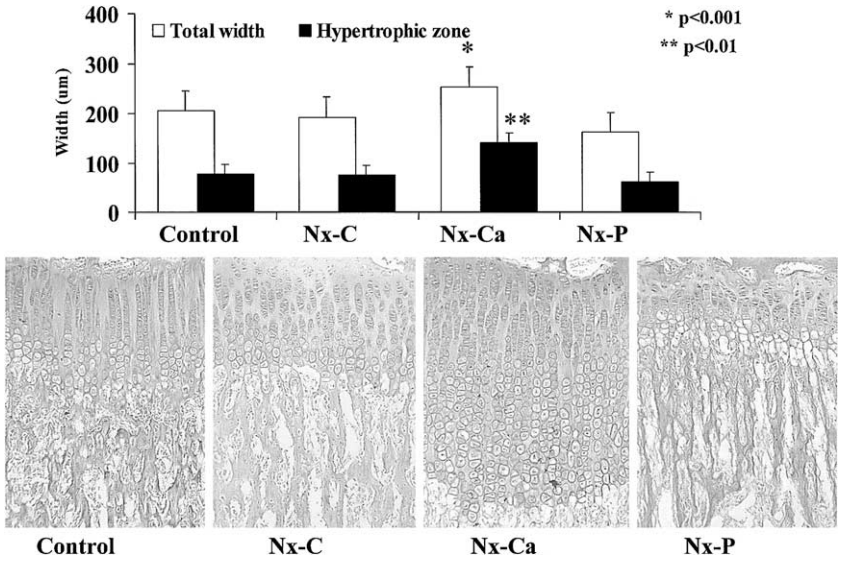

Fig 4. Morphology and width measurements of the growth plate in uremic rats with severe secondary hyperparathyroidism (Nx-P, induced by high-phosphate diet); adynamic bone (Nx-Ca, induced by high-calcium diet), and Nx-C (nephrectomized control).

Disturbances in the expression of the PTH/PTHrP receptor have been reported in renal failure.[68,69] Indeed, mRNA expression of the PTH/PTHrP receptor was down-regulated in kidney of rats with moderate to severe renal failure.[68] Moreover, diminished expression of the PTH/PTHrP receptor has been reported in osteoblasts of adults with CKD-5, particularly in those with low-turnover lesions of bone.[70] In the growth plate, substantial reductions in PTH/PTHrP receptor expression also were found in uremic animals with severe secondary hyperparathyroidism and treatment with GH appears to modify the expression of the PTH/PTHrP receptor in vivo.[44,68] Interestingly, these disturbances were not observed in nephrectomized rats with lesser degrees of secondary hyperparathyroidism or in those given calciumsupplementation to induce adynamic bone.[43] Considering the crucial role of the PTH/PTHrP receptor in the regulation of endochondral bone growth, these findings suggest potential molecular mechanisms by which endochondral bone formation may be altered in renal failure, consequently leading to growth retardation.

Moreover, because longitudinal bone growth in children occurs primarily through endochondral bone formation, the critical role of the epiphyseal growth plate must be considered in the analysis of pathophysiologic mechanisms responsible for growth retardation in chronic renal failure. Further assessment of the growth plate morphology and of potential modifiers of chondrocyte proliferation and/or differentiation in the growth plate would provide meaningful insights to understanding the mechanisms that account for impaired growth and renal osteodystrophy in children with renal failure.

CONCLUSION

The development of growth retardation is the hallmark associated with progression of CKD in children. Although multiple factors have been implicated such as metabolic acidosis, renal osteodystrophy, malnutrition, and disturbances in the IGF/GH system, the specific role of each of them remains to be elucidated. Treatment with calcitriol may lead to the development of adynamic bone in children with CKD stage 5 and patients with such skeletal lesions have more severe growth retardation. Current evidence indicates that therapy with calcitriol may act as a modulator of growth in children with CKD. Further studies are needed to define clearly the relationship between the specific subtype of renal osteodystrophy and growth in pediatric patients with CKD. On the one hand, the same degree of growth retardation was observed in rats with CKD with either skeletal lesions of severe secondary hyperparathyroidism or adynamic bone. However, the width of the growth plate was markedly different between the 2 groups and the expression of different growth factors that are responsible for the process of chondrocyte proliferation and differentiation are markedly different. Because longitudinal growth occurs at the level of the growth plate by endochondral ossification, these

findings may represent potential mechanisms for the relationship between growth retardation and the different subtypes of renal osteodystrophy. These findings may have implications on the treatment of renal osteodystrophy in pediatric patients.

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