Changing bone patterns with progression of chronic kidney disease

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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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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.

The interpretation of measured values of many of the previously mentioned parameters in terms of their biologic activity in CKD is hampered by the fact that they often are present in the circulation not only as entire hormones or growth factors but also as fragments thereof, with sometimes actions opposite to the full-length molecule. Moreover, they may undergo oxidation, AGE-transformation, or carbamylation, which also may greatly alter biologic activity.[19,40,41]

Histopathologic changes of bone structure and protein expression with CKD progression

Bone structure: static and dynamic aspects. Bone histomorphometry informs bone turnover, mineralization, and volume, and, indirectly, bone quality.[42] However, bone biopsy findings reflect skeletal status only at a single time point. Moreover, a biopsy taken from the iliac crest does not necessarily reflect changes at other sites of the skeleton. Another problem is that historically bone histomorphometry has evaluated only changes in trabecular bone, although cortical bone thickness and porosity are equally important in determining fracture risk. This is especially important in CKD, as hyperparathyroidism can cause thinning in the cortex.[43] Simultaneously in the trabeculae, increased remodeling and increased bone volume may be observed, although new trabeculae may be irregular and lack connectivity and strength.[43] Despite these and other issues, bone biopsy remains the gold standard for the diagnosis of the different types of renal osteodystrophy.

Histomorphometry studies of static and dynamic bone parameters have been performed much less frequently in patients with CKD before the stage of ESRD than in patients on renal replacement therapy. Most importantly, knowledge of the initial changes of bone structure in CKD stages 2 and 3 is scarce, and the probable influence of different nephropathy types remains ill-understood. It has long been known that slowly progressive renal disease such as chronic interstitial nephritis or pyelonephritis is more frequently associated with osteomalacia or mixed renal osteodystrophy than more rapidly progressive forms of glomerulonephritis.[44] In the following, we present some of the studies that we think have made important contributions to this issue, without any claim to completeness.

As early as in 1976, Malluche *et al.*[45] performed a bone histomorphometry study in 50 German patients with various stages of CKD, ages 20 to 61 years, 19 males and 31 females. Their creatinine clearance (glomerular filtration rate) values ranged from 80 to 6 ml/min per 1.73 m^2, that is, CKD stages 2 to 5 according to present nomenclature. The underlying renal diseases were glomerulonephritis (19 patients); renal malformation, pyelonephritis, or both (21 patients); polycystic kidney disease (6 patients); and other or unknown causes (4 patients). The bone biopsies of patients with incipient CKD exhibited evidence of PTH excess, with empty osteoclastic lacunae and woven osteoid. Figure 1 shows that the prevalence of woven osteoid, an early expression of osteitis fibrosa, was increasing with decreasing glomerular filtration rate (GFR). However, there was wide interpatient variability at different CKD stages. Notably, even some patients with GFR values as high as 60 to 80 had woven osteoid. Osteoclastic surface resorption was abnormally high when GFR fell below 50 and endosteal fibrosis appeared below 30 ml/min per 1.73 m^2. Using tetracycline double labeling the authors also found evidence of a mineralization defect reflecting osteomalacia in many but not all patients. However, since osteomalacia, which was previously thought to precede osteitis fibrosa,[46] was not consistently observed in all patients, this hypothesis could not be confirmed, although it also could not be definitively excluded. Finally, the authors were unable to recognize a correlation between the nature of renal disease and the severity of histologic lesions. They concluded that despite the absence of frankly increased numbers of osteoclasts, the accumulation of empty resorption cavities as well as the appearance of woven osteoid even in early CKD stages was compatible with an early stimulatory effect of PTH in the skeleton.

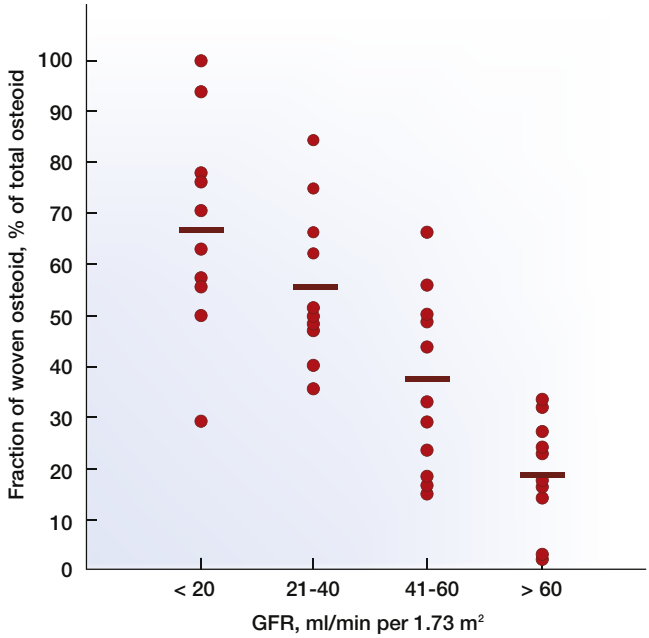


Figure 1 | Prevalence of woven osteoid in patients with chronic kidney disease. The fraction of woven osteoid, an early expression of osteitis fibrosa cystica, increases with the decrease in glomerular filtration rate (GFR). Note that there is large interpatient variability. Reprinted with permission from Malluche HH, Ritz E, Lange HP, et al. Bone histology in incipient and advanced renal failure. *Kidney Int.* 1976;9:355–362.[45]

In 1996, Coen *et al.*[47] reported findings of a cross-sectional, retrospective bone histomorphometry study in 76 unselected Italian CKD patients on conservative treatment, ages 18 to 72 years, 44 males and 32 females, with serum creatinine levels ranging from 1.2 to 11.4 mg/dl and a mean ± SD creatinine clearance of 20 ± 12 ml/min per 1.73 m^2. The causes of CKD were chronic glomerulonephritis in 43 patients, tubulointerstitial nephritis in 16, polycystic kidney disease in 7, and other or unknown in 9 among them.

Eleven patients had non–insulin-dependent diabetes mellitus. None had received corticosteroids in the preceding 12 months. None were receiving anticoagulant and anticonvulsive medication or nonsteroidal anti-inflammatory drugs at the time of bone biopsy. None of them were prescribed native vitamin D, calcitriol, or aluminum-containing phosphate binders. The main findings were normal bone in 10 patients, low-turnover, adynamic bone disease in 9 (all negative for histochemical aluminum staining), mild mixed osteodystrophy in 26, predominant osteomalacia in 7, advanced mixed osteodystrophy in 22, and predominant hyperparathyroidism in 2. Notably, patients with adynamic bone disease had a less severe degree of CKD than the other subgroups, with intact PTH values above the upper normal limit, and normal serum calcium. Osteomalacia was found in patients with more advanced CKD stages, together with a tendency toward hypocalcemia and more severe metabolic acidosis. A GFR of 20 ml/min was indicative of a demarcation line between the patients with osteomalacia and those with adynamic bone disease. Based on these findings the authors postulated that adynamic bone disease in patients with mild to moderate CKD corresponds to a form of renal osteodystrophy separate from osteomalacia, which appears with the development of skeletal resistance to PTH. It might represent a transient stage on the way toward hyperparathyroid bone disease of increasing severity with the progression of CKD.

The 2 reports above appear to be contradictory, at least in part, especially with respect to the prevalence of osteomalacia and adynamic bone disease in CKD patients not yet on dialysis. Reports by other research groups of that time do not allow further clarification of this issue. Thus Dahl *et al.*[48] reported that osteomalacia was extremely rare in the predialysis stage, while Mora Palma *et al.*[44] found a high percentage of cases with osteomalacia, mainly in association with chronic tubulointerstitial nephritis and prevailing metabolic acidosis. The types of underlying nephropathy responsible for a more or less rapid progression of CKD and accompanying metabolic and endocrine abnormalities probably explain these differences in prevalence. Whether oral intake of aluminum-containing phosphate binders has contributed to the osteomalacia in at least some of these patients is unclear. Finally, different diagnostic criteria used to define osteomalacia may also account for the observed difference.[47]

Adynamic bone is predominantly defined by low or absent bone formation in conjunction with thin osteoid seams, decreased cellularity (osteoblasts and osteoclasts), and minimal marrow fibrosis.[49,50] The true prevalence of the adynamic bone condition in CKD is unknown because of a lack of consensus in its definition and diagnosis, with a reported prevalence range of 5% to 50% in dialysis patients.[51] In patients with advanced CKD Hutchison *et al.*[52] and Hernandez *et al.*[53] observed a prevalence of 28% and 30%, respectively, thus higher than Coen *et al.*[47] Their patients also had lower serum intact PTH levels than those with other types of renal osteodystrophy, and they were receiving calcium carbonate treatment for the control of hyperphosphatemia. Adynamic bone disease in patients with CKD was mainly attributed by them and others to overtreatment of secondary hyperparathyroidism with PTH-lowering agents or relative or absolute hypoparathyroidism following surgical parathyroidectomy. Cohen-Solal *et al.*[54] suggested that in the absence of aluminum overload this type of renal osteodystrophy might be due to overtreatment with vitamin D (or its derivative calcidiol), a subsequent increase in serum calcitriol, and excessive lowering of serum PTH. Since circulating PTH levels have generally been found to be higher than normal even in CKD patients with adynamic bone disease, albeit to a lesser extent than in CKD patients with osteitis fibrosa or mixed bone disease,[47] resistance to the skeletal action of PTH is another possible explanation,[55] due to PTH/PTHrp receptor downregulation in CKD[56,57] or other causes. In the past, oral treatment with aluminum-containing phosphate binders was considered to be another culprit, all the more since intestinal aluminum absorption is enhanced in uremic rats as compared to rats without CKD.[58] Although clearly involved in a minority of patients—including the very young,[11] those with inflammatory bowel disease, and those ingesting high amounts of fruits or being on citrate treatment,[59] as also demonstrated in animal experiments[60]—the importance of oral aluminum overload in individuals with CKD not yet on dialysis has probably been overestimated. Other factors favoring the occurrence of low-turnover bone disease are advanced age, diabetes mellitus, metabolic acidosis, and alcoholism. This said, in the patient series of Coen *et al.*[47] low-turnover bone disease apparently was not due to any of these causes, except perhaps diabetes since 3 of the 9 patients with this type of osteopathy had diabetes mellitus.

In 2014, Barreto *et al.*[61] proceeded to a *post hoc* analysis of a previously reported cross-sectional study in patients with CKD stages 2 to 5 who had undergone a bone biopsy and exhibited an inverse association between bone formation rate and coronary artery calcification.[62] The *post hoc* analysis included 49 patients, mean age 52 years, 66% males, 49% of Caucasian ethnicity. Mean estimated GFR (eGFR) was 36 ± 17 ml/min per 1.73 m^2, with 10% of the patients in CKD stage 2, 49% in CKD stage 3, 35% in CKD stage 4, and 6% in CKD stage 5. The most frequent diagnosis of underlying nephropathy was "hypertensive nephrosclerosis" (39%), followed by diabetic nephropathy (31%) and other renal diseases. It is noteworthy that 60% of the patients had normal serum 25 OH vitamin D levels ($\geq$30 ng/ml); only 10% had biochemical evidence of vitamin D deficiency (25 OH vitamin D $\leq$15 ng/ml). The authors compared bone histomorphometry findings of the CKD patients to normal local controls for static parameters and to literature controls for dynamic parameters.[63] The most striking finding was that patients with CKD stages 2 and 3 had remarkably low bone formation rates with low osteoid volume, low osteoblast surface, and greatly prolonged mineralization lag time. In contrast, patients with CKD stages 4 and 5 had higher values of osteoid volume, osteoblast surface, and bone formation rate, and in addition higher osteoclast surface, fibrosis

volume, and a trend toward lower mineralization lag time (Figure 2). There was no intergroup difference in trabecular bone volume. Importantly, none of the study participants exhibited bone surface aluminum staining, in line with the fact that none of the patients had received aluminum-based phosphate binders. They also had not received any calcium-containing phosphate binders, vitamin D derivatives, or drugs associated with low bone turnover. Nutritional status appeared to be good overall. About 50% of them had a body mass index above 25%, and none had a body mass index below 18%, as shown in the primary report.[62] When examining possible associations between bone histomorphometry data and circulating parameters the authors found, as expected, a direct relation of bone formation rate, osteoid volume, osteoblast surface, and bone fibrosis volume with serum intact PTH in univariate analysis. Notably, they found identical positive associations with the uremic toxin, indoxyl sulfate. Most importantly, multivariable regression models showed a positive association of indoxyl sulfate with osteoblast surface and bone fibrosis volume, independent of demographic characteristics and biochemical parameters related to mineral metabolism, such as serum intact PTH, FGF23, 25 OH vitamin D, and bicarbonate. A similar trend ($P = 0.07$) was observed for bone formation rate.

The observation of a positive association of serum indoxyl sulfate levels with osteoblast surface and bone formation rate seems to be in contradiction to an experimental *in vitro* study by Mozar *et al.*[64] and an *in vivo* study by Iwasaki *et al.*,[65] who reported an inhibitory effect of indoxyl sulfate on bone formation, osteoblast-related gene expression, and both osteoblast and osteoclast cell viability. Nii-Kono *et al.*[66] further showed that indoxyl sulfate induced a state of PTH resistance, consisting in a reduction of PTH-induced cyclic adenosine monophosphate production, PTH/PTHrp receptor gene expression, and viability of primary osteoblasts maintained in culture. It is possible that uremic toxins such as indoxyl sulfate induce low bone turnover in initial stages of CKD in which serum PTH is only modestly elevated and resistance to its action is already present. Moreover, in early CKD other conditions such as sex hormone deficiency, low calcitriol levels, diabetes, a chronic inflammatory state, and malnutrition may also favor the occurrence of low turnover bone disease. In later CKD stages, the progressive increase in serum PTH levels could then override the direct inhibitory effects of indoxyl sulfate on bone turnover.[61] Moreover, uremic toxins could stimulate PTH secretion indirectly by decreasing calcitriol synthesis and action. This hypothesis is based on the observation that phosphate-free uremic plasma can directly inhibit 1α-25 OH vitamin D hydroxylase activity and thus decrease calcitriol availability,[67] and that uremic ultrafiltrate interacts with the vitamin D receptor (VDR) to impair its DNA binding capacity within cells such as parathyroid gland cells.[68] This in turn would diminish the normal inhibitory action of calcitriol on PTH synthesis in CKD.

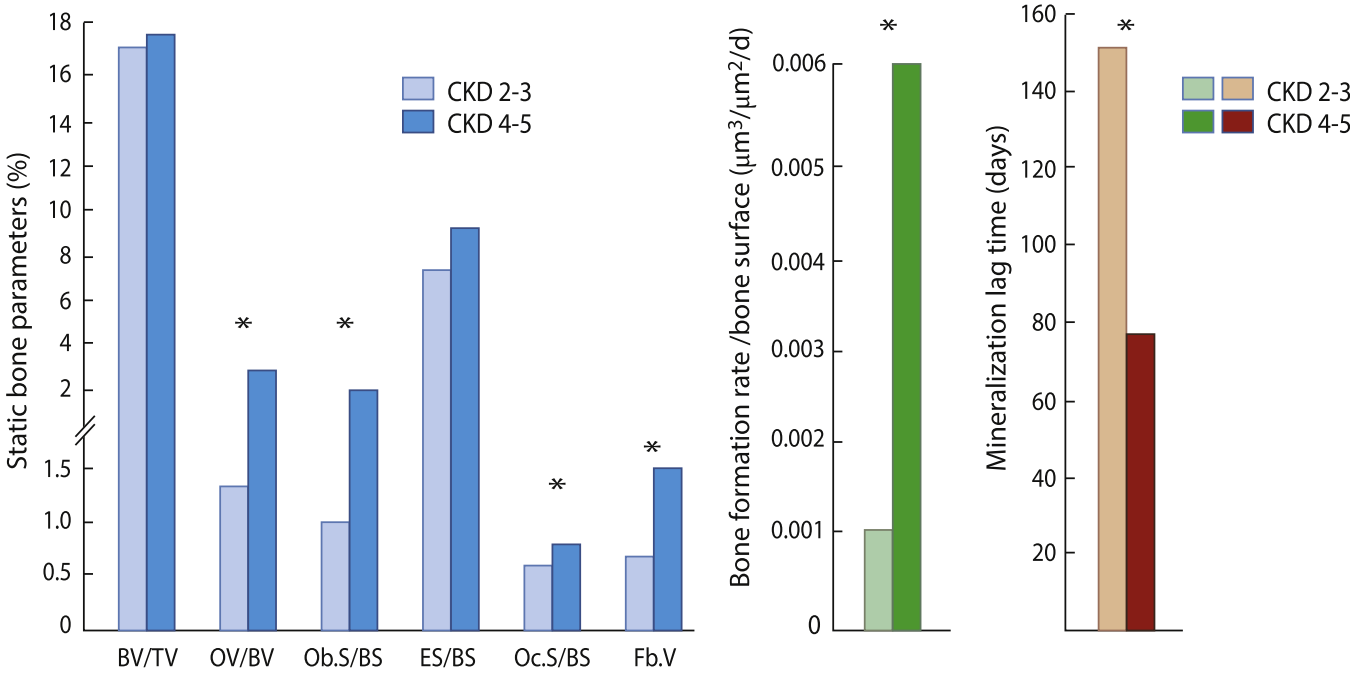


Figure 2 | Evidence of low-turnover bone disease in early, as compared to late, chronic kidney disease. Bone histomorphometry parameters in patients with chronic kidney disease (CKD) stages 2 to 3 and CKD stages 4 to 5, respectively. Columns represent means for variables with Gaussian distribution (BV/TV and ES/BS) or medians for variables with non-Gaussian distribution (OV/BV, Ob.S/BS, Oc.S/BS, and Fb.V). Asterisks indicate significant differences between CKD stages 2–3 and CKD stages 4–5, respectively. BV/TV, trabecular bone volume/tissue volume; OV/BV, osteoid volume/trabecular bone volume; Ob.S/BS, osteoblast surface/bone surface; ES/BS, eroded surface/bone surface; Oc.S/BS, osteoclast surface/bone surface; Fb.V, bone fibrosis volume. Reference values are BV/TV, 20.95% ± 5.94%; OV/BV, 2.18% ± 2.98%; Ob.S/BS, 1.26% ± 2.44%; ES/BS, 1.51% ± 1.27%; Oc.S/BS, 0.01% ± 0.03%; Fb.V, <0.5%; bone formation rate, 0.040 ± 0.002 $\mu m^3/\mu m^2/d$; and mineral lag time, 19 ± 7 days. Data from Barreto *et al* (Table 2, transformed into a figure).[61]

The observation by Barreto *et al.*[61] of a high prevalence of low-turnover, adynamic bone disease in early stages of CKD is in agreement with the findings reported by Coen *et al.*[47] nearly 2 decades earlier. Thus, in contrast to common belief, high bone turnover is not necessarily a continuous process starting with the very onset of CKD, in direct association with a progressive increase in serum PTH. It rather seems that in early CKD stages low bone turnover prevails in a large number of patients.

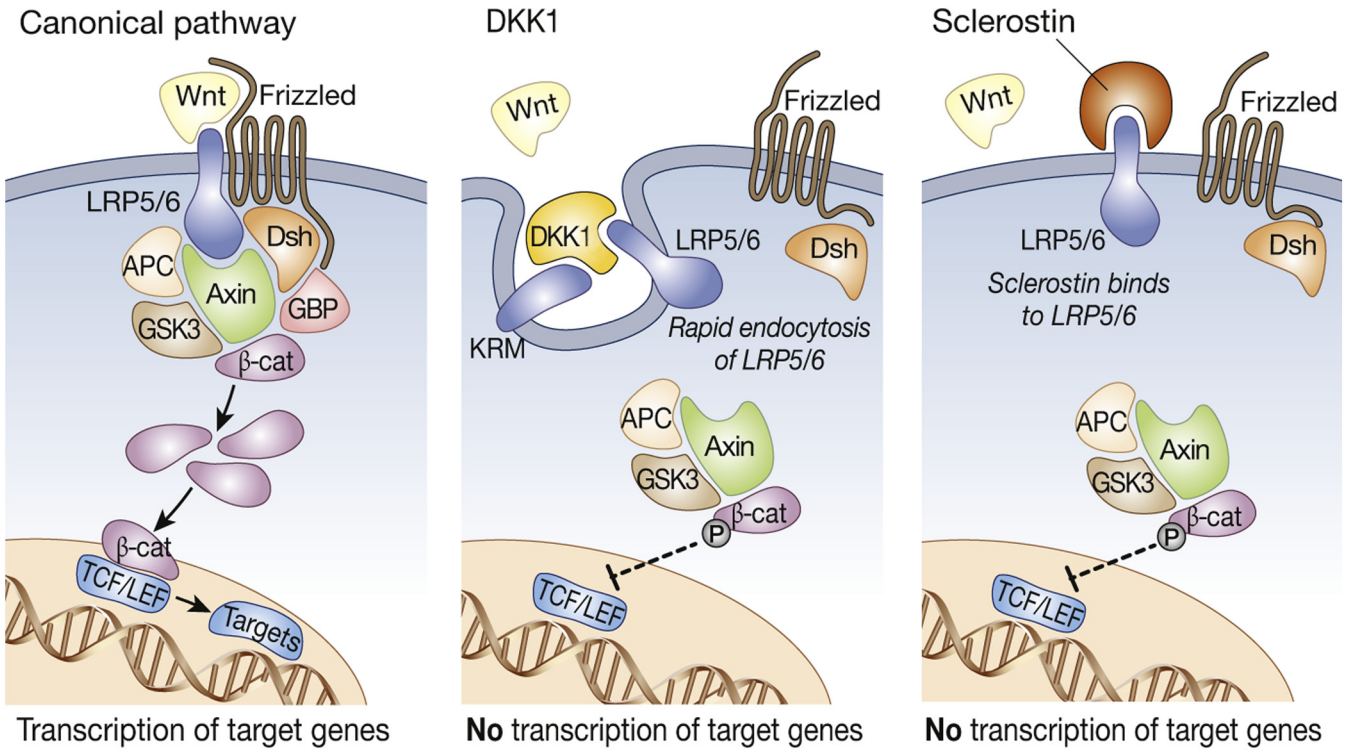
Findings from recent studies in animals with CKD are in support of such a scenario. Under experimental conditions of CKD with normal parathyroid status or with insulin resistance and the metabolic syndrome, low-turnover bone disease will develop initially, whereas in the presence of overt hyperparathyroidism, high-turnover bone disease will prevail, as shown in Table 2. Notably, in low-density lipoprotein receptor knockout mice with the metabolic syndrome the superimposition of mild CKD (stage 2) led to a further aggravation of low-turnover bone disease, in association with increased renal production of Wnt inhibitor family members and higher circulating levels of Dickkopf-1 (Dkk1), sclerostin, and secreted Klotho.[69] The canonical Wnt/β-catenin signaling pathway has been recognized in the last decade as a major player in bone formation and resorption, among many other functions in various tissues, as illustrated in Figure 3.[15,70] It is initiated by the binding of Wnt ligands to the dual receptor complex comprising frizzled (FZD) protein and either low-density lipoprotein receptor–related protein 5 or 6 (LRP5/6). This results in inactivation of the multiprotein β-catenin "destruction complex," thus relieving the central signaling mediator β-catenin from its constitutive proteosomal degradation. β-Catenin subsequently accumulates in the cytoplasm and translocates into the nucleus, where it associates with transcription factors to control target gene transcription.[70] The pathway is tightly regulated by several inhibitors, including Dkk1 and sclerostin. In the above low-density lipoprotein receptor knockout mice with CKD, neutralization of Dkk1 by administration of a monoclonal antibody stimulated bone formation rates, decreased the elevated serum levels of sclerostin, and corrected the low-turnover bone disease.[69] In addition, it prevented CKD-stimulated vascular calcification. However, unlike experimental animals, the various forms of renal osteodystrophy that are observed with the progression of CKD in human patients depend on many other factors as well. We will address these factors in the next paragraph.

Figure 4 shows a schematic view of the possible sequence of events. According to this scenario, the only mild initial increase in serum PTH levels may be insufficient to counterbalance coexisting, bone turnover–inhibitory conditions such as sex hormone deficiency, reduced calcitriol production, diabetes, increased synthesis of Wnt pathway inhibitors, and uremic toxins accumulating in early stages of CKD.[61] The latter could contribute to skeletal resistance to PTH and calcitriol and a decrease in calcitriol synthesis in early CKD, and to repression of Wnt/β-catenin signaling within osteocytes in conjunction with increased expression or circulating levels of Wnt pathway antagonists such as sclerostin, Dkk1, and sFRP4, together with increased osteoclast activity such as receptor activator of nuclear factor-κB ligand (RANKL).[69,71]

Table 2 | Experimental studies in animals with CKD indicating the presence of low bone turnover at early stages (especially stage 2) of CKD

Reference	Model (CKD stage equivalent)	Animal type	Age[a] follow-up[b]	Static bone parameters	Dynamic bone parameters	Experimental/ therapeutic intervention	Bone turnover – volume (mass)
Iwasaki-Ishizuka *et al.*, 2005[123]	5/6 Nx **(stage 3–4)**	Rat	9 wk 10 wk	Yes	Yes	TPTx + physiol. PTH infusion	**Low** – decreased BFR, suppressed OC surface
Moe *et al.*, 2009[124]	Cy/+ **(stage 3–4)**	Rat	20 wk 14 wk	Yes	Yes	Normal (0.7%) versus low (0.2%) Pi diet	**High** – increased OB, OC, fibrosis on high Pi diet
Nikolov *et al.*, 2010[125]	$ApoE^{-/-}$ vs. wild type **(stage 3–4)**	Mouse	10 wk 8 wk	Yes	Yes	None	**High** – bone mass higher than in WT mice
Sabbagh *et al.*, 2012[71]	jck **(stage 2–5)**	Mouse	6 wk 20 wk	Yes	Yes	None	**High**[c] – increase in BFR, mineralization, OC activity
Ferreira *et al.*, 2013[126]	5/6 Nx **(stage 3–4)**	Rat	12 wk 8 wk	Yes	Yes	TPTx + physiol. PTH infusion Normal (0.6%) versus high (1.2%) Pi diet	**Low** – decreased BFR and low bone volume with 1.2% Pi diet
Fang *et al.*, 2014[127]	$LDLr^{-/-}$ **(stage 2)**	Mouse	12 wk 16 wk	Yes	Yes	High-fat diet	**Low** – decrease in BFR > bone resorption; low trabecular volume & thickness
Fang *et al.*, 2014[69]	$LDLr^{-/-}$ **(stage 2)**	Mouse	12 wk 10 wk	Yes	Yes	High-fat diet	**Low** – decreased BFR, suppressed osteoid volume, low OB and OC numbers

$ApoE^{-/-}$, apolipoprotein E knockout mouse; BFR, bone formation rate; Cy/+, Han:SPRD rat with autosomal dominant polycystic kidney disease (PKD); jck, genetic mouse model of recessive PKD; $LDLr^{-/-}$, LDL receptor knockout mouse; Nx, nephrectomy; OB, osteoblast; OC, osteoclast; Pi, inorganic phosphate; TPTx, total thyroparathyroidectomy; wild type, C57 Black 6 mouse.
[a]Age at start of experiment.
[b]Follow-up in uremic state.
[c]Occurrence prior to detectable changes in serum PTH; possibly related to repression of the β-catenin pathway.



Wnt:	Wingless-type MMTV (mouse mammary tumor virus) integration site family member	TCF:	T cell factor
LRP5/6:	Low-density lipoprotein receptor–related protein 5/6	LEF:	Lymphoid enhancing factor
Dsh:	Dishevelled	GSK3:	Glycogen synthase kinase 3
APC:	Adenomatous polyposis coli	GBP:	GSK3 binding protein
β-cat:	Beta-catenin	Dkk1:	Dickkopf-related protein-1
		KRM:	Kremen (kringle containing transmembrane protein)

Figure 3 | The canonical Wnt/β-catenin signaling pathway and its extracellular regulation. Left panel: Extracellular binding of Wnt to the Frz–LRP5/6 receptor complex causes intracellular accumulation of β-catenin that can induce the expression of target genes after translocation to the nucleus. Middle panel: DKK1 dampens Wnt signaling by forming a tertiary complex with LRP5/6 and the cell surface coreceptor, Kremen-1 (KRM), thereby promoting internalization of the receptor complex. Right panel: Sclerostin inhibits Wnt-induced signaling by binding to LRP5/6, thereby preventing Wnt from binding to the Frz–LRP5/6 receptor complex. Reprinted with permission from Evenepoel P, D'Haese P, Brandenburg V. Sclerostin and DKK1: new players in renal bone and vascular disease. *Kidney Int*. 2015;88:235–240.[70]

Altered expression of bone proteins. In addition to PTH, several bone-derived factors involved in phosphate homeostasis also play a role in the regulation of bone metabolism and turnover. Thus the skeletal expression of sclerostin has been shown to increase in early CKD (Figure 5) despite still normal serum PTH levels,[71] and it remains increased in ESRD, although to a lesser extent, despite elevated serum PTH values.[38] As to dentin matrix protein 1 (DMP1), a member of the family of small integrin-binding ligand, N-linked glycoprotein (SIBLING) proteins, although it has been shown to suppress bone FGF23 expression,[72] its osteocytic expression was found to be increased in patients with early CKD despite high osteocytic FGF23 synthesis.[73] Therefore, it is improbable that DMP1 is one of the initial triggers for increased bone FGF23 expression in CKD.

Recently, Pereira *et al.*[74] analyzed in more detail the skeletal expression of FGF23, DMP1, and matrix extracellular phosphoglycoprotein (MEPE) by immunohistochemistry in 32 pediatric and young adult patients with CKD stages 2 to 5. Bone FGF23 and DMP1 expression was increased in all stages of CKD compared to normal controls. There were no significant differences in bone FGF23 and DMP1 expression between predialysis CKD and dialysis patients. The expression of MEPE was comparable in CKD and controls. Although all 3 proteins are expressed in osteocytes, yet their patterns of expression differed markedly. Bone FGF23 expression correlated directly with plasma FGF23 levels and with bone DMP1 expression, and expression of both proteins was inversely related to osteoid accumulation. The simultaneous increase in bone DMP1 and FGF23 expression might reflect the increasing phosphate burden associated with CKD progression. Finally, bone MEPE expression was inversely related to bone volume. These findings could indicate that FGF23 and DMP1 play a role in bone mineralization, and MEPE in the determination

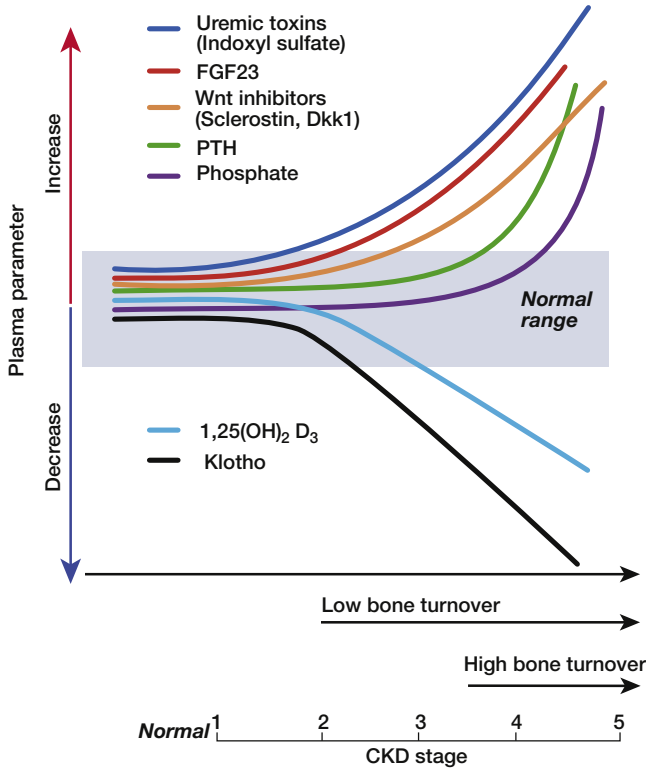


Figure 4 | Schematic view of the time profile of disturbances in mineral hormones and bone turnover with the progression of CKD. CKD, chronic kidney disease; Dkk1, Dickkopf-related protien-1; FGF 23, fibroblast growth factor 23; PTH, parathyroid hormone. Modified with permission from Hu MC, Kuro-o M, Moe OW. The emerging role of Klotho in clinical nephrology. *Nephrol Dial Transplant*. 2012;27:2650–2657.[128]

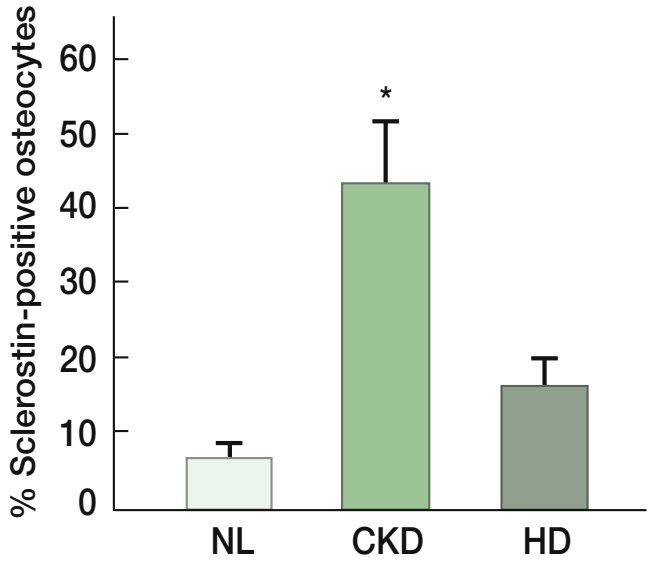


Figure 5 | Increase in osteocyte sclerostin expression in early CKD (stages 2–4). Immunodetection of sclerostin-positive osteocytes reveals increased staining in bones from patients with chronic kidney disease (CKD) stages 2–4 and patients on hemodialysis (HD) therapy, relative to normal (NL) control bones. Expression is greatest in CKD bones. Results are means ± SEM. *$P < 0.05$ for CKD versus normal and HD, respectively. Reprinted with permission from Sabbagh Y, Graciolli FG, O'Brien S, et al. Repression of osteocyte Wnt/beta-catenin signaling is an early event in the progression of renal osteodystrophy. *J Bone Miner Res*. 2012;27:1757–1772.[71]

of bone volume. However, more study is needed to support this hypothesis. In any case, the observed increase in bone FGF23 and DMP1 expression suggests that osteocyte function is already altered early in the course of CKD.

Possible role of CKD-linked disturbances of mineral and endocrine metabolism and medical treatment in abnormal bone structure and function

Endogenous, patient-related factors. As in the general population, age and gender are major modulators of bone structure and function in CKD. Serious disturbances of the hypothalamic–pituitary–gonadal axis are more frequent in women than in men with CKD, with obvious consequences for the bone, in particular the propensity to develop osteoporosis. Genetic background also plays an important role, with sometimes striking ethnic differences in renal osteodystrophy.[75] The differences are manifest in laboratory measurements of mineral metabolism. As an example, Gutierrez *et al.*[76] showed that black patients with CKD stages 3 and 4 had lower postprandial fractional urinary excretion of calcium and phosphate than white patients. In addition, postprandial serum calcium concentration decreased in the white but not the black individuals. It is also well known that serum PTH levels are generally higher and secondary hyperparathyroidism is more severe in black than in white CKD patients.[77] However, this does not necessarily translate into more severe bone disease. Thus Sawaya *et al.*[78] did not observe differences in bone volume or in the prevalence of low bone turnover between African American and white patients on dialysis therapy. However, in a more recent US study of much larger sample size, Malluche *et al.*[79] observed low bone turnover in 62% of white dialysis patients but only in 32% of black dialysis patients. Whether the difference of serum PTH levels between white and black people is responsible for such different prevalences of high and low bone turnover, respectively, remains to be seen. Notably, only 3% of all patients showed mineralization defect. To our knowledge, no large-scale information on such ethnic differences is available for CKD patients not yet on dialysis.

Serum total 25 OH vitamin D levels are usually much lower in black than in white people, but since vitamin D–binding protein is also lower, this results in similar concentrations of estimated bioavailable 25 OH vitamin D, as shown in a recent study done in the United States.[80] In sum, it is important to take into account possible age, gender, and ethnicity differences when interpreting apparently heterogeneous findings of renal osteodystrophy features and fracture incidence in patients with CKD.

Exogenous factors. Nutrient intake and nutritional status clearly determine bone health. Dietary habits may greatly vary from one geographic region to another, with sometimes considerable differences in the intake of calcium, magnesium, phosphate, acid–base equivalents, vitamin D, and trace elements such as fluoride, cobalt, zinc, and copper.

Predominantly vegetarian protein diets, as compared to mainly animal protein diets, play a role as well. As an example, the availability of phosphate for intestinal absorption is much lower when derived from a vegetarian protein than from a meat protein source, as shown in a recent crossover trial in patients with CKD.[81] Patients with advanced stages of CKD are generally asked to limit their protein intake, and this often leads to reduced energy intake as well. This could interfere with skeletal protein and energy requirements, especially in children and adolescents. However, when protein restriction is well controlled and sufficient calorie intake is guaranteed, there is no negative effect on the bone in the majority of patients with CKD, as demonstrated by Lafage-Proust *et al.* in 1999 (Table 3).[82]

Physical activity is another major determinant of bone mass and health, and patients with CKD frequently have reduced physical activity, with probably negative consequences for bone quality and resistance to fracture. Unfortunately, physical fitness is not easy to quantify and has therefore been generally neglected.

Patients with CKD may be receiving or have received in the past drugs with some or even a major impact on bone. The replacement of aluminum-containing compounds by the prescription of often massive oral doses of calcium-containing compounds for the treatment of hyperphosphatemia led not only to an improved control of secondary hyperparathyroidism—a desired, additional benefit—but frequently also to the transformation of high bone turnover to low bone turnover as the consequence of an excessive suppression of parathyroid overfunction.[83] The availability of calcium-free phosphate binders not only allowed the clinician to avoid this caveat but also set the ground for a more liberal use of active vitamin D sterols whose well-known side effects are a stimulation of intestinal calcium and phosphate absorption and hence hypercalcemia and hyperphosphatemia, at least intermittently. Active vitamin D sterols certainly permit controlling secondary hyperparathyroidism in patients with CKD, but when prescribed in high doses they also can induce adynamic bone disease[84–86] and vascular calcification, either directly or indirectly by suppression of parathyroid function.[87,88] The systematic prescription of high doses of paricalcitol to chronic hemodialysis patients in the majority of US centers until recent years probably explains a relatively high prevalence of adynamic bone disease. Treatment with cinacalcet for 9 months has been shown to be able to revert high-turnover bone disease toward normal in the majority of patients, although not all, based on histomorphometry.[89] Similarly, treatment with lanthanum carbonate for 1 year led to normalization of bone turnover in the majority of patients,[90] despite persistent lanthanum accumulation in bone tissue.[91] Long-term sevelamer hydrochloride treatment resulted in no changes in bone turnover or mineralization compared with calcium carbonate.[92] Drugs such as corticosteroids and immunosuppressive agents given to patients with various types of renal disease may exert major negative effects on the bone. All these medications also need to be taken into consideration in interpreting changes in bone structure and function. Finally, the dialysis treatment modality also plays a role. It has long been known that high dialysate calcium concentrations suppress PTH levels and favor the occurrence of both adynamic bone disease and vascular calcification, and that hypoparathyroidism and adynamic bone disease can be reversed by lowering dialysate calcium.[93,94] This is true for both hemodialysis[95,96] and peritoneal dialysis.[97] In peritoneal dialysis patients a high frequency of adynamic bone disease has also been recently attributed to high serum sclerostin levels, based on the finding of an inverse relation between this Wnt pathway inhibitor and bone formation rate.[98] Figure 6

Table 3 | Characteristics according to bone formation rate of patients with CKD on low-protein diet for a mean of 5 years

	High BFR (n = 3)	Normal BFR (n = 7)	Low BFR (n = 6)
Age (yr)	52.6±15.3	46.7±18.4	61.6±12.8
Initial GFR (ml/min)	16.2±1.2	16.6±3.4	12±1.7
Δ wt (kg)	0.8±2.4	0.943±3.4	–3.25±3.4
Duration of diet (mo)	76±25.7	59.5±25.5	69.8±20.2
$CaCO_3$ intake (g/d)	2.6±0.4	1.8±0.6	1.9±0.4
Calorie intake/kg/d	31.3±6.2	35.3±5.4	30.1±2.9
Phosphorus intake (mg/kg/d)	508±196	598±110	484±59
Protein intake (g/kg/d)	0.30±0.05	0.42±0.1	0.31±0.03
Aluminum (μg/l)	4.0±0.8	3.5±1.8	4.5±3.2

Aluminum, serum aluminum concentration; BFR, bone formation rate; GFR, glomerular filtration rate; Δ wt, difference between weights before and after diet.
Reprinted with permission from Lafage-Proust MH, Combe C, Barthe N, Aparicio M. Bone mass and dynamic parathyroid function according to bone histology in non-dialyzed uremic patients after long-term protein and phosphorus restriction. *J Clin Endocrinol Metab.* 1999;84:512–519.[82]

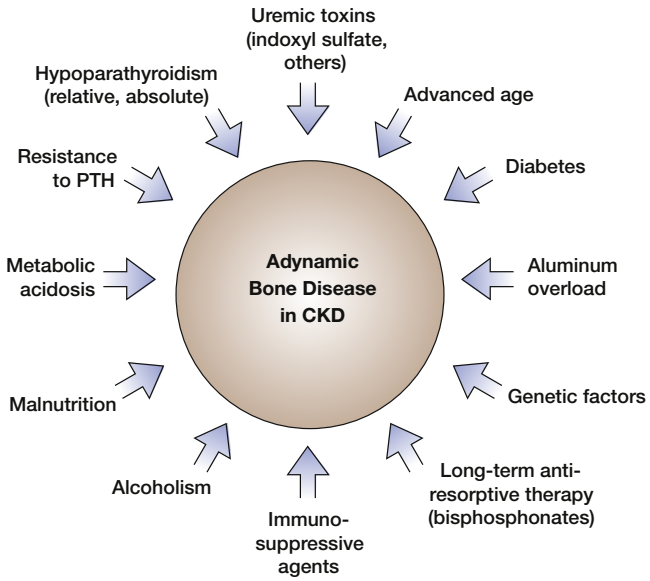


Figure 6 | Schematic representation of factors and conditions favoring low bone turnover (adynamic bone disease). Hypoparathyroidism is generally considered to be the main cause. It may be secondary to many different factors, including oral calcium overload, excessive treatments with native vitamin D or derived vitamin D sterols, high dialysate calcium concentration, and surgical parathyroidectomy.

summarizes the main factors that may contribute to the occurrence of low-turnover bone disease in patients with CKD.

Increase in bone fracture incidence with CKD progression

In recent years evidence has accumulated that fracture incidence is significantly increased in patients with ESRD receiving dialysis therapy as compared to people of comparable age and gender in the general population,[99–101] with notable geographic variations,[101,102] varying fracture incidences over the years,[103–105] and high rates of hospitalization and death.[101]

Similarly to the finding of increased fracture incidence in dialysis patients, the majority of published reports in patients with CKD not yet on dialysis show that fracture incidence increases when the GFR falls below 60 ml/min per 1.73 m^2. In a survey in the US non-institutionalized civilian population, Nickolas *et al.*[106] found a 3-fold increase in hip fracture prevalence in people with an eGFR below 60, age 50 to 74, as compared to individuals of the same age with better kidney function. Similarly, in a community-dwelling elderly population in Germany, Dukas *et al.*[107] observed an increase in the risk of hip fracture, radial fracture, total vertebral fracture, and fall-associated vertebral fracture in those with a creatinine clearance below 65 ml/min per 1.73 m^2. Ensrud *et al.*[108] performed a case–control study within a cohort of 9704 women 65 years or older to compare baseline eGFR in 149 women who subsequently had hip fractures plus 150 women who subsequently had vertebral fractures with eGFR in 396 randomly selected women. They found that decreasing eGFR was associated with increased risk of hip fracture. Compared with eGFR 60 ml/min per 1.73 m^2 or greater, the hazard ratio for hip fracture was 1.57 in women with eGFR 45 to 59 and 2.32 in those with eGFR less than 45. Risk of vertebral fracture was not independently associated with renal function when eGFR was below 60. Surprisingly, 2 recent large-sized studies from Canada on fracture incidence in patients with CKD reached conflicting conclusions. Elliott *et al.*[109] identified 1,815,943 community-dwelling adults in Alberta, Canada, median age 47 years, who had at least 1 outpatient serum creatinine measurement between 2002 and 2008, excluding those with eGFR <15 ml/min per 1.73 m^2. Over a median follow-up of 4.4 years, fracture rates increased with age at hip, wrist, and vertebral sites. Within each age stratum, unadjusted rates increased with declining eGFR; however, adjusted rates were similar across eGFR categories. Similar results were observed for wrist and vertebral fractures. They thus failed to confirm previous reports on increased fracture risk in CKD. Naylor *et al.*[110] used health care databases from Ontario, Canada, for a cohort study in 679,114 adults of 40 years and over, mean age 62 years, stratified at cohort entry by eGFR 60 and over, 45 to 59, 30 to 44, 15 to 29, and under 15 ml/min per 1.73 m^2, gender, and age (40–65 and over 65 years). The primary outcome was the 3-year cumulative incidence of fracture at hip, forearm, pelvis, or proximal humerus sites at least once within that follow-up. They found, in contrast to Elliott *et al.*, that the incidence of fracture significantly increased in a graded manner in adults with a lower eGFR for both genders and both age groups. The 3-year cumulative incidence of fracture in women over 65 years of age across the 5 eGFR groups was 4.3%, 5.8%, 6.5%, 7.8%, and 9.6%, respectively. Corresponding estimates for men over 65 years were 1.6%, 2.0%, 2.7%, 3.8%, and 5.0%, respectively. Similar graded relationships were found for falls with hospitalization.

In sum, although existing studies vary with respect to included populations, definitions of fracture sites and mechanisms, determination and classification of eGFR, and consideration of potential effect modification by patient age and sex,[109] there is overwhelming evidence in favor of an increased incidence of fractures in the CKD patient population. The discrepancy between the findings by Naylor *et al.*[110] and those by Elliott *et al.*[109] could be due to different adjustments and potential for misclassification based on only 1 eGFR determination in the study by Elliott *et al.*

Diagnosis of the different types of renal osteodystrophy and prediction of fracture risk by serum biochemistry or imaging?

An ideal biomarker should be easy and cheap to measure, should not accumulate with GFR loss, and should have low circadian variability.[42] In clinical practice, the biochemical diagnosis of the different types of renal osteodystrophy is mainly based on serum concentrations of PTH and alkaline phosphatases, either tAP or bAP. However, the predictive value of the circulating levels of PTH and tAP or bAP for bone turnover is limited.[111,112] In particular, it remains impossible to discriminate normal from moderately low or moderately high bone turnover in patients with CKD without proceeding to a bone biopsy. Bone-derived collagen-based biomarkers were not found to be useful in predicting histomorphometry, fractures, and bone mineral density (BMD) in an analysis made by the Kidney Disease: Improving Global Outcomes group in 2009. However, a recent study from Japan showed that high serum tAP levels were independently associated with the incidence of hip fracture and also with mortality in patients on long-term hemodialysis therapy.[113] Another approach could consist in the use of bAP isoforms[111] or other, yet unknown bone-derived biomarkers that could allow better discrimination in the future. Serum 25 OH vitamin D measurement allows detection of vitamin D insufficiency and deficiency. Very low levels may be associated with osteomalacia. A possible diagnostic value of serum FGF23 in the differential diagnosis of high versus low bone turnover and normal versus abnormal mineralization has been suggested.[114] However, further study is needed to confirm this observation. Increased serum sclerostin levels were found to be associated with higher fracture risk in patients with osteoporosis and type 2 diabetes, respectively.[115,116] No such link has been reported so far in patients with CKD. The relation of serum sclerostin with bone formation and bone mass remains unclear.[117]

The noninvasive diagnosis of early changes in bone structure by imaging techniques is extremely limited. X-ray

examination may allow detection of osteomalacia when Looser–Milkman zones are present. X-ray signs of osteitis fibrosa such as subperiosteal bone resorption, salt and pepper aspect of the skull, rugger jersey features of the spine, and cystic lesions characteristic of brown tumors are only observed in severe forms of the disease.

BMD by dual-energy X-ray absorptiometry (DXA) cannot discriminate between the different types of renal osteodystrophy but is probably useful in the diagnosis of bone loss[118] and the prediction of fractures in CKD.[119] Quantitative computed tomography (QCT) provides more precise information but is expensive and requires high radiation exposure. West *et al.*[120] recently compared the 2 techniques for prediction of bone loss and fractures in patients with CKD stages 3 to 5 (mean age 62 years, 80% men, 93% white subjects), and Malluche *et al.*[121] in patients on dialysis treatment (mean age 53 years, 56% men, and 53% African Americans). In the study by West *et al.*,[120] BMD was measured by DXA (at total hip, lumbar spine, ultradistal, and 1/3 radius) and by QCT (at radius), and subjects were followed for 2 years for incident morphometric spine fractures and low-trauma clinical fractures. There were 51 fractures in 35 subjects. BMD by DXA at baseline was significantly lower at all sites among those with incident fractures versus those without. Similarly, almost all baseline QCT measures were lower in those with incident fracture. Bone loss occurred in all subjects, but was significantly greater among those with incident fractures. The authors concluded that low BMD (by DXA and QCT) and a greater annualized percentage decrease in BMD are risk factors for subsequent fracture in men and women with predialysis CKD. In the study by Malluche *et al.*,[121] BMD of the spine and hip was measured at baseline and after 1 year by DXA and QCT. Rates of detection of osteoporosis by DXA and QCT were compared. At baseline, QCT and DXA of the spine identified similar rates of osteoporosis (13.6% and 13.6%), but at the hip, DXA identified more osteoporosis (22.2% vs. 13.6%). At any site and by either method, 33.3% of the patients were osteoporotic. At 1 year, hip QCT identified a higher number of patients experiencing bone loss (51.3%) than DXA (38.5%). After multivariable adjustment, baseline sclerostin and tartrate-resistant acid phosphatase-5b (TRAP-5b) predicted bone loss measured by QCT of the hip; P1NP predicted cortical spine bone gain by QCT. The authors concluded that QCT identified prospectively more bone loss at the hip than DXA. The baseline serum biochemical parameters sclerostin and TRAP-5b were noninvasive independent predictors of bone loss in CKD patients on dialysis. Note, however, that bone strength as indirectly assessed by BMD and QCT, although being generally considered as the most important factor for fracture risk, is certainly not the only one in the occurrence of fractures in patients with CKD. Increased fragility, muscle weakness, and fall risk also play important roles.

Perhaps combinations of collagen-based biomarkers with imaging techniques might be most useful for fracture prediction. Thus Nickolas *et al.*[122] examined 82 patients with CKD stages 3 to 5, 23 of whom had prevalent fractures. They found that the highest tertiles of bone formation marker P1NP and resorption marker TRAP-5b were associated with prevalent fracture. In addition, the combination of the highest tertile of s-P1NP or TRAP-5b with femoral neck t-score assessed by DXA improved fracture discrimination over the t-score alone.

CONCLUSION

For decades the study of the different types of renal osteodystrophy has mainly focused on patients with ESRD. Osteitis fibrosa and mixed uremic osteodystrophy were considered to be the predominant types, with osteomalacia being of low prevalence. The discovery of aluminum-induced osteomalacia and adynamic bone disease in the 1980s radically changed the prevalence, at least in several geographic areas around the world, yet this again mainly concerned patients receiving dialysis therapy. Reports at that time of adynamic bone disease in patients with CKD not yet on dialysis, in the absence of aluminum overload, were considered as a curiosity. Subsequently, clinical and experimental evidence has been accumulating in favor of the development of low-turnover bone disease in early stages of CKD, as a result of resistance to the action of PTH and several other mechanisms. We and others propose the role of uremic toxins such as indoxyl sulfate and of a repression of the osteocyte Wnt/β-catenin signaling pathway in the initial stage of renal osteodystrophy.

DISCLOSURE

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