Changing bone patterns with progression of chronic kidney disease

Tilman B. Drüeke[1] and Ziad A. Massy[1,2]

[1]Institut National de la Santé et de la Recherche Médicale (Inserm) Unité 1018, Centre de recherche en épidémiologie et santé des populations, Equipe 5, Villejuif; Paris-Sud University and University of Paris–Ouest, Versailles-Saint-Quentin-en-Yvelines; Paris, France; and [2]Division of Nephrology, Ambroise Paré Hospital, Assistance Publique Hôpitaux de Paris, Boulogne-Billancourt/Paris; University of Paris–Ouest, Versailles-Saint-Quentin-en-Yvelines; Paris, France

It is commonly held that osteitis fibrosa and mixed uremic osteodystrophy are the predominant forms of renal osteodystrophy in patients with chronic kidney disease. Osteitis fibrosa is a high-turnover bone disease resulting mainly from secondary hyperparathyroidism, and mixed uremic osteodystrophy is in addition characterized by a mineralization defect most often attributed to vitamin D deficiency. However, there is ancient and more recent evidence that in early chronic kidney disease stages adynamic bone disease characterized by low bone turnover occurs first, at least in a significant proportion of patients. This could be due to the initial predominance of bone turnover–inhibitory conditions such as resistance to the action of parathyroid hormone (PTH), reduced calcitriol levels, sex hormone deficiency, diabetes, and, last but not least, uremic toxins leading to repression of osteocyte Wnt/β-catenin signaling and increased expression of Wnt antagonists such as sclerostin, Dickkopf-1, and sFRP4. The development of high-turnover bone disease would occur only later on, when serum PTH levels are able to overcome peripheral PTH resistance and the other inhibitory factors of bone formation. Whether FGF23 and Klotho play a direct role in the transition from low- to high-turnover bone disease or participate only indirectly via regulating PTH secretion remains to be seen.

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Correspondence: *Tilman B. Drüeke, Inserm U-1018, Hôpital Paul Brousse, Bat. 15/16, 16 Avenue Paul Vaillant Couturier, 94807 Villejuif Cedex, France. E-mail: tilman.drueke@inserm.fr*

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Following the first description of osteitis fibrosa cystica by Davies in 1915[1] and the discovery by Bauer and his colleagues of its association with parathyroid gland overactivity in 1930,[2] Albright's group postulated in 1937 that phosphate retention and concomitant blood calcium lowering in patients with chronic kidney disease (CKD) might cause parathyroid hyperplasia and renal osteitis fibrosa.[3] To the best of our knowledge, the term renal osteodystrophy was coined in the 1940s.[4,5] Very early the question arose whether renal bone disease might also be due to vitamin D deficiency or resistance to its action, with the histologic expression of osteomalacia.[2] The subsequent elegant studies by Bricker and Slatopolsky *et al.* led to the "trade-off hypothesis."[6,7] It suggests that in the setting of CKD the progressive loss of functioning nephrons brings into play a number of compensatory mechanisms, including an increase in parathyroid hormone (PTH) secretion in response to the progressive inability of the kidneys to excrete appropriate amounts of phosphate, delaying the occurrence of hyperphosphatemia.

This theory, together with the frequent observation of severe secondary hyperparathyroidism in patients with end-stage renal disease (ESRD) undergoing dialysis therapy, led to the common belief that osteitis fibrosa and mixed uremic osteodystrophy are the predominant forms of renal osteodystrophy observed as nephropathies progress from early to more advanced stages of CKD.

Although the predominance of these 2 forms of renal osteodystrophy was certainly true for patients with ESRD in the 1960s and early 1970s, the situation changed dramatically in the 1980s, at least in many regions of the world, as a consequence of aluminum intoxication. This new disease was mainly, although not exclusively, observed in patients undergoing long-term hemodialysis treatment. It was characterized by peculiar types of osteomalacia or adynamic bone disease,[8] and often accompanied by microcytic anemia[9] and encephalopathy.[10] It was mainly induced by heavy aluminum contamination of tap water used for hemodialysis in certain geographic areas.[8] It could also be caused by the oral intake of high amounts of aluminum-containing phosphate binders.[11] Another possible etiologic factor in the pathogenesis of adynamic bone disease was the increasingly vigorous use of active vitamin D sterols and analogs in the subsequent decade, with considerable overlap between the tail end of the

aluminum epidemic and the overzealous use of active vitamin D compounds.[12,13] Fortunately, the incidence of this "iatrogenic" disease has rapidly waned as a consequence of better dialysis water purification and the declining prescription of aluminum-containing phosphate chelators to patients with CKD. It has become exceptional at present. We will not address here this iatrogenic disease.

With the progression of CKD a series of changes occur in bone and mineral metabolism that are encompassed by the term CKD-MBD,[14] a systemic disorder due to CKD that is 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. According to this definition, renal osteodystrophy is an alteration of bone morphology in patients with CKD. It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by bone histomorphometry.

The majority of studies devoted to renal osteodystrophy have been done in patients with ESRD, that is, in the setting of long-term exposure to the uremic milieu with complex, major disturbances of mineral and endocrine metabolism. The availability of studies on renal osteodystrophy in patients with less advanced stages of CKD is much more limited. Therefore, knowledge on the development and progression of renal bone disease in CKD stages 3 to 5 before the start of renal replacement therapies is relatively scarce. Fortunately, in recent years there has been an increasing number of studies using either light microscopy or physical imaging techniques in these patients. Moreover, in the nephrology community there has been a progressive shift from a predominant interest in the X-ray and histologic aspects of renal bone disease associated with parathyroid overfunction and vitamin D deficiency toward an earlier assessment of bony changes that may favor the occurrence of fractures, under the concomitant influence of conditions leading to osteoporosis as observed in the general population. The quest for a better understanding of underlying mechanisms has evolved together with an increasing interest in fracture prevention and treatment.

In the past, the perception of uremic bone was mainly that of a passive organ suffering from the disturbances of mineral and hormonal metabolism associated with CKD. Interestingly, in recent years this perception has changed to that of an endocrine organ that also plays an active part in the cardiovascular complications and metabolic anomalies occurring with the progression of CKD.[15]

In this Review we present a synthesis of studies that examined changes in bone-related serum parameters with the progression of CKD, alterations of bone structure and protein expression, and possible interactions of CKD-linked disturbances of mineral and endocrine metabolism with changes in bone structure. The contribution of experimental animal studies to a better understanding of the skeletal changes observed with the progression of CKD is discussed only briefly. A personal interpretation of the possible causes underlying the sequential features of renal osteodystrophy is provided.

Changes in bone-related serum parameters and CKD progression

They include progressive changes in serum calcium, phosphorus, and magnesium levels (either increases or decreases depending on underlying type of nephropathy, CKD stage, and a variety of endogenous and exogenous factors); metabolic acidosis or—less frequently—metabolic alkalosis; a progressive increase in serum or tissue concentrations of PTH, total alkaline phosphatases (tAP) or bone-specific alkaline phosphatase (bAP), procollagen type 1 N-terminal propeptide (P1NP), tartrate-resistant acid phosphatase-5b (TRAP-5b), fibroblast growth factor 23 (FGF23), osteocalcin, osteoprotegerin, and sclerostin;[15–18] variable increases in advanced glycation end products (AGEs),[19–21] oxidative stress markers including advanced oxidation protein products,[19,22,23] and protein carbamylation products;[19,24,25] increases in numerous other compounds summarized under the term "uremic toxins";[26–28] decreases in serum concentrations of 25 OH vitamin D and 1,25 diOH vitamin D;[29–31] and decreases in serum and or tissue concentrations of αKlotho.[32–34] FGF23 processing appears to change with CKD progression. Although circulating FGF23 undergoes cleavage in patients with normal kidney function and in those with mild CKD,[35] most circulating FGF23 in dialysis patients is in its full-length form.[36] It remains to be seen whether CKD-associated alterations in mineral and endocrine metabolism or other factors are responsible for this change in FGF23 catabolism. The serum levels of secreted frizzled-related protein 4 (sFRP4) do not change with the progression of CKD or the development of hyperphosphatemia.[37] Finally, the role of circulating Dickkopf-1 (Dkk1) is still uncertain, with either no changes[38,39] or a slight decrease[18] of mean serum values in patients with CKD. Table 1 summarizes the possible role of bone-related, CKD-modified circulating parameters in bone formation, mineralization, and resorption.

Table 1 | Possible associations of bone-related, CKD-modified blood parameters with bone formation, mineralization, and resorption

Parameter	Direction of change in bone		
	Formation	Mineralization	Resorption
Metabolic acidosis	↓	↓	↑
High PTH	↑	Normal	↑↑
High FGF23	?	?	?
High osteocalcin	↑	Normal	
High osteoprotegerin	↑		↓
High sclerostin	↓		
Low 25 OH vitamin D	↓	↓	
Low 1,25 diOH vitamin D	↑	↓	↑
Low Klotho	↑	?	↑

CKD, chronic kidney disease; FGF23, fibroblast growth factor 23; Klotho, soluble αKlotho; PTH, parathyroid hormone.