Mineral and bone disorder in chronic kidney disease: pioneering studies

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Chronic kidney disease (CKD) leads to numerous disturbances of mineral and bone metabolism, which in turn are an important cause of morbidity and mortality and of decreased quality of life. These disturbances comprise abnormalities in circulating biomarkers such as calcium, phosphate, parathyroid hormone (PTH), fibroblast growth factor 23, vitamin D sterols, and alkaline phosphatases; abnormal bone morphology; and extraskeletal calcifications. During the past century, the term "renal osteodystrophy" was used for the morphologic changes of CKD. In 2006, the unifying term "CKD-associated mineral and bone disorder" (CKD-MBD) was proposed for all bone and mineral abnormalities combined[1] and has been widely accepted by the nephrology community since. It is defined as "a systemic disorder of mineral and bone metabolism due to CKD manifested by either 1 or a combination of the following: abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism; abnormalities in bone turnover, mineralization, volume, linear growth, or strength; and vascular or other soft tissue calcification."

The pathogenesis, development, and clinical features of CKD-MBD depend on numerous factors. They comprise the type of nephropathy, speed of CKD progression, age, gender, ethnicity, geographic area, nutritional habits, medications, and concomitant pathologic conditions such as diabetes. Many reports published in *Kidney International* made essential contributions to a better understanding of the complex influences and interactions leading to CKD-MBD. Because of space limits we had the difficult task of selecting only 5 of them.

Bone histology changes in CKD

Malluche HH, Ritz E, Lange HP, et al. Bone histology in incipient and advanced renal failure. Kidney Int. 1976;9:355–362. In the early 1970s, the skeletal lesions of patients undergoing long-term hemodialysis therapy were already well known.[2,3] By contrast, bone histology in early stages of CKD had not been investigated to any large extent. Therefore, Malluche *et al.*[4] decided to perform a systematic bone histomorphometry study in patients with glomerular filtration rates (GFRs) ranging from 80 ml to 6 ml/min per 1.73 m^2. The underlying renal diseases were highly variable. None of the patients had received vitamin D sterols, phosphate binders, or calcium supplements. Victims of traffic accidents without known skeletal or renal disease served as normal controls for the bone histomorphometry analyses. The authors observed that osteosclerosis (i.e., an increase of the fraction of spongious bone volume represented by mineralized bone) was seen first in individual patients with GFRs <60 ml/min. Accumulation of osteoid increased with CKD progression, as reflected by a significant correlation between osteoid seams and GFR, starting at GFR <70 ml/min. Osteoclastic surface resorption increased in some patients at early CKD stages, whereas endosteal fibrosis appeared only at GFR <30 ml/min. Both an increase of empty lacunae on the trabecular surface as evidence of past osteoclastic activity, and the presence of woven osteoid (Figure 1) defined by disordered collagen texture and its characteristic pattern of birefringence, were seen in some patients already

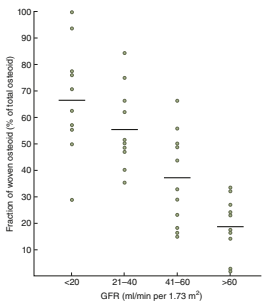

Figure 1 |

Editor's Note

This article is part of the *KI* 60th anniversary series. This month's topic is related to seminal papers dealing with bone and mineral disorders in chronic kidney disease.

at GFR 80 ml/min. The appearance of woven osteoid even in incipient CKD stages was considered to reflect an early stimulatory effect of PTH on the skeleton. Although individual patients with GFRs >40 ml/min had an increased fraction of nonlabeled osteoid seams, severe mineralization defects were not present before GFR <40 ml/min. Because of methodologic problems with PTH determinations before the later introduction of "intact" PTH ($PTH_{1\text{-}84}$) measurement assays,[5] correlations between serum PTH levels and bone histology findings were suspected to be unreliable. Finally, the authors did not find an association between the nature of kidney disease and the severity of histologic lesions. Thus, this study provided evidence for the effects of parathyroid overactivity in the bones of patients even in early stages of CKD.

Figure 1 shows the prevalence of woven osteoid at various levels of GFR. Reprinted with permission from Malluche HH, Ritz E, Lange HP, et al. Bone histology in incipient and advanced renal failure. *Kidney Int.* 1976;9:355–362.[4] Copyright © 1976, by the International Society of Nephrology.

Prevention of secondary hyperparathyroidism in CKD by reducing phosphorus intake

Slatopolsky E, Caglar S, Gradowska L, et al. On the prevention of secondary hyperparathyroidism in experimental chronic renal disease using "proportional reduction" of dietary phosphorus intake. Kidney Int. 1972;2:147–151. Secondary hyperparathyroidism (HPT) is a serious complication of CKD. It has been repeatedly shown to begin relatively early in the course of progressive nephron destruction and to worsen with advancing nephron loss. Bricker *et al.*[6] hypothesized that secondary HPT occurred, to a major degree, as an expression of the adaptation of the biologic control system governing the maintenance of external phosphorus balance. To prove this concept, Slatopolsky *et al.*[7] performed an experimental study in a group of 7 dogs in whom dietary phosphorus intake was decreased proportionally to a concomitant, surgically created reduction in nephron mass.

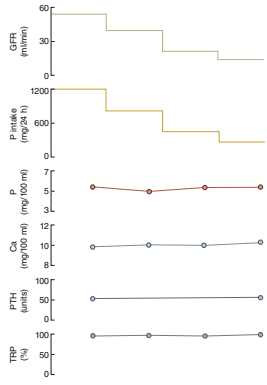

Figure 2|

Studies were performed at 4 levels of GFR (56, 40, 19, and 12 ml/min) and 4 levels of phosphorus intake (1200, 800, 400, and 250 mg/d). Despite the stepwise decrease in GFR, tubular reabsorption of phosphorus remained constant at 92%. Serum PTH levels remained stable, with 43 units in the control phase and 45 units in the final phase of the study (Figure 2). This study was preceded 1 year earlier by a first experiment of stepwise nephron mass reduction in which phosphorus intake was maintained at 1200 mg/d in 1 group of dogs, and in another group of dogs phosphorus intake was maintained at <100 mg/d.[8] Whereas in the first group fractional phosphate excretion rose reciprocally to the decline in GFR, and PTH levels increased >20-fold, in the second group fractional phosphate excretion changed little, and no increment in PTH levels occurred. Taken together, these studies showed that the adaptation in phosphorus excretion imposed by a constant phosphorus intake and a decreasing nephron population plays an important role in the pathogenesis of secondary HPT.

Figure 2 shows the effects of proportional reduction in phosphate intake in a representative dog with an experimental decrease in GFR. TRP, tubular reabsorption of phosphorus; PTH, parathyroid hormone. Reprinted with permission from Slatopolsky E, Caglar S, Gradowska L, et al. On the prevention of secondary hyperparathyroidism in experimental chronic renal disease using "proportional reduction" of dietary phosphorus intake. *Kidney Int.* 1972;2:147–151.[7] Copyright © 1972, by the International Society of Nephrology.

Depressed calcium-sensing receptor expression in hyperparathyroidism

Gogusev J, Duchambon P, Hory B, et al. Depressed expression of calcium receptor in parathyroid gland tissue of patients with hyperparathyroidism. Kidney Int. 1997;51:328–336. It has long been known that calcium is the primary factor controlling parathyroid hormone (PTH) secretion under physiological conditions, but until the early 1990s its mode of cellular and molecular action remained unclear. The cloning and characterization of the extracellular calcium-

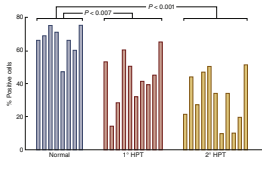

Figure 3|

sensing receptor (CaSR) by Brown *et al.*[9] in 1993 finally clarified this issue. This was a revolutionary finding because receptor-mediated cellular sensing of extracellular solutes was until then considered to be limited to concentrations in the micromolar and nanomolar range. The discovery of the CaSR allowed new insights into the physiology and pathophysiology of the cellular sensing of calcium and other cations in the millimolar range and of their action in numerous tissues, including the parathyroid glands. Gogusev *et al.*[10] wondered whether the expression of the CaSR might be reduced in uremic patients with secondary HPT. They thought that this might explain, at least partially, the impaired response of parathyroid tissue to extracellular calcium, analogous to the previously described impairment of calcitriol response linked to decreased parathyroid vitamin D receptor expression in such patients.[11] The authors compared the expression of CaSR at the mRNA and protein levels in parathyroid tissue obtained from patients with severe uremic HPT with that in normal parathyroid tissue, using in situ hybridization and immunohistochemistry techniques. The expression of both CaSR mRNA and protein was reduced in most cases, compared with the strong expression in normal parathyroid tissue (Figure 3). It was also reduced in primary HPT. In patients with secondary uremic HPT, expression of CaSR mRNA and protein was often particularly depressed in nodular areas, probably representing clonal parathyroid growth,[12] compared with adjacent nonnodular hyperplasia. These findings were confirmed by another report published in the same time period.[13] The observed downregulation of the CaSR probably plays an important role in the abnormal secretory and growth patterns of parathyroid glands in uremic patients with secondary HPT and also in nonrenal patients with primary HPT.

Figure 3 shows a histogram of CaSR protein expression by immunohistochemistry, expressed as percentage of positive cells of total number of cells examined in parathyroid tissue from patients with normal parathyroid glands, primary (1°) HPT (solitary adenoma), and secondary (2°) uremic HPT. Reprinted with permission from Gogusev J, Duchambon P, Hory B, et al. Depressed expression of calcium receptor in parathyroid gland tissue of patients with hyperparathyroidism. *Kidney Int.* 1997;51:328–336.[10] © 1997 by the International Society of Nephrology.

Abnormal calcium homeostasis in adynamic bone disease

Kurz P, Monier-Faugere M-C, Bognar B, et al. Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. Kidney Int. 1994;46:855–861. The term "adynamic bone disease" replaced the previous term "aplastic bone disease" in 1985.[14] It designates a state of low bone turnover in patients with CKD, characterized by a primary reduction in the formation of osteoid in the presence or absence of defective matrix calcification, and a secondary reduction in bone resorption.[14,15] It is often accompanied by extraosseous calcifications. However, this is not a hallmark of this type of renal osteodystrophy because high-turnover bone disease also favors soft tissue calcification.[16,17] Kurz *et al.*[18] undertook the present study to answer the question whether derangements in calcium homeostasis are similar or different among the 3 major histologic forms of renal osteodystrophy (i.e., hyperparathyroid bone disease, mixed uremic osteodystrophy, and adynamic bone disease) in an attempt to unravel factors associated with abnormal calcium metabolism in CKD in the absence of treatment with vitamin D metabolites or calcium salts. They recruited 43 patients receiving maintenance dialysis therapy who agreed to undergo calcium kinetic studies by use of the double isotope technique, iliac crest bone biopsies for histomorphometry, and determinations of serum indices of calcium and bone metabolism. Calcium kinetics data were compared with values previously obtained in healthy subjects by use of the same method. Intestinal calcium absorption was not different among the 3 histologic groups. Patients with hyperparathyroid bone disease showed plasma calcium efflux, calcium accretion rates, and calcium retention markedly above normal values. Patients with low-turnover bone disease showed a normal or slightly decreased plasma calcium efflux and calcium accretion rate together with a disproportionately low calcium retention in bone. Patients with mixed uremic osteodystrophy had intermediary values (Figure 4). Although there were some degrees of correlation between plasma calcium efflux, calcium

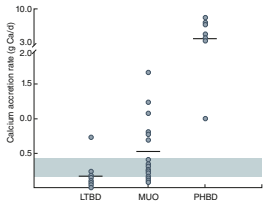

Figure 4 |

accretion rates, calcium retention, histomorphometric parameters, and PTH, no serum parameter could indicate with certainty the underlying bone disease. The authors concluded that adynamic bone disease, in the absence of aluminum intoxication, does not merely represent an academic finding but is characterized by a very low bone capacity to buffer calcium and an inability of bone to handle an extra calcium load.

Figure 4 shows the calcium accretion rate values in 43 dialyzed patients with low-turnover bone disease (LTBD), mixed uremic osteodystrophy (MUO), and predominant hyperparathyroid bone disease (PHBD). The horizontal lines indicate mean values of plasma calcium efflux for each group. The mean value in patients with PHBD was statistically different from those in the other 2 groups ($P < 0.001$, analysis of variance). Shaded area indicates normal range. Reprinted with permission from Kurz P, Monier-Faugere MC, Bognar B, et al. Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. *Kidney Int.* 1994;46:855–861.[18] © 1994 by the International Society of Nephrology.

Dialysis-associated amyloidosis and periarticular bone resorption

Gejyo F, Odani S, Yamada T, et al. β_2-microglobulin: a new form of amyloid protein associated with chronic hemodialysis. Kidney Int. 1986;30:385–390. Strictly speaking, the definition of CKD-MBD does not encompass β_2-microglobulin amyloidosis (AB2M). However, in our opinion it deserves to be presented here because periarticular resorption of bone and associated arthropathies with sometimes massive AB2M deposits are among its major clinical manifestations.[19,20] Figure 5 shows 2 lytic lesions in a femoral head filled with β_2-microglobulin amyloid.[21] The first full study of this dismal complication of ESRD was reported by Gejyo et al[22] in *Kidney International.* It followed the initial discovery by the same authors of the β_2-microglobulin nature of amyloid fibrils located in carpal tunnel tissue of a single patient receiving hemodialysis therapy.[23] In the present study, the Japanese workers analyzed systematically 4 cases of patients receiving long-term hemodialysis who had carpal tunnel syndrome. They isolated amyloid fibrils from amyloid-laden perineurium of the median nerve or synovium inside the carpal tunnel. The fibrils were Congo-red positive and showed typical green birefringence in polarized light. After solubilization in guanidine HCI, a significant amount of the protein was located in a homogeneous, low-molecular-weight fraction. Each protein was found to be identical to β_2-microglobulin with regard to its molecular weight of 11,800 on SDS-PAGE and amino acid composition. In a direct immunofluorescent staining study on a piece of amyloid-rich tissue snap-frozen at the time of operation, anti–β_2-microglobulin antiserum reacted positively with amyloid deposits. Control staining with antisera to IgG, IgA, IgM, κ chains, C5, and fibrinogen yielded negative results in the same sections. Thus, Gejyo *et al.*[22] demonstrated that the amyloidosis associated with ESRD contained a hitherto unknown form of amyloid fibril protein, termed AB2M amyloidosis, or "dialysis amyloidosis." Dialysate-related factors probably contribute to the pathogenesis, including dialyzer-induced generation of inflammatory mediators, protease activation, and oxygen radical release, and also the dialysate buffer and microbiological purity of the dialysate.[24] However, there was no evidence of local inflammatory tissue alterations preceding periarticular AB2M.[25] Of note, since the 1990s, AB2M has become a very rare complication of long-term hemodialysis, probably related to improved dialysate composition and purity.[24]

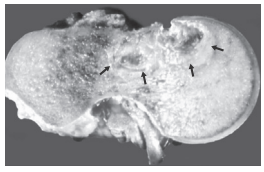

Figure 5 | Figure 5 shows the resected femoral head of a long-term hemodialysis patient, showing 2 lytic lesions (*arrows*) filled with AB2M amyloid. Adapted with permission Floege J, Burchert W, Brandis A, et al. Imaging of dialysis-related amyloid (AB-amyloid) deposits with ^{131}I- β_2-microglobulin. *Kidney Int.* 1990;38:1169–1176.[21] © 1990 by the International Society of Nephrology.

DISCLOSURE

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