Fractures in patients with CKD—diagnosis, treatment, and prevention: a review by members of the European Calcified Tissue Society and the European Renal Association of Nephrology Dialysis and Transplantation

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Mineral and bone disease is omnipresent in patients with chronic kidney disease (CKD) and leads to a diverse range of clinical manifestations, including bone pain and fractures. The accumulation of traditional clinical risk factors, in addition to those related to CKD, enhances the risk of comorbidity and mortality. Despite significant advances in understanding bone disease in CKD, most clinical and biochemical targets used in clinical practice remain controversial, resulting in an undermanagement of bone fragility. Vitamin D supplementation is widely used, but only a few studies have shown beneficial effects and a reduced risk of fracture and mortality. The achievement of serum levels of 25-hydroxyvitamin D is recommended for CKD patients to reduce a high parathyroid hormone level, which is associated with skeletal fractures. Optimal control of parathyroid hormone also improves bone mineralization and lowers circulating bone biomarkers such as alkaline phosphatase and cross-linked collagen type I peptide. The potential value of more recent biomarkers such as sclerostin and fibroblast growth factor 23, as surrogates for bone fragility, is an encouraging new direction in clinical research but is far from being firmly established. This article reviews the literature related to the pathophysiological role of various mineral and biochemical factors involved in renal osteodystrophy. To better understand bone fragility in CKD, new information related to the impact of disturbances of mineral metabolism on bone strength is urgently needed. The combined expertise of clinicians from various medical disciplines appears crucial for the most successful prevention of fractures in these patients.

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Preventing or delaying the progressive metabolic complications related to chronic kidney disease (CKD) is essential to reduce the high morbidity and mortality rates associated with it. The mineral and bone disorder (MBD) associated with CKD (CKD-MBD) is an evolving entity. Guidelines from the 2009 Kidney Disease Improving Global Outcomes (KDIGO)[1] and the 2017 revised version (in press) have incorporated recommendations on the assessment and treatment of bone, biochemical, and cardiovascular abnormalities. In addition to the initial criteria for renal osteodystrophy based on bone biopsy findings, bone volume and mineralization have been added as other bone markers of fragility.

The new CKD-MBD definition aims at a better awareness of bone events. Skeletal fractures are the main clinical outcome, and their prevention should be a major target of renal osteodystrophy. The evaluation of fracture risk is required in light of high mortality and hospitalization costs related to fractures in dialysis patients,[2–6] which enhances the economic burden of CKD-MBD. In contrast to the 2009 KDIGO guidelines, systematic bone mineral density (BMD) measurement is recommended in CKD patients by the revised 2017 KDIGO guidelines because this might influence treatment decisions.

EPIDEMIOLOGY OF SKELETAL FRACTURES IN CKD

Peripheral fractures

CKD patients are living longer at present than at the end of the past century. Because bone loss increases with aging, the prevalence of skeletal fractures has increased in recent years. Table 1 summarizes several longitudinal studies reporting the incidence of fractures.[4,7–25] Most of them found the fracture incidence to progressively increase by 15.0, 20.5, 24.2, 31.2, and 46.3 per 1000 person-years for CKD stages 1 to 2, 3a, 3b,

Table 1 | Fracture incidence per 1000 persons-years and increased risk in CKD population

Study	Type of study	Total no. of patients	Fracture (*N*)	Fracture type	CKD stage	Incidence of fractures (1000 person-years)	Incidence (1000 person-years)		Global OR fracture risk	95% CI	
							Men	Women		Men RR	Women RR
Alem *et al.*[7]	RC	326,464	6542	Hip	5D	NR	7.45	13.63	NR	4.44 (4.16–4.75)	4.40 (4.17–4.64)
Coco and Rush[8]	RC	1272	56	Hip	5D HD	13.9	11.7	24.1	NR	14.2 (9.3–28.6)	17.2 (7.1–19.4)
Stehman-Breen *et al.*[9]	RC	4952	103	Hip	5D HD	NR	NR	NR	NR	3.12 (2.13–4.59)	3.35 (2.59–4.40)
Dukas *et al.*[10]	CS	5313	NR	Hip	<65	NR	NR	NR	1.57 (1.18–2.09)	NR	NR
				Wrist		NR	NR	NR	1.79 (1.39–2.31)	NR	NR
				Vertebral		NR	NR	NR	1.31 (1.19–1.55)	NR	NR
Jadoul *et al.*[11]	RC	12,782	174	Hip	5D HD	8.9 (8.4–9.4)	NR	1.41 (1. –1.89)	NR	NR	NR
			489	Any		25.6 (24.4–27.0)	NR	1.59 (1.32–1.92)	NR	NR	NR
Nickolas *et al.*[12]	CS	6270	159	Hip	<60	NR	NR	NR	2.32 (1.13–4.74)	NR	NR
Ensrud *et al.*[13]	PC	9704	149	Hip	<45	NR	NA	NR	NA	NA	2.32 (1.15–4.68)
				Trochanteric	<45	NR	NA	NR	NA	NA	7.17 (1.93–26.67)
			150	Vertebral	<45	NR	NA	NR	NA	NA	1.33 (0.63–2.80)
Fried *et al.*[14]	PC	4699	274	Hip	3–5	NR	5.9	9.7	NR	1.48 (0.95–2.31)	1.74 (1.33–2.28)
					Cystatin C	NR	NR	NR	NR	1.14 (0.86–1.52)	1.16 (1.01–1.33)
Dooley *et al.*[15]	RC	33,091	176	Hip	3	NR	NR	NA	NA	1.28 (0.88–1.66)	NA
					4	NR	NR	NA	NA	3.98 (2.25–7.74)	NA
LaCroix *et al.*[16]	PC	397	NR	Hip	3–5	NR	NA	NR	NR	NA	2.50 (1.32–4.72)
Ambrus *et al.*[17]	RC	130	21	All	HD	30.5	17	48.8	NR	NR	NR
Iimori *et al.*[18]	PC	485	46	All	5D HD	1.9 each 100 patient-year	NR	NR	NR	NR	NR
Wakasugi *et al.*[19]	RC	128,141	1437	Hip	HD	NR	7.5	17.43	NR	6.2 (5.7–6.8)	4.9 (4.6–5.3)
Arneson *et al.*[20]	RC	86,387	831	Hip	HD	1993: 11.9	NR	NR	NR	NR	–NR
		146,835	3256			2004: 21.9	NR	NR	NR	NR	NR
		203,857	2912			2010: 16.6	NR	NR	NR	NR	NR
Elliott *et al.*[21]	RC	1,815,943	10,188	Hip				65–74 yr			
			670		2	NR	NA	279.86	NR	NA	2.25 (1.78–2.72)
			425		2	NR	274.15	NA	NR	1.48 (1.12–1.84)	NA
			18,762	Wrist				>85 yr			
			279		2	NR	NA	31.27	NR	NA	8.02 (5.66–10.38)
			46		2	NR	14.07	NA	NR	2.58 (0.69–4.47)	NA
			12,070	Vertebral				65–74 yr			
			766		2	NR	NA	278.95	NR	NA	2.68 (1.98–3.39)
			560		2	NR	273.78	NA	NR	1.82 (1.24–2.40)	NA
Nair *et al.*[22]	PC	409,040	17,887	Hip	1–5	33.3	NR	NR	NR	1.50 (1.45–1.55)	1.03 (1.03–1.03)
Maravic *et al.*[4]	RC	68,953	362	Hip	5D	NR	1.1%	1.40%	NR	NR	NR
			68,591		1–5	NR	0.16%	0.41%	NR	NR	NR
Mathew *et al.*[23]	RC	929,114	842,028	Hip	5D HD	18.4	NR	NR	NR	NR	NR
Delgado *et al.*[24]	PC	1646	283	All	5D HD	Nonfrail: 66	NR	NR	NR	NR	NR
						Frail: 126	NR	NR	1.6 (1.16–2.20)	NR	NR
Yamamoto *et al.*[25]	PC	3276	178	All use ACEI/ARB	5D HD	1.48/100 patient-years	NR	NR	0.65 (0.45–0.92)	NR	NR
				All do not use ACEI/ARB		2.33/100 patient-years	NR	NR	NR	NR	NR

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker; CI, confidence interval; CKD, chronic kidney disease; CS, cross-sectional; HD, hemodialysis; NA, not applied; NR, not reported; OR, odds ratio; PC, prospective cohort study; RC, retrospective cohort study; RR, relative risk.

and 4, respectively.[26] The risk of skeletal fracture is up to 5 times higher in individuals with an estimated glomerular filtration rate (eGFR) <15 versus >60 ml/min per 1.73 m^2. Patients with CKD and older than 65 years of age exhibit a particularly high rate of fractures, with 1 in 10 women and 1 in 20 men experiencing at least 1 fracture in the subsequent 3 years of follow-up.[27] In a recent Dialysis Outcomes and Practice Patterns Study (DOPPS) report, the incidence of fractures was significantly higher for patients receiving hemodialysis therapy than in the general population, with a 3.7-fold increase in the unadjusted relative risk of death.[5]

The incidence of hip fractures is also 4-fold higher for dialysis patients than for the general population after adjustment for age, sex, and ethnicity.[7,28] The incidence of hip fracture in CKD patients differs by ethnicity and sex, being 3 times higher for Caucasian than African-American individuals[2] and twice as high for women than men.[4,9,15,29] Demographic risk factors include older age, low body mass index, and long dialysis vintage; a history of a hip fracture is also highly associated with an increased risk of hip fracture.[11] US Medicare data on hemodialysis patients identified downward hip fracture incidence trends from 2000 to late 2009,[2] most prominent in older adults of both sexes.[30] Indeed, the incidence of hip fracture increased when dialysis treatment was initiated from 1996 to 2004 and then declined until 2009, although it remained higher than in 1996.[22] The relative risk of hip fractures starts to increase as early as age 55 years and is high for CKD patients with high bone turnover rather than with low turnover disease.[11,15] The mortality risk after a hip fracture is high in CKD patients,[31,32] but has essentially not changed after 1998 for either sex.[29]

The risk of skeletal fractures combines classic risk factors with those associated with CKD. After 4 years of dialysis, the age-standardized incidence ratio of hip fracture was 9.83 (95% confidence interval 8.61–11.2) for men and 8.10 (95% confidence interval 7.23–9.07) for women.[7] Even in renal transplant recipients, previous dialysis vintage is associated with an increased risk of hip fracture.[3,33] The 30-day mortality rate after hip fracture is 16% for CKD patients initiating dialysis after age 67 years in the United States.[22] Hip fracture–related mortality risk is 2 times higher with an eGFR <45 than with an eGFR ≥45 ml/min per 1.73 m^2.[34] In 2010, the French national database exhibited significantly higher mortality rates after hip fracture in patients on dialysis therapy than in those without dialysis, as high as 12% for men and 8% for women, as well as a longer hospital stay in the intensive care unit.[4] Several risk factors were associated, particularly vascular-related diseases and dementia.

Vertebral fractures

The prevalence of vertebral fractures is poorly documented in cohorts and dialysis registries. This has been reported to be low, ranging from 7% to 20%,[35,36] and only 1% of patients had vertebral fractures based on clinical diagnosis in 1 clinical trial.[37] This may be an underestimation because radiographic imaging is not systematically performed. In case-control studies with a small number of dialysis patients, low BMD at the lumbar spine was associated with vertebral and prevalent or self-reported peripheral fractures.[38] However, in these patients, lumbar BMD did not have the same predictive value as in those without CKD. In a meta-analysis of 13 studies,[39] only 1 study mentioned a relationship between vertebral fracture and dialysis vintage, but did not find any association between risk of fracture and BMD.[17] This indicates that low BMD could not be considered as strong a risk factor as it is in patients without CKD. The 2017 KDIGO guidelines recommend using BMD measurement in patients with stages 3a to 5D CKD for predicting peripheral fractures, but we have no evidence that BMD could predict vertebral fractures in them.

DETERMINANTS OF FRACTURE RISK IN CKD-MBD

The evaluation of bone strength includes several factors that influence the quality of bone extracellular matrix. Bone quantity might be estimated by bone density, whereas bone quality might be estimated by the microarchitecture, both leading to a reduced mechanical bone adaptation (Figure 1). Occurrence of a fracture is the result of a fall in addition to failure in mechanical strength. Several imaging and biochemical tests are available and used to assess the fracture risk in the non-CKD population (Figure 2). These factors are reviewed in the following with regard to CKD.

Clinical factors

The KDIGO Working Group recommended using the same definition of osteoporosis for CKD patients as that advocated by the WHO for the general population. WHO defines osteoporosis as a bone disorder resulting in decreased bone strength and increased fracture risk. We believe that this definition could be recommended for the diagnosis and management of stages 1 to 3a CKD. However, bone disease related to CKD stages 3b to 5-5D features a large spectrum of clinical phenotypes, all associated with a high risk of fracture. Indeed, the high fracture risk results from the combination of CKD-induced changes in bone and mineral metabolism and

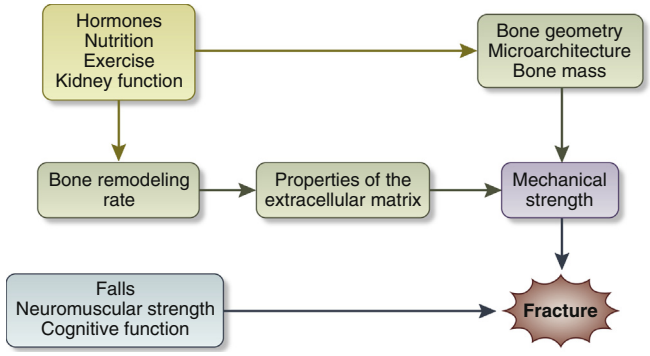

Figure 1 | Factors determining bone quantity and quality. Several factors determine the rate of bone remodeling that influence the quality of the bone extracellular matrix, which is part of the bone strength. Bone architecture and bone mass are additional determinants. The failure of mechanical strength and falls combined with unstable conditions precipitate the occurrence of fractures.

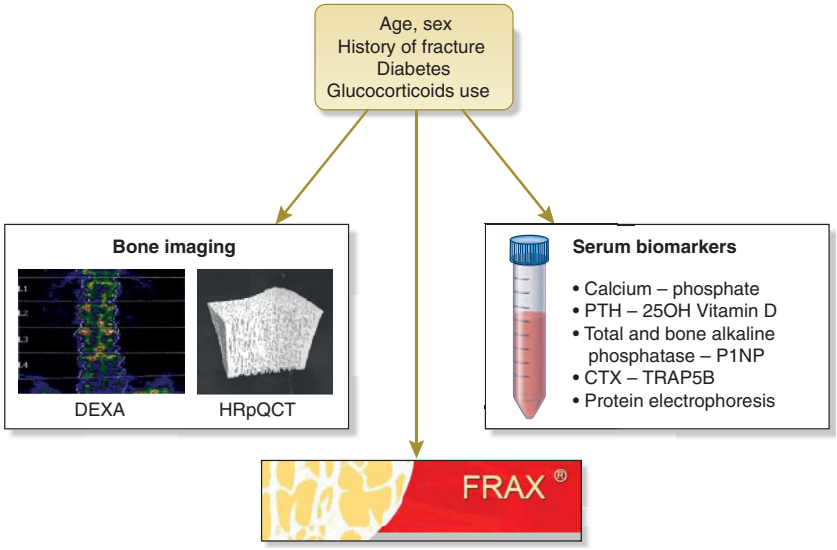

Figure 2 | Assessment of fracture risk in chronic kidney disease. In the presence of a fracture, investigations include the collection of clinical risk factors, imaging (dual-energy X-ray absorptiometry [DEXA], high-resolution peripheral quantitative computed tomography [HRpQCT], if available) and biochemical tests. The 3 are required to properly evaluate the risk of further fractures. CTX, cross-linked collagen type I peptide; FRAX, Fracture Risk Assessment Tool; P1NP, procollagen type 1 N-terminal pro-peptide; PTH, parathyroid hormone; TRAP5B, tartrate-resistant acid phosphatase 5B. To optimize viewing of this image, please see the online version of this article at www.kidney-international.org.

the classic fracture risk factors observed in the non-CKD population including age, sex, medical history of fracture, diabetes, and glucocorticoid use. Moreover, the association of the fracture risk with clinical risk factors assessed by the Fracture Risk Assessment Tool in addition to BMD is poor in CKD.[40,41]

Bone histology

Bone histomorphometry is the gold standard with which to evaluate bone abnormalities of CKD-MBD,[42] although not routinely recommended except if results would affect therapeutic decisions. Most patients with CKD stages 3 to 5 are expected to have histologic signs of high bone turnover in that 85% to 90% show an increased serum parathyroid hormone (PTH) level.[43,44] Accordingly, this assumption was confirmed by a study reporting histologic high bone turnover in 47.2% of patients with CKD stages 3 to 4 and in 61.4% in those with CKD stage 5.[45] However, low-turnover bone disease has also been reported as being the predominant MBD in 2 small populations with predialysis and a wide eGFR range (<5 to 90 ml/min per 1.73 m^2)[46,47] and in most CKD patients on dialysis.[48,49] These apparent controversial data might be biased by the recruitment of patients; bone biopsies are mostly performed in symptomatic patients with no systematic analysis for epidemiologic purposes and are influenced by several confounding factors. Moreover, the lack of a clear-cut and quantitative definition of adynamic bone disease (ABD) and the absence of previous labeling lessen any clear conclusion. ABD is often used to classify patients with low PTH. Indeed, the major question is what could be considered as normal remodeling rate in CKD. Recent studies showed changes from low to high bone turnover during CKD progression.[50] Unfortunately, we lack evidence of an association between fracture incidence and the histologic type of bone disease. Despite definitive proof, low or high bone turnover favors fractures as both increase bone fragility. This might be explained in part by the absence of analysis of cortical bone, which is predominantly affected in CKD. Finally, the major contribution of a bone biopsy is the diagnosis of osteomalacia, which cannot be detected by circulating biomarkers. Osteomalacia was first reported with aluminum overload,[51] this cause now being rare in developed countries. However, osteomalacia is still observed in patients on long-term dialysis therapy, without obvious causes reported.

Bone mineral density

In non-CKD patients, the reduction of 1 SD in BMD as measured by dual-energy X-ray absorptiometry (DEXA) doubles the fracture risk and is therefore useful for evaluating fracture risk. However, the relevance is limited in CKD patients because of frequent scoliosis, osteoarthritis at the lumbar spine, and the presence of vascular or joint calcifications, which may overestimate BMD. Moreover, BMD does not evaluate bone strength. Thus, the usefulness of BMD for evaluating fracture risk in CKD, especially in dialysis patients, is controversial. For CKD stages 1 to 3, BMD should be measured if biochemical test results do not suggest any additional CKD-MBD such as altered serum PTH or calcium level. A meta-analysis revealed that BMD is lower in predialysis and dialysis CKD patients with than in those without fractures.[39] Despite these findings, BMD measurement was not recommended in the 2009 KDIGO guidelines because of

inconsistency in the results of mostly cross-sectional studies. More recently, the results of 4 prospective cohort studies showed a good predictive value of BMD for the risk of fracture in CKD stages 3 to 5D,[18,26,41,52] which allows for recommending BMD measurement.

The Fracture Risk Assessment Tool can be used to predict peripheral fractures in older patients with CKD stages 2 to 5.[40] Clinical risk factors such as weight, height, prevalent fracture, family history of hip fracture, and steroid use are sufficient for 10-year prediction and are as efficient alone as together with hip BMD.[40] Altogether, low BMD appears to be 1 important risk of fracture but cannot be the only criterion for the initiation of any antifracture treatment as in non-CKD patients.

Femoral neck geometry and hip structural analysis

Bone geometry is essential for determining bone strength; altered hip geometry, as derived from DEXA hip measurement, has been associated with the risk of fracture. Thus, non-CKD women with hip fractures have thinner femoral cortices and a longer femoral-neck axis length than women without fractures. Such information has not been reported in patients with CKD. Although hip structural values are correlated with BMD, whether they provide additional information independent of BMD and improve fracture prediction is controversial.[53]

Trabecular bone score

The trabecular bone score is a gray-level textural index derived by an algorithm that analyzes the spatial organization of pixel intensity from lumbar spine DEXA images. The trabecular bone score is not a direct measurement of bone microarchitecture but might be related to it. The trabecular bone score can be used to predict fractures independent of major clinical risk factors or a real BMD measured in the general population.[54] In a cohort of 1426 participants (40 years of age and older) followed for a mean of 4.7 years, including 199 with an eGFR $<$60 ml/mm per 1.73 m^2 (72.4% CKD stage 3a, 25.1% CKD stage 3b, and 2.5% CKD stage 4), the low lumbar spine trabecular bone score was independently associated with an increased fracture risk in adults with reduced kidney function.[55]

High-resolution peripheral quantitative computed tomography measurement

BMD measurement by DEXA is not sufficient to assess the fracture risk, in part because of a weak discriminating power between cortical and trabecular bone. Besides bone geometry, bone strength greatly depends on the quantity and quality of cortical bone, which are highly altered in CKD. Elements have been provided by bone biopsy performed in CKD patients for research purposes and regardless of fracture status. They revealed that low-bone turnover is associated with normal cortical porosity, whereas high cancellous bone volume and normal cortical thickness are observed when serum PTH levels are moderately increased.[48] Consequently, assessment of cortical bone structure in CKD would contribute to CKD because bone loss is predominantly of cortical origin and is highly associated with peripheral fractures at both weight-bearing and nonweight-bearing sites.[56] Conventional quantitative computed tomography (QCT) has been shown to reveal a higher number of patients experiencing bone loss at the hip compared with BMD measured by DEXA (51.3% vs. 38.5%).[57] Using the peripheral QCT (pQCT) device from Stratec Biomedical Systems (Birkenfeld, Germany), which measures only BMD at the mid-radius and then mainly cortical bone, high PTH, longer dialysis vintage, and cortical BMD were the most significant predictors of skeletal changes.[58] BMD and microarchitecture assessed by high-resolution pQCT (SCANCO Medical AG, Brüttisellen, Switzerland) raised some hope because this allows a separate measurement of cortical and trabecular bone[59] and helps to determine the underlying mechanisms of bone loss.[60] In CKD stages 2 to 4, high-resolution QCT showed early impairment of trabecular bone, before the onset of secondary hyperparathyroidism. This could explain in part the high risk of fractures in early CKD[61] but also in patients with a long CKD history.[59] Bone loss observed in CKD stage 5D affected cortical BMD and thickness, which is correlated with high PTH and dialysis vintage, but not with trabecular bone.[56] However, levels of neither calciotropic hormones such as PTH nor bone remodeling markers were associated with changes in trabecular density, number, and heterogeneity. These data have been challenged more recently by a study using bone biopsy data that correlated cortical BMD with biochemical markers.[62] Cortical BMD was negatively correlated with serum PTH, tartrate-resistant acid phosphatase 5b, and bone-specific alkaline phosphatase levels, suggesting that a low remodeling rate is associated with higher bone density and strength. These controversial data are likely related to changes that occur at different remodeling rates, biomarkers reflecting the level of bone remodeling in the short term and cortical thickness integrating remodeling rates for a long period. However, new imaging of the appendicular skeleton could be helpful to estimate cortical bone loss that is strongly associated with fractures.[59] At present, it is possible to analyze bone at higher resolutions from 10 μm to 10 nm by using bone biopsy samples and nano-QCT or synchrotron radiation CT. These approaches allow a deep analysis of bone matrix, including collagen and mineral properties as well as osteocyte lacunae and the canaliculi network.[63,64] Despite the great interest in predicting the risk of fracture and identifying those who will benefit from therapeutic interventions, most of these tools are not widely available, and data concerning their superiority compared with DEXA are thus far lacking.[65]

Serum biochemistry

Vitamin D sterols. The classic therapeutic goal of any type of vitamin D in CKD is to improve calcium, phosphate, and PTH parameters for managing MBD. Circulating values of native vitamin D (i.e., calcidiol or 25-hydroxyvitamin D [25OHD]) allow determination of vitamin D storage. Nevertheless, the optimal circulating 25OHD level in CKD

that protects against skeletal fractures is controversial. For CKD patients not on dialysis, the 2017 KDIGO guidelines recommend using the same 30 ng/ml cutoff value used for the general population. For patients at CKD stage 5D, applying this threshold led to an estimated prevalence of vitamin D insufficiency (15–30 ng/ml) and/or deficiency (<15 ng/ml) ranging from 50% to 98%, with a combined mean prevalence of 82% in a total sample size of 3722 patients.[66] A survival benefit and a significant degree of PTH suppression have been observed for a putative optimal serum 25OHD level.[67] In CKD stages 2 to 5, serum PTH levels were inversely correlated with serum 25OHD.[68] With 25OHD values >20 ng/ml, PTH was within normal limits, reaching a nadir value with 25OHD values >30 ng/ml and an inflexion point ≤8 ng/ml. A cross-sectional analysis of 14,289 unselected CKD stage 1 to 5 patients showed that the serum 25OHD level above which the suppressed PTH level progressively vanished was 48 ng/ml. This plateau for PTH was observed for all 5 CKD stages, with no episode of hypercalcemia or hyperphosphatemia with higher serum 25OHD levels. Increasing serum 25OHD levels above 40 ng/ml are associated with decreased bone turnover biomarkers.[56,69,70] Nevertheless, we have insufficient evidence correlating the correction of serum vitamin D level with improved patient outcomes such as fracture risk and pain,[17,56] parathyroidectomy, CKD progression, and cardiovascular events, including all-cause mortality in CKD patients not requiring dialysis and those on dialysis.[71,72] Whether nutritional or vitamin D derivatives modify cardiac or immune functions remains controversial.[73–75]

Table 2 summarizes the studies assessing changes in serum 25OHD and PTH with vitamin D supplementation.[76–92] Supplementation with calcidiol in CKD stage 5D improved bone mineralization but had a limited effect on reducing serum PTH similar to non-CKD patients.[93,94]

Several studies have also looked at the correlation between serum vitamin D level and BMD in CKD and non-CKD populations. In postmenopausal women of southern Europe, BMD was lower in vitamin D–deficient groups who also had high levels of bone resorption and formation markers.[95] In 70 patients with CKD stage 5D, BMD was significantly low only at the mid-radius, but did not predict the risk of fracture and was not correlated with circulating 25OHD and 1,25OH2D levels. Rib fractures were associated with a poor nutritional status.[36] In non-CKD populations, pooled data from 11 double-blind, randomized, controlled trials of oral vitamin D supplementation demonstrated an association, although not significant, of vitamin D (≥800 IU daily) and reduced hip fracture and any nonvertebral fracture in participants 65 years of age and older.[93] Unexpectedly, in a randomized controlled trial of older women considered at high risk of fracture, annual administration of high-dose cholecalciferol (500,000 IU) increased the risk of fractures.[96] A systematic review and meta-analysis of a younger population, mainly women, showed little evidence of overall benefit of vitamin D supplementation on BMD.[94]

Vitamin D dose regimen and temporal fracture risk pattern remain undefined, being particularly poorly addressed in vitamin D–deficient populations, independent of the presence or the absence of CKD. Several studies favored a higher vitamin D cutoff value in CKD patients in relation to the general population (Table 3).[56,66,68,69,97–101] Overall, we believe that a higher 25OHD cutoff value might be necessary to prevent bone fractures, permitting a significant decrease in serum PTH and ameliorating bone biomarkers. Increased supplementation doses may be necessary to stimulate residual renal 1α-hydroxylase activity, to compensate for high osteoid activity, and to have a significant impact on reducing PTH. The 1α-hydroxylase activity is not restricted to renal cells; CKD patients with reduced or even no renal mass can hydroxylate 25OHD to 1,25OH2D in extrarenal tissues and at very low 25OHD concentration.[102,103] Vitamin D receptor agonists aim to control secondary hyperparathyroidism, which starts at earlier CKD stages. We believe that instead of restricting active vitamin D therapy to the control of secondary hyperparathyroidism, physiological doses of vitamin D receptor agonists should be given to all CKD patients, even those with normal or low PTH, to add to all vitamin D beneficial effects.[104] Calcitriol is efficient in lowering PTH but has detrimental or no effect on bone mineralization. No benefit was reported with administration of vitamin D receptor agonists in terms of fractures, bone pain, or the need for surgical parathyroidectomy.[105] CKD stage 1 to 5D patients also show increased serum fibroblast growth factor 23 (FGF23) levels[97] that can be related to the direct stimulatory effect of 25OHD but also from local osteoblastic conversion to 1,25OHD.[106] FGF23 reduces 25OHD and 1,25OH2D, which suggests that the current doses of vitamin D that we are using may be insufficient to achieve 25OHD targets in CKD.[66] Additionally, vitamin D supplementation in CKD might be tailored based on a putative optimal 25OHD target value and on 1,25OHD, FGF23, and PTH baseline values as well as their change over time.

Phosphate. In population-based cohorts, serum phosphate levels are positively associated with fracture risk in both sexes and in a subgroup of men with CKD.[107] This was maintained after adjustment for FGF23 and PTH, which indicates that high phosphate itself and not underlying hormonal disturbances may explain the high fracture risk. Reduced bone mass and increased fracture risk associated with hyperphosphatemia could be mediated by a lower osteoblastic proliferation through insulin growth factor 1 and osteopontin gene expression.[108,109] High phosphate can also increase osteoblast apoptosis and reduce bone formation.[110–112] Moreover, high phosphate inhibits bone resorption through the stimulation of osteoblast-produced osteoprotegerin.[113–115] Currently, the feasibility of a multicenter randomized trial testing whether lowering phosphate level can decrease several clinical outcomes, including bone pain and fracture risk, in CKD patients is being evaluated.[116]

Parathyroid hormone. PTH remains the best surrogate biomarker for bone histology in CKD in addition to new

Table 2 | Changes in serum 25(OH)D and PTH levels with vitamin D supplementation at the end of treatment period

Study	Design	Total no. of patients	Control group	CKD stage	Vitamin D	Dose (IU/d)	Comparison group	Duration	Mean increase 25(OH)D (ng/ml)	Mean decrease PTH (pg/ml)
Al-Aly *et al.*[76]	RC	66	No	3–4	Ergocalc	50,000/wk for 12 wk, then once monthly	NA	6 mo	16.6 ± 0.7 to 27.2 ± 1.8 ($P < 0.05$)	231 ± 26 to 192 ± 25 ($P < 0.05$)
Saab *et al.*[77]	RC	118	No	5D	Ergocalc	50,000/wk	NA	6 mo	53.6 ± 16.3 ($P < 0.001$)	NS
Blair *et al.*[78]	RC	318	No	5D	Ergocalc	50,000/wk	NA	6 mo	18.4 ± 9.0 to 42.0 ± 24.7 ($P < 0.0005$)	NS
Chandra *et al.*[79]	RCT, B	20	Yes	3–4	Cholecal	50,000/wk	NA	12 wk	17.3 (95% CI 11.8–25.2) to 49.4 (95% CI 33.9–72.0); ($P = 0.002$)	NS
Dogan *et al.*[80]	RCT	40	Yes	3–5	Cholecal	30,000/mo	NA	1 mo	6.8 ± 3.5 to 17.8 ± 21.4 ($P < 0.001$)	368 ± 274 to 279 ± 179 ($P < 0.001$)
Oksa *et al.*[81]	RCT	87	No	2–4	Cholecal	5000/wk	NA	1 yr	15 (95% CI 5–60) to 28 (95% CI 14–72); ($P < 0.001$)	63 (95% CI 13–224) to 48 (95% CI 11–181); ($P < 0.001$)
						20,000/wk			16 (95% CI 4–49) to 37 (95% CI 8–81); ($P < 0.001$)	NS
Tokmak *et al.*[82]	PC	64	Yes	5D	Cholecal	20,000/wk	NA	15 mo	6.66 ± 3.84 to 31.79 ± 10.86 ($P < 0.001$)	NS
Jean *et al.*[83]	PC	316	No	5D	Cholecal and calcifediol	100,000/mo	10–50 mg/d	3 yr	25(OH)D > 75 nmol/l: 18% to 59% ($P < 0.0001$)	PTH >300 pg/ml: 35% to 12% ($P < 0.0001$)
Kooienga *et al.*[84]	RCT, DB	610	Yes	2–4	Cholecal and calcium	800/d and 1200 mg/d	eGFR <60	6 mo	NA	30% ($P < 0.001$)
							eGFR <45	24 mo	33.5 ± 12.1 ($P < 0.001$)	NR
Matias *et al.*[85]	PC	158	No	5D	Cholecal	8100-50,000/wk	NA	6 mo	22.3 ± 12.0 to 42.0 ± 12.1 ($P < 0.001$)	233 to 208 ($P < 0.001$)
Moe *et al.*[86]	RCT, B	47	No	3–4	Cholecal and doxercalciferol	2000/d	1 μg/d	3 mo	Cholecalciferol 14 ± 6 to 37 ± 10 ($P < 0.001$)	Doxercalciferol 106.5 ± 44.3 to 80.4 ± 48.6 ($P = 0.006$)
Jakopin *et al.*[87]	PC	101	No	5D	Cholecal	40,000/mo	NA	24 mo	28.6 ± 16.7 to 54.9 ± 15.5 ($P < 0.001$)	NS
Kovesdy *et al.*[88]	RCT	80	Yes	3–4	Ergocalc and paricalcitol	50,000/wk	1–2 μg/d	16 wk	Ergocalc 7.08 (95% CI, 4.32–9.85) ($P < 0.001$)	Paricalcitol 43.9 (95% CI 11.2–76.6); ($P = 0.009$)
Alvarez *et al.*[89]	RCT, DB	48	Yes	2–3	Cholecal	50,000/2 wk	NA	1 yr	26.7 ± 6.8 to 42.8 ± 16.9 ($P < 0.05$)	NS
Wasse *et al.*[90]	RCT, DB	52	Yes	5D	Cholecal	200,000/wk	NA	6 wk	14.6 ± 16.2 ($P < 0.001$)	NS
Delanaye *et al.*[91]	RCT, DB	43	Yes	5D	Cholecal	25,000/2 wk	NA	1 yr	NS	115 (95% CI 192–81) ($P = 0.02$)
Del Valle *et al.*[92]	PC	82	No	5D	Ergocalc	72,000/wk	NA	12 wk	15.2 ± 5.4 to 42.5 ± 13.2 ($P < 0.01$)	No change

B, blinded; Cholecal, cholecalciferol; CI, confidence interval; CKD, chronic kidney disease; Ctr, control; DB, double-blinded; ergocalc, ergocalciferol; 25(OH)D, hydroxyvitamin D; eGFR, estimated glomerular filtration rate; NA, not applied; NR, not reported; NS, not significant; PTH, parathyroid hormone; PC, prospective cohort study; RC, retrospective cohort study; RCT, randomized controlled trial.

Table 3 | Arguments that favor the use of a higher vitamin D cutoff value in CKD patients in relation to the general population

References	Arguments	CKD stage	Recommended ^{25}OHD (ng/ml) value
Coen *et al.*[69]	Downslope of bone turnover parameters	5D	>40
Gutierrez[97]	FGF23 is the strongest determinant of calcitriol levels Increased FGF23 means lower 25OHD and 1,25OH2D	1–5	NR
Bhan *et al.*[98]	Bioavailable serum 25OHD levels are better correlated with both corrected serum calcium levels and PTH, measures of mineral metabolism, than total 25OHD levels	5D	NR
Metzger *et al.*[68]	Threshold of PTH	1–5	>20
Nickolas *et al.*[56]	Increased trabecular density Decreased heterogeneity of trabecular network	2–5D	Change adjusted for baseline measurement 28.6 ± 69.0
Singer[66]	At 30 ng/ml, vitamin D deficiency ranges from 50% to 98%; combined mean prevalence of 82%	5D HD	>30
Kim *et al.*[99]	Nutritional vitamin D supplementation takes longer to successfully normalize serum 25OHD levels in most patients with vitamin D deficiency and overt proteinuria Baseline vitamin D level was the principal factor to determine nonresponsiveness to supplementation	1–5	NR
Ennis *et al.*[100]	Cutoff that allows no significant further reduction of PTH	1–5	42–48
Obi *et al.*[101]	25OHD has a weak binding capacity for vitamin D receptors and has 100 times higher serum concentration than 1,25OH2D FGF23 inhibits the renal expression of 1α-hydroxylase, resulting in the decrease in serum 1,25OH2D concentrations	1–5	NR
Multiple studies, see Table 2	Mean decrease in PTH was not significant	2–4; 5D	>20–30

CKD, chronic kidney disease; FGF23, fibroblast growth factor 23; NR, not reported; PTH, parathyroid hormone.

biomarkers of bone turnover (i.e., cross-linked collagen type I peptide) and tartrate-resistant acid phosphatase 5B (TRAP5b for bone resorption, bone-specific alkaline phosphatase, and procollagen type 1 N-terminal pro-peptide for bone formation.[57] Most CKD patients with ABD show a serum PTH level <150 pg/ml,[117] and those with histologic secondary hyperparathyroidism show PTH values >600 pg/ml.[118] Although within the PTH range of 150 to 300 pg/ml, many patients may exhibit either one or the other forms of renal osteodystrophy.[119] In addition, both high and low circulating PTH levels can be associated with a high fracture rate and mortality risk.[5,6,8,11,35,120–122] Interestingly, serum PTH levels, just before the occurrence of a new fracture, are associated with the increased risk of fracture, in contrast to baseline or time-averaged serum PTH levels. The upper and lower PTH values of the U-shaped PTH curve are associated with a significantly increased risk of fracture compared with PTH values within the recommended National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/K-DOQI) target values.[18] Of note, the decision to treat CKD-MBD is often based on a single PTH level. The revised KDIGO 2017 guidelines has now included the term *persistently* above the upper normal PTH level as well as *progressively rising* PTH level, rather than *above the upper normal limit*. Therefore, treatment should not be based on a single PTH value but rather on a trend of PTH within the previous months. Long-term exposure to high PTH could induce a preferential loss of cortical bone, which could be even more pronounced in female than in male patients with CKD stage 5D.[123] Parathyroidectomy reduces bone turnover and may improve BMD and reduce the long-term risk of fractures in CKD stage 5D patients.[124–126]

Phosphate/FGF23/klotho axis. Reduced extracellular phosphate concentration is crucial for apoptosis of mature chondrocytes in the growth plate and the cascade of events leading to normal bone growth such as blood vessel invasion and mineralization.[111] Abnormal serum phosphate is undeniably one of the most important components of CKD-BMD. Circulating phosphate levels slowly increase as CKD progresses and both directly and indirectly contributes to the skeletal fragility associated with CKD-MBD, in part via the stimulation of PTH and FGF23 production.[127] Serum FGF23 levels significantly increase in early CKD stages and coincides with the decrease of 1,25OH2D.[128] FGF23 is mainly produced by osteocytes and osteoblasts and exerts its major physiological actions in the kidney, stimulating urinary phosphate excretion and inhibiting calcitriol synthesis after binding to a complex formed by alpha-klotho and canonical FGF receptors.

FGF23 plays an important role in regulating bone mineralization. The absence of FGF23 (FGF23 knockout mice) and excess FGF23 (klotho knockout mice) result in severe bone demineralization. However, in CKD stage 5D patients, BMD is not correlated with serum FGF23 levels.[129] High FGF23 was associated with reduced osteoid thickness in children with normal renal function and in CKD children on dialysis.[130] This enigma appears to be deciphered as FGF23 modulates bone mineralization by specifically regulating tissue nonspecific alkaline phosphatase activity via FGFR-3, vitamin D and klotho independent manner. FGF23 inhibits tissue nonspecific alkaline phosphatase transcription, increases the extracellular concentration of pyrophosphate, reduces the amount of inorganic (free) phosphate, and indirectly stimulates expression of osteopontin, a known mineralization

inhibitor.[131] Excessive FGF23 also contributes to bone loss in CKD via a klotho-dependent mechanism and the stimulation of the osteoblast Wnt inhibitor Dkk1.[132] Therefore, inactivation of the Wnt/b-catenin signaling pathway by the altered phosphate/FGF23/Klotho axis may provide another autocrine/paracrine mechanism favoring bone loss in CKD-MBD.

PREVENTION AND MANAGEMENT OF FRACTURES IN CKD

Treatment available for CKD patients

In patients with CKD stages 1 to 3b, the prevention of fractures does not differ from that in osteoporosis patients without CKD. In any case, correction of low 25OHD is recommended. In those with an eGFR >30 ml/min per 173 m^2, treatment such as raloxifene, bisphosphonates, and teriparatide (human recombinant PTH) will follow the same recommendations as in non-CKD patients. However, raloxifene should be used cautiously in relation to an increased risk of thromboembolism in CKD as in non-CKD patients.

The challenge is the treatment of CKD stage 4 to 5D patients with osteoporosis. The 2017 KDIGO guidelines recommend that in patients with CKD stage 3a to 5D with biochemical abnormalities of CDK-MBD and low BMD/fragility fractures, the treatment choice should consider the magnitude and reversibility of biochemical abnormalities and the progression of CKD with consideration of bone biopsy. Thus, a follow-up of 6 to 12 months after the correction of mineral biomarkers should precede the instauration of a specific antifracture therapy.

In our opinion, patients with a low BMD alone should not be treated as no trial shows any evidence of antifracture efficacy. Treatment should first address patients with osteoporotic fracture because they show bone fragility. The initial step is to identify the causes of the fracture. These might be primarily due to mineralization defects that are rare, but still observed in many CKD patients. Osteomalacia is suggested by low serum 25OHD and calcium levels with consistently high alkaline phosphatase levels and requires a bone biopsy. In the absence of hypocalcemia, osteomalacia could be associated with low phosphate level that is also responsible for mineralization failure. The hypophosphatemia could be associated with severe phosphate diet restriction, excessive dialysis, parathyroidectomy, or alcohol abuse.[133] Oral administration of vitamin D or phosphate or adding phosphate to the dialysate reverses clinical and biochemical signs. If there is no low calcium or phosphate, other causes might be the origin of osteomalacia including high fluoride content that could be measured in the bone biopsy specimen.[134]

Most antifracture treatments are contraindicated in patients with an eGFR <30 ml/min per 173 m^2. Bisphosphonates accumulate in bone tissue regardless of kidney function, but reduced renal clearance promotes high storage. This is associated with defective bone mineralization and osteomalacia[135] or else may induce ABD. For this reason, no proper randomized trial has ever examined the efficacy of these drugs for fractures in CKD. Few studies and early *post hoc* analyses showed increased BMD with bisphosphonates, but did not have sufficient power to show a reduction in fracture risk. A recent systematic review provided no clear evidence that these treatments could be helpful in CKD.[136] Low-dose bisphosphonates could be another option, but this remains to be proven in clinical trials.

Recently, denosumab, an anti–receptor activator of nuclear factor κB ligand biologic therapy, offered new hope for managing osteoporosis and bone fragility. Denosumab is associated with a reduced risk of vertebral, nonvertebral, and hip fractures in osteoporotic women.[137] In a subgroup of 73 women with CKD stage 4 who participated in this trial, the denosumab-induced increase in BMD was comparable to that in women with CKD stages 1 to 3, but no conclusions could be drawn as to a possible reduction in fracture risk.[138] In CKD stages 4 to 5D with severe secondary hyperparathyroidism, denosumab may promote marked hypocalcemia and increase PTH within 15 days, requiring calcium supplementation. Thus, denosumab administration should be monitored closely in CKD patients because of these potential adverse effects. Clinical trials in osteoporotic women with CKD stage 5D are ongoing and would provide answers regarding its effects on BMD and mineral metabolism (NCT01464931). Most importantly, further trials are awaited to test the effect on fracture risk.

Management of fracture

There are now no clear recommendations for the management of fractures in CKD patients. Here we provide some guidelines based on our own experience (Figure 3). As fractures occurred regardless of the circulating levels of bone biomarkers, therapeutic decisions first require the corrections of mineral disturbances. In patients with high PTH, decreasing PTH will improve the bone status. Indeed, cinacalcet was found to efficiently reduce fracture rates in elderly dialysis patients with secondary hyperparathyroidism.[37] We recommend lowering PTH as a first action to reduce cortical bone loss and to limit the risk of peripheral fractures. Because of the lack of data on denosumab in high PTH conditions,[139] its use would be considered when PTH has been normalized.

The major question is the treatment of fractures in patients with low PTH. There is some fear of further reducing low bone remodeling by antiresorptive therapy, supported by the idea that this could promote ABD, the risk of fracture, and vascular calcification. In non-CKD patients, denosumab reduces efficiently the rate of fractures in osteoporotic patients regardless of bone turnover markers, suggesting that the antifracture effect is obtained in low bone turnover and independent of the rate of bone remodeling. However, restoration of PTH levels to the "2 to 9 time-fold" target is recommended to ensure proper function of bone cells and replacement of old with new bone matrix. This could be achieved by reducing calcium content in the dialysate.[140] The hypothesis that reducing bone turnover would increase the risk of vascular calcification is not supported by any data in humans, but, in contrast, denosumab reduces the deposition of calcium in vessels of osteopenic mice.[141] Denosumab does not promote any aortic calcifications in postmenopausal

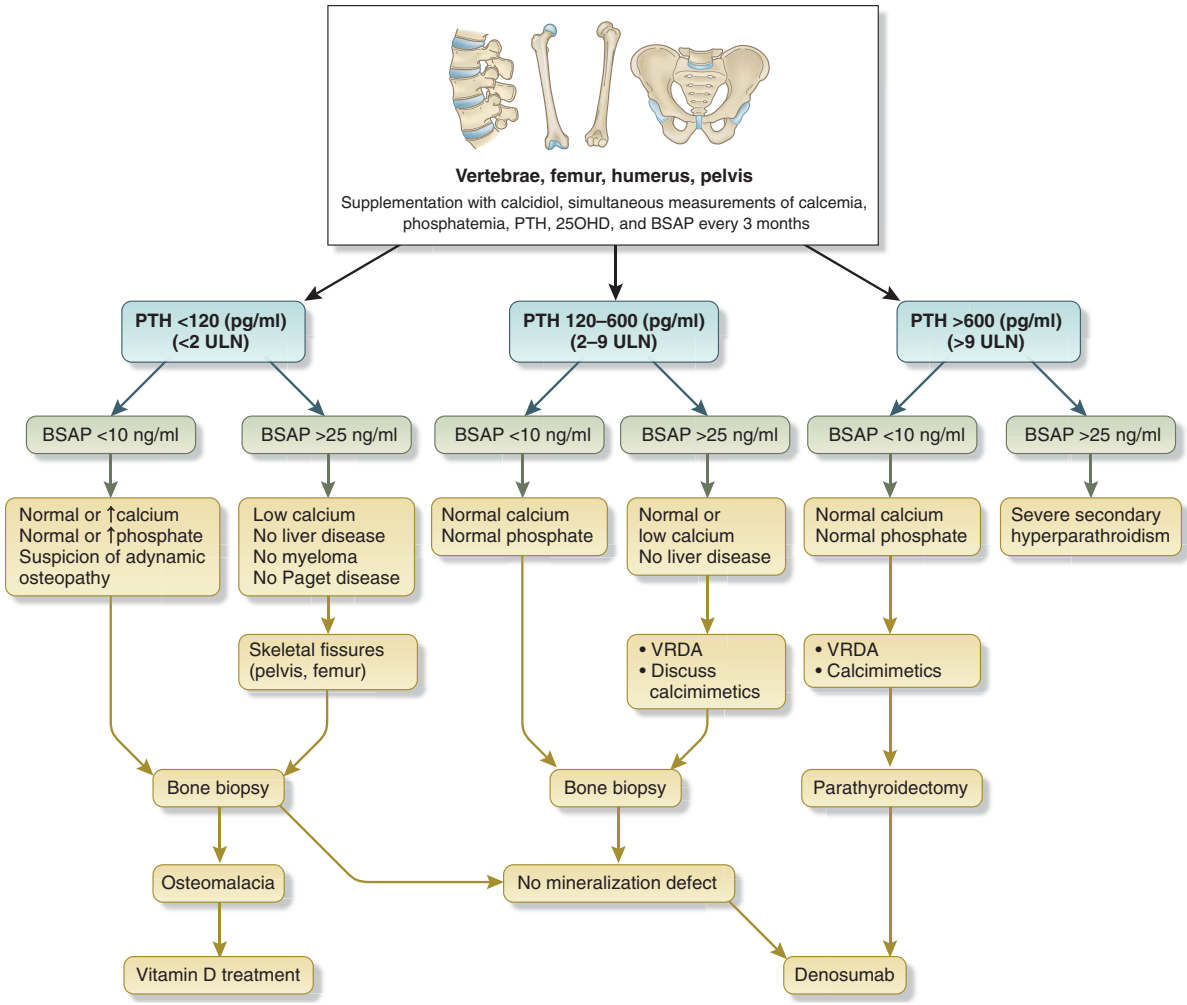

Figure 3 | Guidelines for the management of fractures. A fragility fracture requires a deep analysis of mineral metabolism markers. First, the analysis aims to eliminate an osteomalacia or low turnover bone disease with the use of a bone biopsy. Then guidelines are proposed as a function of PTH levels. Reduction of PTH should be achieved before the introduction of any anti-resorbing agents. BSAP, bone-specific alkaline phosphatase; PTH, parathyroid hormone; ULN, upper limit of normal; VRDA, vitamin D receptor activators.

women without renal failure.[142] Studies are needed to determine whether this drug has an impact on vascular calcifications in CKD. Meanwhile, the use of denosumab in dialysis patients should be followed by a close monitoring of vascular calcifications.

The best option for osteoporosis is to enhance bone formation to restore bone mass. Few anabolic treatments are available. The effect of teriparatide has only been examined in a small pilot study including 7 hemodialysis patients. There was a significant increase in lumbar and femoral BMD after 6 months of treatment and in 6 of the 7 patients.[143] Nothing is known regarding the effect of teriparatide on the prevention of fractures and is forbidden in case of a history of cancer. Anti-sclerostin antibody is a promising anabolic agent as it promotes bone formation by binding to sclerostin, a natural antagonist of Wnt signaling. Indeed, romosozumab increases BMD and prevents bone fractures in postmenopausal women without CKD.[144] Interestingly, antisclerostin antibody increases bone formation and bone mass in rats with CKD only with low, but not with high, PTH.[145] Although data are awaited, this new therapy raises new hopes and provides elements to personalize treatment according to the rate of bone turnover in CKD.

CONCLUSION

The high incidence of fractures and mortality in patients with CKD requires new tools for evaluating fracture risk. Randomized controlled trials on fracture prevention and treatment in the CKD population are urgently needed including bone biopsy and imaging data. Because of the complexity of bone fragility in CKD, a multidisciplinary discussion including renal and bone experts in CKD-MBD would be desirable before any initiation of bone antiresorptive treatment or future new anabolic treatments.

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