# Bone and mineral disorders in chronic kidney disease: implications for cardiovascular health and ageing in the general population

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**The patient with chronic kidney disease (CKD) represents an extreme model for arteriosclerosis, vascular calcification, and bone disorders, all of which are also associated with ageing in the general population. These pathological features are also relevant to other common chronic health disorders such as diabetes, and chronic inflammatory and cardiovascular diseases. Although management and interventions for these major risk factors are now incorporated into most public health guidelines (eg, smoking cessation and control of bodyweight and blood pressure, as well as glucose and cholesterol concentrations), some residual cardiovascular risk is not reduced by implementation of these interventions. CKD should be regarded as an atypical disease in which both traditional and novel cardiovascular risk factors have effects on outcomes. But CKD can also be viewed conceptually as an accelerator of traditional cardiovascular risk factors. Findings from research into mineral bone disorder associated with CKD (CKD–MBD) could help the medical community to better understand the vascular actions of certain molecules, such as phosphates, fibroblast growth factor 23, parathyroid hormone, sclerostin, or vitamin D and their relevance to the management of different pathologies in the general population. Importantly, these components, which are recognised in nephrology, could help to explain residual risk of cardiovascular events in the general population. Thus, achieving a better understanding of CKD–MBDs could provide substantial insight into future treatments for arteriosclerosis and osteoporosis, which are strongly associated with ageing and morbidity in the general population.**

## Introduction

Chronic kidney disease (CKD) is a systemic condition affecting about 10% of the general population, although estimates of CKD prevalence vary widely, both within and between countries.[1] Mineral and bone disorders are common in patients with CKD and contribute to the large burden of cardiovascular and bone diseases characteristic of CKD. Although end-stage renal disease requiring dialysis is well recognised, it is also rare and unique in terms of its physiological disturbances. Much more common are the less severe forms of CKD (eg, stages 3b–4)[1] that already show distinct features and characteristics such as hyperphosphataemia, hyperparathyroidism, increased fibroblast growth factor 23 (FGF23) concentration, klotho deficiency, or vitamin D concentration abnormalities.

The kidneys are the major source of the anti-ageing protein klotho, and CKD is a state of klotho deficiency.[2] In fact, patients with renal disease show decreased klotho expression as early as CKD stage 1[3]—klotho deficiency being one of the first mineral and bone disorders that occur in the setting of CKD. As CKD progresses, klotho concentrations continue to decline, causing FGF23 resistance and therefore leading to large increases in serum concentrations of FGF23 and parathyroid hormone, as well as decreases in serum vitamin D concentration.[3] Many of these changes predispose patients to develop vascular calcifications and their sequelae. Increasing evidence is indicating that klotho deficiency could contribute to salt-sensitive hypertension,[4] aberrant cardiac remodelling,[5] vascular calcification,[2] bone loss,[6] neurodegenerative diseases,[7] and renal fibrosis.[5] Thus, CKD can be considered a state of premature ageing and a model for similar processes associated with ageing in the general population.

Collectively, these alterations have been termed CKD–mineral and bone disorders (CKD–MBDs). The additional health risks imposed by CKD–MBDs on CKD risk factors such as systemic hypertension, hypercholesterolaemia, left ventricular hypertrophy, coronary heart disease, and diabetes, could provide an opportunity for improved risk management beyond controlling traditional factors. In this Review we will discuss how several components considered to be CKD-specific risk factors could also contribute to the cardiovascular and ageing risk profiles in the general population.[8] We will also summarise key elements of the CKD-derived pro-ageing process that could be of relevance for clinical practice in general internal medicine; discuss phosphate exposure, FGF23 elevation and klotho deficiency, and bone disease; and review their potential contribution to all-cause or cardiovascular mortality in patients with CKD and the general population.

## CKD–MBDs and vascular, skeletal, and renal ageing

In the general population, age-related arteriosclerosis and bone-mineral loss are both regarded as inevitable consequences of ageing. The temporal association of these two processes was initially regarded as coincidental; only much later was a causal relationship considered.[9] Since CT and dual-energy X-ray absorptiometry (DXA) scans in postmenopausal women showed[10] that the annual percent gain in aortic calcification was proportional to the annual loss in bone-mineral density,

*Lancet Diabetes Endocrinol 2017*

Published Online
October 16, 2017
http://dx.doi.org/10.1016/S2213-8587(17)30310-8

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it was suggested that these processes could be connected features of ageing. Of note, individuals with progeria—a disease characterised by premature ageing—have osteoporotic lesions as well as atherosclerosis,[11] reinforcing the idea of common pathophysiological pathways between diseases associated with ageing, such as osteoporosis, cardiovascular disease, and CKD.[12,13]

## Vascular ageing

Regarded as a structural and functional remodelling of the vessel wall, vascular ageing involves endothelial and vascular smooth muscle cells that are stimulated by low-grade inflammation[9,14] and ultimately results in calcification of the intimal layer or media layer, or both. Major pathogenic factors include, but are not limited to, angiotensin II signalling, activation of matrix metalloproteinase, and production of advanced glycation end-product.[15] Until recently, the final change from vascular ageing into vascular calcification was thought to be due to passive precipitation of calcium salts. However, the observation[16] that hyperphosphataemia was associated with increased cardiovascular mortality in patients with end-stage renal disease receiving dialysis, prompted experimental efforts that unravelled the mechanism at work (figure; table 1). Importantly, these same mechanisms, which are reported in the general population during ageing, seem to operate at a much younger age in patients with CKD. Although vascular calcification could be regarded as protection for atherosclerotic lesions,[12] evidence[14,17] indicates that coronary artery calcification is significantly prevalent in young adults at low risk for cardiovascular disease and is indicative of higher cardiovascular mortality. Furthermore, vascular calcification is closely associated with calcification of the heart valves, which is in turn associated with high mortality in individuals of advanced age, or with congestive heart failure or CKD. Calcification of the heart valves is promoted by the systemic inflammatory conditions characteristic of metabolic syndrome, type 2 diabetes, and CKD; these active processes are mediated by *WNT* signalling, similar to that seen in the vascular calcification associated with atherosclerosis.[18] On the basis of observational (ie, associative) data,[19] vascular calcification is thought to be a strong predictor of cardiovascular mortality and morbidity in patients with CKD and in the general population; therefore, prevention and treatment of vascular calcification is important. Unfortunately, to date, no treatments have been proven to prevent or completely reverse vascular calcification; once established, a vascular calcification will tend to progress, and cannot be completely arrested or reversed. Interventional trials are warranted to show whether a reduction in vascular calcification is associated with longer life.

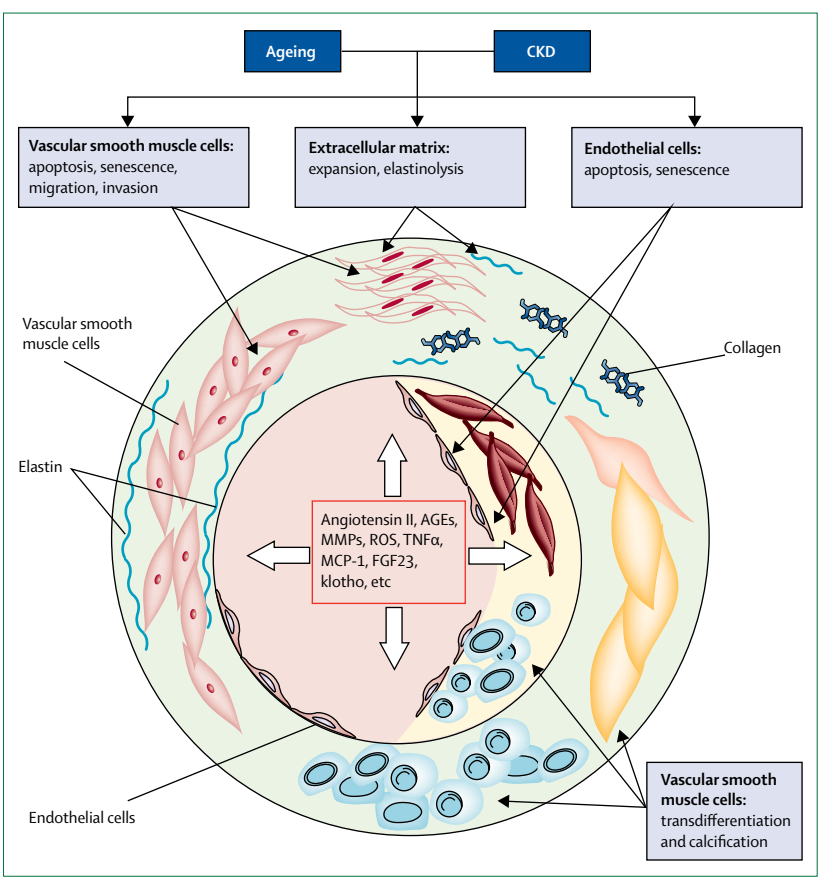


***Figure*: Main steps of vascular ageing and CKD**

A low-grade proinflammatory profile driven by, among others, angiotensin II signalling, MMP activation, and AGE production, results in structural and functional remodelling of endothelial cells and vascular smooth muscle cells. Endothelial cells undergo apoptosis and senescence. Vascular smooth muscle cells proliferate and migrate into the subendothelial space, enhancing collagen and extracellular matrix production. The subsequent metabolic stress also leads to premature senescence, apoptosis, and fracturing of elastin fibres. Vascular smooth muscle cells undergo phenotypic transdifferentiation into osteoblast-like cells that are involved in the eventual vascular calcification process. These abnormalities are present in the cells of patients who have CKD, but at an earlier stage of the cell's lifespan, indicating that CKD is a model of accelerated ageing. AGEs=advanced glycation end-products. CKD=chronic kidney disease. FGF23=fibroblast growth factor 23. MCP-1=monocyte chemoattractant protein-1. MMPs=matrix metalloproteinases. ROS=reactive oxygen species. TNFα=tumour necrosis factor alpha.

## Bone ageing

Typically synonymous with osteoporosis, bone ageing results from inadequate refilling of the resorptive osteoclastic lacunae by osteoblasts, leading to progressive reduction in bone mass during life and thus increased risk of bone fracturing. Until recently, the characteristic determinants of osteoporosis have been the highest bone mass reached in adolescence and the rate of its subsequent loss with ageing; however, in the past decade, bone quality has also been considered relevant for future fracture risk.[20,21] Bone turnover, mineralisation, and volume, together with microarchitecture and collagen composition, are relevant components of bone quality.[20]

Similarly to osteoporosis, the bone pathologies of CKD (typically identified as renal osteodystrophy) negatively affect bone quality, promote bone fractures, and are associated with increased morbidity and mortality.[22–27] CKD-specific abnormalities in bone turnover, mineralisation, and volume could be regarded as additional

| | CKD | General population |
|---|---|---|
| Hyperphosphataemia | Experimental evidence: phosphate loading indicated by ossification of vascular smooth muscle cells and decreased ossification resorption in monocytes<br>Clinical correlates: high mortality; vascular calcification; endothelial dysfunction; progression of left ventricular hypertrophy; premature ageing; and anaemia, independent of other mineral and bone parameters | Inverse correlation with longevity, environmental phosphate burden leading to accelerated vascular calcification and mortality, phosphate levels >3·5 mg/dL associated with an increased risk of anaemia |
| High FGF23 concentrations | Experimental evidence: direct induction of myocardial hypertrophy in humans beings<br>Clinical correlates: strong positive association with cardiovascular and all-cause mortality | FGF23 concentrations are generally much lower than in patients with CKD; increased FGF23 concentrations are associated with all-cause mortality and heart failure, but not with myocardial infarction or other atherosclerotic events; high concentrations of FGF23 identify patients at the highest cardiovascular risk; slightly increased FGF23 concentrations indicate kidney dysfunction that cannot be detected by eGFR measurement |
| Klotho deficiency | Kidneys are the major source of the anti-ageing protein klotho; CKD is a state of klotho deficiency, which is associated with vascular calcification | Klotho deficiency can result in salt-sensitive hypertension, aberrant cardiac remodelling, vascular calcification, bone loss, and neurodegenerative diseases |
| Adynamic bone disease | Appears early in the disease progression of CKD; a result of the bone's resistance to PTH actions or dysregulation of vitamin D metabolites, or both, and elevated concentrations of FGF23, sclerostin, and DKK-1; promotes vascular calcification; associated with increased risk of bone fracture; increases morbidity and mortality | Associated with ageing, diabetes, excessive calcium loads, malnutrition, inflammation, and PTH resistance; assessment of adynamic bone disease is very important when starting treatment with bisphosphonates; consider bone biopsy to determine diagnosis |

CKD=chronic kidney disease. FGF23=fibroblast growth factor 23. eGFR=estimated glomerular filtration rate. PTH=parathyroid hormone. DDK-1= dickkopf-related protein-1. MBD=mineral and bone disorder.

***Table 1:*** **Key findings in CKD–MBDs and their implications for the general population**

components that impinge on bone quality and quantity—in addition to the better known and recognised osteoporotic lesions—since these abnormalities appear as early as stage 2 of CKD.[6]

### The ageing kidney

The ageing kidney is characterised by structural and functional changes, and frequently by reduction of glomerular filtration rate (GFR). The wide implementation of estimated GFR (eGFR) and reporting calculations has substantially increased the recognition of CKD and highlighted the increased morbidity and mortality associated with the disease.[28,29] A large proportion of this increased mortality is related to cardiovascular diseases that are pathogenically linked to diffuse or extensive vascular calcifications, or both.[19] Derangements in mineral metabolism occur early in the progression of CKD, and involve the disturbance of bone endocrine functions, leading to changes in bone remodelling. The existence of a link between divalent ion derangements (eg, calcium, phosphate, and magnesium), bone disease, and vascular calcification in CKD is now recognised. A recent perspective in the medical community[30] suggests that the first bone histological pattern in patients who have CKD stage 2–3 (ie, patients who are usually seen by general practitioners) could be adynamic bone disease, supported by the very early occurrence of bone resistance to actions of parathyroid hormone (PTH) or dysregulation of other modulators of bone remodelling such as vitamin D metabolites, FGF23, sclerostin, and dickkopf-related protein 1 (DKK-1). Adynamic bone disease is considered to represent, especially in patients with CKD, a metabolic condition of bone which promotes the development of vascular calcifications. The exchange of reciprocal signals between the cardiovascular, skeletal, and renal systems seems to—in the case of ageing—modulate the behaviour of calcium to direct it from bone to blood vessels and myocardium. Taken together, these abnormalities, first recognised in CKD, have now been shown[31] to contribute to ageing in the general population.

## Phosphate: a vascular toxin in CKD and beyond

Serum phosphate concentrations are determined by a balance between absorption from the intestine, exchange with bone, and excretion by the kidneys. Several endocrine factors coordinate these processes, including vitamin D, PTH, FGF23, and klotho. Unlike PTH and FGF23, serum phosphate concentrations only rise late in the progression of CKD (ie, once the eGFR drops below 30 mL/min per 1·73 $m^2$)[6] but this rise in phosphate concentration does not preclude disturbed phosphate metabolism being of relevance for early CKD-associated morbidity. If CKD is considered a state of premature ageing, disordered phosphate metabolism could be a major driver.[4,5] Disordered phosphate metabolism in CKD has also been associated with vascular calcification, endothelial dysfunction, left ventricular hypertrophy, progression of kidney disease, and bone disease.[32,33] However, to what extent phosphate concentration per se, or the compensatory endocrine homoeostatic response associated with changes in phosphate concentration, drives these adverse outcomes is not clear. Controlling hyperphosphataemia is a major therapeutic goal in patients with advanced CKD. Treatment focuses on

limiting net gastrointestinal phosphate absorption by restriction of dietary phosphate, and administration of orally active phosphate binders or blockers of intestinal phosphate transport.[13] To date, clinical intervention studies[34,35] testing one or a combination of these approaches have yielded promising results with regard to biochemical or intermediate endpoints, but have not shown a survival benefit.[34,35]

High circulating phosphate concentrations, even within the normal range, in the general population are also associated with increased risk of cardiovascular morbidity and mortality, and development of CKD.[36,37] This epidemiological evidence highlights that individuals with relatively preserved kidney function might also benefit from active phosphate management.[38] Limiting dietary phosphate intake would be the most logical first approach in individuals with hyperphosphataemia. Studies exploring the association between dietary phosphate intake and hard outcomes (eg, cardiovascular or all-cause mortality) have not yielded clear results, with some observational studies reporting a positive association, and other studies showing no or even a negative association.[39,40] No interventional study has proven that reducing phosphates has any beneficial effect, either in patients with CKD or the general population. Therefore, alternative possibilities must be considered, for instance, that hyperphosphataemia indicates the presence of another detrimental biological process, or that strategies to control hyperphosphataemia have additional, unnoticed side-effects, as has been suggested for protein malnutrition as a consequence of dietary intervention[41] or calcium loading due to use of some phosphate binders.[42]

Inadequate statistical power and residual confounding could have contributed to these discrepant findings. Awaiting additional evidence from prospective studies, we advocate dietary counselling to focus on limiting consumption of inorganic phosphate, rather than organic phosphate, which is predominantly found in high-protein foods. This approach will prevent side-effects such as protein energy malnutrition. The intake of inorganic phosphate has substantially increased in the past decade because of its non-restrictive use as a food additive to add flavour and as a preservative. In high-income countries, these food additives might lead to a daily surplus intake of 300–1000 mg of inorganic phosphate.[10] Individuals with a low socioeconomic status are particularly at risk of excessive phosphate loading, probably owing to a high intake of inexpensive fast foods, highly processed foods, soft drinks, and food items heavily enriched with phosphate additives.[43] Although high dietary phosphate intake will not necessarily result in high fasting serum phosphate concentrations, it will definitely translate into a larger area under the curve for serum phosphate concentration versus time and increased phosphate burden for each nephron. Moreover, the consumption of inorganic phosphate might induce transient postprandial hyperphosphataemia due to its high bioavailability. Like individuals with hypervolaemia or hypertension who benefit most from dietary salt reduction, individuals with even slightly reduced renal reserves (eg, elderly people, patients with diabetes, patients with early-stage renal disease, and kidney donors) will probably benefit most from restriction of dietary phosphate. At least for end-stage renal disease, it was shown[44–46] that educating patients to avoid phosphorus-containing food additives resulted in modest improvements in hyperphosphataemia. Although definitive proof does not exist, restricting consumption of phosphate additives could also be hypothesised to confer health benefits to the general population since a high-to-normal serum phosphate concentration has also been found to be an independent predictor of hard endpoints (eg, cardiovascular and all-cause mortality) in this population.[47]

## FGF23 and klotho: from nephrology to the general population

Insights into FGF23, a bone-derived phosphatonin, and its coreceptor klotho, represent an important step towards the understanding of molecular and cellular mechanisms of vascular senescence in CKD–MBDs.[48,49] These insights implicate the FGF23–klotho system as a causal contributor to cardiovascular disease—ie, the direct induction of left ventricular hypertrophy by FGF23.[50]

FGF23 is a 32 kDa protein that is synthesised primarily by osteocytes. In adverse health conditions, FGF23 synthesis is stimulated by the constitutive phosphate pool and plays a pivotal role as a regulator of phosphate homoeostasis through inhibition of tubular phosphate reabsorption and vitamin D activation, and down-regulation of PTH secretion.[51–54] Thus, the kidney and parathyroid glands represent major targets for the effects of FGF23.

Plasma concentrations of FGF23 increase as CKD progresses, reaching concentrations 1000 times above the normal range in patients with end-stage renal disease.[55] In part, this high concentration is driven by a progressive positive phosphate balance during the progression of CKD, even in patients whose serum phosphate levels remain within the normal range. FGF23 resistance, resulting from reduced klotho expression during the early stages of CKD, further promotes FGF23 synthesis.[56] Additionally, FGF23 itself could perpetuate its own receptor resistance through a feed-forward loop since it downregulates its coreceptor klotho.

Epidemiological studies[57,58] that have addressed the association between FGF23 and several clinical outcomes, including cardiovascular and all-cause mortality, are remarkable because of the consistency of findings across all cohorts studied, the magnitude of relative risk shown to be driven by FGF23, and that correcting for potential confounding factors did not negate the effect of FGF23 on these outcomes.[57,58] A post-hoc analysis[59] of the EVOLVE trial supported the hypothesis of a causal role for FGF23 in cardiovascular disease and mortality. In this analysis,[59]

 Published online October 16, 2017 http://dx.doi.org/10.1016/S2213-8587(17)30310-8

the calcimemetic cinacalcet was shown to reduce not only PTH concentrations, but also FGF23 concentrations. Another intriguing finding was a strong association between the attained reduction in FGF23 concentration and the reduction in the risk of death or major cardiovascular event.[59] In the general population, an association has been shown[60–64] between high FGF23 concentrations and poor clinical outcomes—including heart failure, incident coronary events, and cardiovascular and all-cause mortality—even though FGF23 concentrations are generally much lower in the general population than in patients with CKD. An explanation for this somewhat puzzling observation could be that the background risk in CKD is so huge that any effect of small increases in FGF23 concentration are masked. Alternately, patients with CKD could have resistance to the biological effects of FGF23, exemplified by uraemia-induced loss of tissue klotho[65] or by the earlier mentioned induction of klotho downregulation by FGF23 itself.[56] The increased risks of all-cause mortality and heart failure associated with increased concentrations of FGF23 in the general population were consistent with increased risks in patients with CKD, but were not consistent for myocardial infarction or other atherosclerotic events,[60,66] with the exception of two large studies[61,63] that also found increased risks for these morbidities (ARIC study, n=11638; MESA cohort, n=6547). In the Framingham Heart Study,[66] a community-based, longitudinal, epidemiological cohort study, FGF23 was associated with all-cause mortality but not with arterial stiffness or endothelial function. Overall, these epidemiological data show that increased serum FGF23 concentrations are associated with an increased risk for a wide range of clinical events, including mortality, in the general population as is the case in patients with CKD.

The implications of this novel insight for clinicians treating patients without renal disease could be at least twofold. First, high concentrations of FGF23 could be used to identify patients at the highest cardiovascular risk, and management and monitoring of their FGF23 concentrations could be considered in future risk management strategies. A post-hoc analysis[67] of 3627 participants in the PEACE trial, which compared treatment with the angiotensin-converting-enzyme inhibitor trandolapril with placebo in patients without CKD and with stable ischaemic heart disease, showed that treatment with an angiotensin-converting-enzyme inhibitor prevented cardiovascular death and incident heart failure in those with high concentrations of FGF23. Second, FGF23 should be considered not just as a marker for cardiovascular disease, but also as a causal contributory factor. Indeed, biological plausibility exists for this assumption, with evidence showing the direct induction of myocardial hypertrophy due to elevated FGF23 concentrations.[68] Additionally, increased FGF23 concentrations are associated with arterial endothelial dysfunction.[69,70] Thus, targeting the causes of increasing FGF23 concentrations might translate into risk reduction in the general population. Restriction of dietary phosphate absorption in individuals with high concentrations of FGF23 within the normal range is an attractive option.

Another possibility might be that slightly increased FGF23 concentrations indicate kidney dysfunction associated with renal klotho deficiency that is not detected by eGFR measurement.[71] An important feature of FGF23 is that it requires klotho as an obligate coreceptor for several of its key functions. The FGF23–klotho system has emerged as an endocrine axis that is essential for maintaining phosphate and vitamin D homoeostasis. Notably, in addition to being expressed in the kidneys, klotho is also localised in the choroid plexus and, to a lesser extent, in the hippocampal neurons of rats and rhesus monkeys. Gene profile analysis[72] has shown that brain ageing in rhesus monkeys is associated with a substantial downregulation of klotho expression. This downregulation was caused by increased methylation of CpG-rich segments in the klotho gene promoter, which limits its transcription.[73] A study[74] using both a murine model and in-vitro studies of human renal tubular cells showed that hypermethylation of the klotho gene promotor could be caused by uraemic toxins, such as indoxyl sulphate. Uraemic toxins accumulate in patients with CKD, including patients with end-stage renal disease, and the retention of these solutes is attributable to deficient renal clearance. Whether a reduction in uraemic toxin concentrations could lead to enhanced expression of klotho in the brain and therefore reduced age-related neurodegeneration could be explored. Uncovering the details of this crosstalk and its derangements could have substantial therapeutic implications for people with CKD and the general population with regards to age-related changes in the brain.

## Bone disease in patients with CKD and possible links with the general population

As discussed, bone disease starts very early in disease progression in patients with CKD with mild histological features, and therefore many years can pass before patients with CKD-associated bone disease come to the attention of nephrologists. Consequently, better understanding of the nature of renal osteodystrophy and development is important for physicians treating patients with mild CKD. The most clinically relevant features of renal bone disease are low bone-mineral density and reduced mechanical strength, which increases risk of hip fracture.[22,75–79] Hence, patients with CKD have a similar skeletal risk as other well accepted at-risk populations who are prone to fractures (eg, postmenopausal women, people receiving glucocorticoid therapy). Fracture risk is four times higher in patients with end-stage renal disease than in the general population, and it affects patients with CKD at a younger age than does age-associated osteoporosis in the general population.[76,79,80] Importantly, on the basis of epidemiological and experimental data obtained from patients

with CKD, nephrologists know that bone disease is not an isolated entity but is associated with increased morbidity and mortality.[22–27] It is conceivable that this association is also true for the general population.[81,82] The high mortality associated with osteoporosis is usually attributed to fractures, advanced age, and comorbidities. However, since osteoporosis and vascular calcification are now known to progress in parallel, the presence of osteoporosis also suggests an increased risk of atherosclerosis and cardiovascular disease.[83]

Early CKD as a causal factor for bone disease and fractures is underestimated, since experts responsible for patients with assumed primary bone disease could overlook high serum creatinine concentrations within the normal range—which would in fact be indicative of a low GFR—and misdiagnose the symptoms as a simple concomitant condition of old age. Conversely, although the high incidence of fractures in patients with CKD might be due to kidney-related specific bone pathology (eg, renal osteodystrophy)—encompassing abnormalities in bone turnover, mineralisation, and volume[84]—age-related or sex-related osteoporosis is increasingly being recognised as potentially having a concomitant and important role in influencing outcomes for these patients.[85] The term renal osteodystrophy should be exclusively used to define the distinct histological bone-biopsy lesion changes observed in CKD.[84,86] These changes occur in mainly high-turnover bone diseases (eg, osteitis fibrosa, which is associated with secondary hyperparathyroidism), low-turnover bone diseases (eg, osteomalacia or adynamic bone disease), and mixed forms. With high-turnover renal osteodystrophy, bone resorption occurs faster than bone formation, and so osteopenia can progress to osteoporosis. In low-turnover renal osteodystrophy, although rates of both bone formation and resorption might be reduced, resorption is still relatively faster than formation, and bone mass is lost as a result.[87] Therefore, in CKD a low bone-mass density measured by DXA—which is indicative of osteoporosis in the general population—might be observed with either high-turnover or low-turnover renal osteodystrophy and suggests an increased fracture risk irrespective of histological type.[88]

Notably, the spectrum of renal osteodystrophy has evolved during the past four decades from high-turnover secondary hyperparathyroidism-related bone disease to multifactorial adynamic bone disease.[89,90] Nowadays, adynamic bone disease, characterised by low bone turnover with normal mineralisation, is a common finding in patients with CKD. Adynamic bone disease can be secondary to ageing, diabetes, excessive calcium loads, malnutrition, inflammation, PTH resistance, and the use of bisphosphonates, among many other factors.[89–91] Adynamic bone disease has also been associated with an increased risk of fractures, reduced bone strength (by affecting mineral and matrix), an inability to handle excess calcium loads, and increased vascular calcification.[92–94] Nephrologists recognise adynamic bone disease as a true clinical challenge owing to the presence of specific iatrogenic risk factors, systemic consequences, and resistance to established therapies. Knowledge from the area of nephrology regarding the diagnosis and management of adynamic bone disease could affect patient care in other settings of presumed suppressed bone turnover in the general population, such as diabetes and ageing—eg, avoiding undesirable calcium loading or additional permanent bone oversupression by molecules such as bisphosphonates.

The potential presence of CKD should be considered in the differential diagnosis of patients with osteoporosis because several diagnostic and therapeutic implications accompany CKD. Increasing attention should probably be given to low-turnover bone disease in patients in the general population who have diabetes, inflammation, or malnutrition, those who are of advanced age, or people with a combination of these conditions.

## Diagnosis of bone disease in individuals with CKD and in the general population

Clinicians should weigh an individual patient's risk of fractures against untoward consequences of treatment because, to date, if an intervention has proven to be effective in the general population it has generally been denied to patients with CKD because of the potential side-effects (panel). Several diagnostic methods are available to ascertain a patients' stage of CKD and risk of fracture, each with their advantages and disadvantages for use in patients with CKD and the general population (table 2).

Diagnosing osteoporosis in patients with CKD (particularly those with eGFR <30 mL/min per 1·73 m²) can be challenging, especially in patients with diabetes and in older patients who present with many fragility fractures, reduced GFR, and low bone mineral density. The ageing population with CKD and low bone mineral density or fragility fractures, or both, might have osteoporosis or another bone and mineral disorder related to early CKD. The recognition in nephrology that bone disease—diagnosed by presence of low-impact fractures, DXA, or bone biopsy—might indicate increased risk of not only additional fractures, but also cardiovascular morbidity. This association probably applies to both individuals with CKD and the general population. The best alternative to DXA for assessing the risk of fractures is the fracture risk assessment tool (FRAX). Even if FRAX does not include any adjustment of risk according to GFR, we believe that clinicians could use FRAX in patients with stage 2 (mild) to 3 (moderate) CKD with signs of mineral bone disorders. Then the absolute risk of fracture, and hence possibly other complications as mentioned earlier, should be adjusted to take into account that the presence of CKD further increases the risk of fractures, as do falls or the frequency of falls (which are also not captured in FRAX). Thus, algorithms that incorporate GFR and other factors that are not validated by the original FRAX score into the calculation of potential fracture and clinical risk are needed.

## Therapeutic challenges for bone disease in early stage CKD and implications for the general population

CKD–MBD has a central role in cardiovascular disease, renal ageing, and bone disease. Scarce data are available to suggest valid therapeutic options for cardiovascular disease and renal ageing that could be safely extrapolated to the general population. By contrast, CKD and age-related or sex-related bone disease (ie, osteoporosis) are highly prevalent diseases in the general population, and their concomitant diagnosis and specific treatment are likely to increase in the future.[108,109] The 2017 Kidney Disease: Improving Global Outcomes (KDIGO) guidelines[100] suggest that testing of bone mineral density should be done to assess the risk of fracture in patients with CKD stages 3a–5D who have risk factors for osteoporosis or evidence of CKD–MBD, or both, if the results of those tests could affect treatment decisions (panel).[100] These patients need an integral and holistic approach to their management including general modifications in lifestyle and dietary habits, and prevention of falls. Fall prevention is often neglected in patients with CKD.

### Calcium and vitamin D

Generally accepted standard treatments for osteoporosis, such as calcium supplementation, are being challenged by study data obtained from patients with CKD,[110,111] and a common misconception is to believe that age-related or sex-related bone loss can be largely avoided with the use of these treatments.[110,112,113] Moreover, studies[110,114,115] have raised concerns about increased cardiovascular risk with the use of calcium supplements;[114] although we acknowledge that these findings are inconsistent and inconclusive.[110,115] Supplemental calcium intake, but not increased dietary intake, modestly increases the risk of nephrolithiasis.[110,111] Arrhythmias and increased progression of vascular calcification have also been linked to increased calcium intake.[116] Data[117,118] have shown that

***Panel:*** **Comparison of KDIGO guidelines from 2009 and 2017 for patients with CKD–MBD**

**2009 KDIGO guidelines**

- In patients with CKD stages 3–5D, with evidence of CKD–MBD, testing of bone mineral density should not be performed routinely, because bone mineral density does not predict fracture risk in patients with CKD–MBD like it does in the general population, and bone mineral density does not predict the type of renal osteodystrophy (evidence 2B)
- In patients with CKD stages 3–5D, bone biopsies should be performed in various settings including, but not limited to: unexplained fractures, persistent bone pain, unexplained hypercalcaemia or hypophosphataemia, possible aluminium poisoning, and before treatment with bisphosphonates in patients with CKD–MBD (not graded as a level of evidence)
- In patients with CKD stage 3 with biochemical abnormalities of CKD–MBD and low bone mineral density or fragility fractures, or both, treatment choices should account for the magnitude and reversibility of the biochemical abnormalities and progression of CKD, with consideration of a bone biopsy (evidence 2D)
- In patients with CKD stages 4–5D with biochemical abnormalities of CKD–MBD and low bone mineral density or fragility fractures, or both, additional investigation with bone biopsy should be done before treatment with antiresorptive drugs

**2017 KDIGO**

- In patients with CKD stages 3a–5D with evidence of CKD–MBD or risk factors for osteoporosis, or both, testing of bone mineral density should be done to assess fracture risk if the results will affect treatment decisions (evidence 2B)
- In patients with CKD stages 3a–5D, a bone biopsy should be performed if knowledge of the type of renal osteodystrophy will affect treatment decisions (not graded as a level of evidence)
- In patients with CKD stage 3a–5D with biochemical abnormalities of CKD–MBD and low bone mineral density or fragility fractures, or both, treatment choices should account for the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy

**Rationale for updating guidelines**

- Several prospective studies[95–99] showed that lower bone mineral density measured by DXA predicted incident fractures in patients with CKD stages 3a–5D and would affect the decision to do a bone biopsy
- Growing knowledge of the effect of drugs for osteoporosis in patients with CKD, low bone mineral density, and a high risk of fracture meant that the inability to perform a bone biopsy in patients at high risk of fractures should not justify withholding antiresorptive therapy
- The need to rule out unrecognised CKD and to define the stage of CKD before initiating antiresorptive treatment were emphasised on the basis that studies to date in patients with CKD have not definitively shown that bisphosphonates cause adynamic bone disease, since the concerns in patients with CKD are more theoretical than evidence based; this fact is particularly relevant for the ageing general population, in whom fragility fractures, reduced GFR, and low bone mineral density are all highly prevalent
- Recommendations for bone biopsy before treatment with antiresorptive and other osteoporosis therapies was broadened to patients with CKD stage 3a–5D only if it was known that the type of renal osteodystrophy would affect treatment decisions

KDIGO guidelines adapted from reference 100. KDIGO=Kidney Disease: Improving Global Outcomes. CKD=chronic kidney disease. MBD=mineral and bone disorder. DXA=dual-energy X-ray absorptiometry. GFR=glomerular filtration rate.

| | CKD | General population |
|---|---|---|
| DXA | Not accurate enough to predict the specific type of renal osteodystrophy; multiple prospective studies[88,101-104] have documented that a lower bone mineral density reflects bone fragility and predicts incident fractures in patients with CKD stages 3a–5D[88,101-103] and after renal transplantation;[104] the 2017 KDIGO CKD–MBD guidelines[100] suggest that bone mineral density is valid to assess risk of fractures in patients with CKD stages 3a–5D | The best available clinical tool for the diagnosis of osteoporosis and monitoring changes in bone mineral density |
| FRAX | Does not include any adjustment of risk according to GFR; predicts risk of fracture in patients with mild (GFR <90 mL/min) to moderate (GFR <60 mL/min) CKD stages[105] and transplant recipients,[106] but it is not a better predictor of risk of fracture than bone mineral density | Estimates the 10-year probability of hip fracture and major osteoporotic fracture for those who have and have not been previously treated for osteoporosis; to be used for patients aged 40–90 years using easily obtainable clinical risk factors for fracture and femoral neck bone mineral density when available |
| Bone-turnover biomarkers | PTH, despite being known as a prominent renal biomarker for decades, is a suboptimal bone biomarker and does not sufficiently support a reliable diagnosis of renal osteodystrophy or fracture risk assessment; sclerostin and tartrate-resistant acid phosphatase-5b have been reported[107] as non-invasive predictors of bone loss in patients with CKD on dialysis | The role of bone biomarkers is limited to the monitoring of osteoporosis treatments, not for the diagnosis of osteoporosis; the use of sclerostin and tartrate-resistant acid phosphatase-5b is not recommended in regular clinical practice |
| Bone biopsy | Remains the most accurate diagnostic tool to define alterations in bone morphology in patients with CKD; bone biomarkers or bone mineral density measured with DXA have low predictive diagnosis value; patients might have had an underlying bone disease before developing kidney failure or could have been treated with drugs such as aluminium hydroxide, calcium-based phosphate binders, or high doses of vitamin D compounds, that alter the typical pathological features of bones their interaction with PTH—these patients could develop adynamic bone disease, and bone biopsy is the only way to diagnose low bone turnover | Mainly restricted to atypical, unclear, and complicated situations (eg, unexplained primary osteoporosis or failure to respond to anti-osteoporotic treatments), and to obtain additional data regarding bone resorption and remodelling, degree of bone mineralisation, and bone structure |

CKD=chronic kidney disease. DXA=dual-energy X-ray absorptiometry. KDIGO=Kidney Disease: Improving Global Outcomes. FRAX=fracture risk assessment tool. GFR=glomerular filtration rate. PTH=parathyroid hormone.

*Table 2:* **Methods to diagnose bone disease in patients with CKD and in the general population**

excess exogenous calcium in adults might be especially harmful to patients at all stages of CKD, particularly in the presence of hypercalcaemia, low PTH concentrations, and adynamic bone disease or arterial calcification, or both.[119] Thus, the use of excessive calcium supplements could be of particular concern for patients with undiagnosed, possibly hidden, CKD in the general population[120] and among older patients with osteoporosis. Until more data are available, a reasonable approach for treating these patients is to encourage increased dietary calcium intake and vitamin D supplementation (in 2010 the Institute of Medicine panel increased the safe upper limit of daily calcium intake from 2000 IU to 4000 IU for adults[121]), and discourage the routine use of high-dose calcium supplements in patients with osteoporosis[113] with or without CKD.[110,111]

## Bisphosphonates

A consensus is growing that in patients with CKD who have a GFR of more than or equal to 30 mL/min per 1·73m², in the absence of abnormalities of mineral metabolism such as elevated phosphate concentrations or noteworthy hyperparathyroidism, the use of therapies that are approved for people in the general population who have osteoporosis is appropriate for those with osteoporosis or high risk of fracture, or both.[119,122] Post-hoc analyses of large randomised clinical trials[123–126] evaluating antiresorptive medications for the treatment of postmenopausal osteoporosis (eg, risedronate, aleonate, raloxifene) or anabolic teriparatide, found that these drugs had similar efficacy in improving bone mineral density and reducing fracture risk in individuals (mainly women) with moderate reductions in eGFR (mostly in those who had stage 3 CKD, and fewer with stage 4). Other small prospective studies[127–129] in patients with end-stage renal disease showed an increase in bone mineral density in parallel with a decrease in bone resorption markers. However, most of the results of these studies are not consistent, have a high risk of bias, and the overall strength of evidence is low or very low.[130]

All bisphosphonates carry warnings or contraindications for patients with low creatinine clearance since they are largely excreted by the kidney and thus accumulate in bone in patients with advanced CKD (table 3).[27] Moreover, treatment with bisphosphonates could induce kidney injury and proteinuria.[133] Most importantly, bisphosphonates could oversuppress bone turnover, particularly in patients with pre-existing reduced bone metabolism.[135,136] This knowledge increased clinicians' understanding of why treatment with bisphosphonates might lead to atypical fragility fractures or worsen undiagnosed adynamic bone disease.[134] In a small 2017 study,[135] investigators found that bone in patients from the general population who had fractures and had been treated with bisphosphonates had more microcracks (detected by synchrotron X-ray micro-CT) than did bones from people with fractures who were not treated and from healthy ageing people who had not had fractures.

| | Description | Advantages |
|---|---|---|
| **Anabolic drugs** | | |
| Romosozumab | Monoclonal antibody against sclerostin; to date, in phase 3 studies in the general population; cardiovascular effects not known | No renal clearance; increases bone mass and turnover, no risk of adynamic bone disease, potential indication for adynamic bone disease |
| Teriparatide | Recombinant PTH; side-effects include hypercalcaemia and hypercalciuria; expensive and can only be used over a short period (ie, 2 years) considering the risk of osteosarcoma | No renal clearance; increases bone mass and turnover, no risk of adynamic bone disease, actually a potential treatment for adynamic bone disease; increased bone mineral density and decreased fractures in predialysis patients with CKD in post-hoc analysis, but high risk of bias |
| **Antiresorptive drugs** | | |
| Bisphosphonates | P-C-P structure, similar to the P-O-P structure of native pyrophosphate (pyrophosphate analogue); accumulate in bone tissues independent of renal function, but when renal clearance is reduced, have high storage because of extended half-life; potential risk of adynamic bone disease and systemic toxic effects | Low cost and worldwide availability; increased bone mineral density and decreased fractures in predialysis patients with CKD in post-hoc analysis, but with a high risk of bias;[131,132] and potential attenuation of progression of vascular calcification—reports of benefits in patients with calciphylaxis |
| Denosumab | Monoclonal antibody which inhibits the osteoprotegerin–RANK–RANKL interaction by blocking RANKL; higher cost than bisphosphates; potential risk of adynamic bone disease, hypocalcaemia, and rebound hyperparathyroidism, therefore treatment needs to be monitored in patients with advanced CKD | No renal clearance; increased bone mineral density and decreased fractures in predialysis patients with CKD in post-hoc analysis, but high risk of bias; fewer renal side-effects than bisphosphates; shorter half-life than bisphosphonates |

Data compiled from Goldenstein and colleagues,[27] a US Food and Drug Association drug safety communication,[133] Amerling and colleagues,[134] Ma and colleagues,[135] West and colleagues,[136] Jamal and colleagues,[137] Launay-Vacher and colleagues,[138] Block and colleagues,[139] Cejka and colleagues,[140] and Suminda and colleagues.[141] CKD=chronic kidney disease. PTH=parathyroid hormone. RANK=receptor activator of nuclear factor κβ. RANKL=RANK ligand.

***Table 3*: Comparison of anabolic and antiresorptive drugs for the treatment of osteoporosis in patients with CKD**

Therefore, awareness of the potential presence of advanced CKD and pre-existing adynamic bone disease is important, particularly in ageing and diabetic populations that might be treated with bisphosphonates.[100,136]

### Denosumab

Denosumab is a monoclonal antibody that binds to the receptor activator of nuclear factor κβ (RANKL) to inhibit osteoclastogenesis and is not cleared by the kidney. It has been shown to reduce fracture risk in the general population and, in a post-hoc analysis, in women with osteoporosis with CKD stages 3 and stage 4.[137] However, although denosumab did not increase adverse events in patients with impaired renal function, renal side-effects have been described in patients with cancer who were treated with denosumab.[138] Importantly, denosumab could induce hypocalcaemia if patients are not vitamin D sufficient,[139] hence this drug should be used with caution, especially if patients concomitantly receive calcium-sensing receptor agonists (table 3). Importantly, the aforementioned trials[137,138] essentially excluded patients with elevated serum creatinine concentrations (but did not necessarily exclude patients with low estimated GFR), and those with hyperparathyroidism or abnormal alkaline phosphatase concentrations.

Despite these uncertainties about the applicability of denosumab to patients with CKD, the 2017 KDIGO guidelines consider that bone biopsy should not be mandatory before treatment with antiresorptive drugs, especially when the patient with CKD is at high risk of fracture or fragility fractures, or both, and subsequent mortality.[100] Increasing awareness of risk of adynamic bone disease among general physicians could increase the long-term net clinical benefit of treatments that focus on improving bone mineral density in older patients with or without CKD by avoiding inappropriate use of antiresorptive drugs.[134] From an alternate perspective, in some case reports[140,141] an increase in bone turnover has been shown following treatment with subcutaneous teriparatide (an anabolic drug; table 3) in patients with adynamic bone disease that has been confirmed by bone biopsy or with hypoparathyroidism and low bone mass. Treatment with antiresorptive drugs for low or declining bone mineral density would need to be carefully individualised, particularly considering that further diminishing the speed of bone formation is undesirable in patients with CKD and adynamic bone disease that mimics osteopenia or osteoporosis. Furthermore, antiresorptive therapy cannot restore bone mass and structure that has been lost because of increased remodelling; in such a situation, recombinant PTH analogues like teriparatide could be a valid treatment option, even for patients with end-stage renal disease.[141]

## Conclusion

The patient with uraemia might be considered a prototype for several conditions, which include atherosclerosis, vascular calcification, and other bone disorders—conditions which are associated with ageing in the general population. For such conditions, CKD should be regarded both as an atypical disease, but also as a precursor or accelerator, or both, of common pathologies seen in patients without renal disorders. Additionally,

### Search strategy and selection criteria

We searched Embase and MEDLINE for publications in English, using "bone" and "skeleton" as obligate terms, with the following MeSH terms (on MEDLINE) or abstract words in all combinations of a minimum of two: "chronic kidney disease", "metabolic bone disorders", "cardiovascular", "vascular", "osteoporosis", "calcification", "vitamin D", "phosphate", "FGF23", "klotho", "anemia", "heart", "cardiac", and "metabolism". We searched for publications from inception until Aug 31, 2017, and largely selected publications from the past 5 years, but did not exclude commonly referenced and highly regarded older publications. We also searched the reference lists of articles identified for relevant publications. Review articles and book chapters are cited to provide readers with more details and more references than this Review has room for. Our reference list was modified on the basis of comments from peer reviewers. Because of the nature of this Review, the selection of search and selection criteria inevitably remained arbitrary.

management of conditions associated with ageing is often hindered by the presence of CKD, in part due to the substantial scarcity of evidence of efficacy since older patients with CKD are often excluded from randomised controlled trials.[142]

In this Review we have summarised several insights that point to early CKD–MBD as a phenotype that allows identification of factors involved in the development of morbidities that, in the general population, are usually ascribed to ageing or senescence (panel). Although traditional approaches to the reduction of cardiovascular disease in general and disease-specific populations have successfully focused on control of blood pressure, cholesterol, and glucose concentrations, along with smoking cessation, cardiovascular disease is still widespread. This residual risk in the general population could include modifiable risk factors that, up until now, have only been recognised as such in the field of nephrology. Data from CKD–MBD research could serve to better explain the toxic effects of certain molecules and the management of different pathologies in the general population. For example, FGF23 has been shown to be a relevant risk predictor in the general population as it is in patients with kidney disease.[67–70]

We have learnt from nephrology that adynamic bone disease, characterised by low bone turnover, is a substantial challenge in patients with CKD that is frequently unconsidered. Management of the disease should initially focus on patients with osteoporotic fractures, which are evidence of bone fragility. Although treatment options are poorly defined in these patients, the benefits of treatment probably outweigh the risks.[143] This weighing of the benefits and risks is why the 2017 KDIGO CKD–MBD guideline update is more open-ended than the 2007 guidelines, and recommends that clinicians weigh the individual's risk of fractures against the consequences of treatment.[143] Additionally, there are a few ongoing clinical trials that could help to assess some of the issues surrounding benefit versus risk (NCT02792413; NCT02440581). However, adynamic bone disease is not exclusively found in patients who have CKD; it is also associated with ageing, diabetes, excessive calcium intake, malnutrition, inflammation, and the use of bisphosphonates or other antiresorptive drugs (eg, anti-RANKL), among many other factors. Limiting exogenous calcium intake, better management of vitamin D, treatment with teriparatide (or other PTH analogues), and use of monoclonal antibodies against sclerostin could represent promising treatment options for increasing bone formation, preserving skeletal structural and functional integrity, and attenuating cardiovascular risk in people from the general population who have bone disease. Although these treatment options could be attractive, the case is now very strong for properly conducted trials of patients with normal renal function that address these hypotheses with clinically relevant endpoints.

#### Contributors

AC and MA contributed to general editing and wrote the introduction, therapeutic section, conclusion, tables, and figures. MA also contributed to reference formatting and the search strategy. MV contributed to general editing, PE contributed to the literature search, and PE and MV wrote the section on FGF23 and klotho. ZAM and SM wrote the section on CKD–MBDs and vascular, skeletal, and renal ageing, and designed the figure. PUT contributed to general editing, and PUT and DG wrote the section on therapeutic challenges for bone disease in early stage CKD and implications for the general population. VB wrote the section on bone disease in patients with CKD and possible links with the general population. JB and MC wrote the section on bone disease in patients with CKD and possible links with the general population, and MC contributed to general editing.

#### Declaration of interests

PE reports grants from Diasorin, Tecomedical, and Amgen, and personal fees from Amgen and Vifor FMC outside the submitted work. JB reports personal fees from Amgen, Abbvie, Sanofi-Genzyme, Shire, Vifor-Fresenius-Pharma, Chugai, and Medice outside the submitted work. ZAM reports grants from Amgen, Baxter, Fresenius Medical Care, GlaxoSmithKline, Merck Sharp and Dohme-Chibret, Genzyme, Lilly, Otsuka, and French Government support, and personal fees from Amgen and Genzyme during the conduct of the study. AC reports personal fees from Fresenius Medical Care, Amgen, and Vifor Pharma outside the submitted work. All other authors (DG, MA, SM, PUT, MV, VB, and MC) declare no competing interests.

#### References

1 Hill NR, Fatoba ST, Oke JL, et al. Global prevalence of chronic kidney disease—a systematic review and meta-analysis. *PLoS One* 2016; **11:** e0158765.

2 Hu MC, Shi M, Zhang J, et al. Klotho deficiency causes vascular calcification in chronic kidney disease. *J Am Soc Nephrol* 2011; **22:** 124–36.

3 Kuro-o M. Phosphate and klotho. *Kidney Int Suppl* 2011; **79:** S20–23.

4 Zhou X, Chen K, Lei H, Sun Z. Klotho gene deficiency causes salt-sensitive hypertension via monocyte chemotactic protein-1/CC chemokine receptor 2-mediated inflammation. *J Am Soc Nephrol* 2015; **26:** 121–32.

5 Hu MC, Shi M, Gillings N, et al. Recombinant α-klotho may be prophylactic and therapeutic for acute to chronic kidney disease progression and uremic cardiomyopathy. *Kidney Int* 2017; **91:** 1104–14.

6 Drüeke TB, Massy ZA. Changing bone patterns with progression of chronic kidney disease. *Kidney Int* 2016; **89:** 289–302.

7 Abraham CR, Chen C, Cuny GD, Glicksman MA, Zeldich E. Small-molecule klotho enhancers as novel treatment of neurodegeneration. *Future Med Chem* 2012; **4:** 1671–79.

8 Hillege HL, Fidler V, Diercks GFH, et al, for the Prevention of Renal and Vascular End Stage Disease (PREVEND) Study Group. Urinary albumin excretion predicts cardiovascular and noncardiovascular mortality in general population. *Circulation* 2002; **106:** 1777–82.

9 Kiel DP, Kauppila LI, Cupples LA, Hannan MT, O'Donnell CJ, Wilson PW. Bone loss and the progression of abdominal aortic calcification over a 25 year period: the Framingham Heart Study. *Calcif Tissue Int* 2001; **68:** 271–76.

10 Wu M, Rementer C, Giachelli CM. Vascular calcification: an update on mechanisms and challenges in treatment. *Calcif Tissue Int* 2013; **93:** 365–73.

11 Ye C, Xu M, Wang S, et al. Decreased bone mineral density is an independent predictor for the development of atherosclerosis: a systematic review and meta-analysis. *PLoS One* 2016; **11:** e0154740.

12 Nicoll R, Henein M. Arterial calcification: a new perspective? *Int J Cardiol* 2017; **228:** 11–22.

13 Jilka RL. The relevance of mouse models for investigating age-related bone loss in humans. *J Gerontol A Biol Sci Med Sci* 2013; **68:** 1209–17.

14 Kavousi M, Desai CS, Ayers C, et al. Prevalence and prognostic implications of coronary artery calcification in low-risk women: a meta-analysis. *JAMA* 2016; **316:** 2126–34.

15 Wang M, Kim SH, Monticone RE, Lakatta EG. Matrix metalloproteinases promote arterial remodeling in aging, hypertension, and atherosclerosis. *Hypertension* 2015; **65:** 698–703.

16 Block GA, Hulbert-Shearon TE, Levin NW, Port FK. Association of serum phosphorus and calcium x phosphate product with mortality risk in chronic hemodialysis patients: a national study. *Am J Kidney Dis* 1998; **31:** 607–17.

17 Lee CD, Jacobs DR Jr, Hankinson A, Iribarren C, Sidney S. Cardiorespiratory fitness and coronary artery calcification in young adults: the CARDIA Study. *Atherosclerosis* 2009; **203:** 263–68.

18 Caira FC, Stock SR, Gleason TG, et al. Human degenerative valve disease is associated with up-regulation of low-density lipoprotein receptor-related protein 5 receptor-mediated bone formation. *J Am Coll Cardiol* 2006; **47:** 1707–12.

19 Chen J, Budoff MJ, Reilly MP, et al. Coronary artery calcification and risk of cardiovascular disease and death among patients with chronic kidney disease. *JAMA Cardiol* 2017; **2:** 635–43.

20 Seeman E, Delmas PD. Bone quality—the material and structural basis of bone strength and fragility. *N Engl J Med* 2006; **354:** 2250–61.

21 Martineau P, Leslie WD. Trabecular bone score (TBS): method and applications. *Bone* 2017; **104:** 66–72.

22 Maravic M, Ostertag A, Torres PU, Cohen-Solal M. Incidence and risk factors for hip fractures in dialysis patients. *Osteoporos Int* 2014; **25:** 159–65.

23 Beaubrun AC, Kilpatrick RD, Freburger JK, Bradbury BD, Wang L, Brookhart MA. Temporal trends in fracture rates and postdischarge outcomes among hemodialysis patients. *J Am Soc Nephrol* 2013; **24:** 1461–69.

24 Lin ZZ, Wang JJ, Chung CR, et al. Epidemiology and mortality of hip fracture among patients on dialysis: Taiwan National Cohort Study. *Bone* 2014; **64:** 235–39.

25 Mittalhenkle A, Gillen DL, Stehman-Breen CO. Increased risk of mortality associated with hip fracture in the dialysis population. *Am J Kidney Dis* 2004; **44:** 672–79.

26 Tentori F, McCullough K, Kilpatrick RD, et al. High rates of death and hospitalization follow bone fracture among hemodialysis patients. *Kidney Int* 2014; **85:** 166–73.

27 Goldenstein PT, Jamal SA, Moysés RM. Fractures in chronic kidney disease: pursuing the best screening and management. *Curr Opin Nephrol Hypertens* 2015; **24:** 317–23.

28 Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. *N Engl J Med* 2004; **351:** 1296–305.

29 Levey AS, de Jong PE, Coresh J, et al. The definition, classification, and prognosis of chronic kidney disease: a KDIGO Controversies Conference report. *Kidney Int* 2011; **80:** 17–28.

30 Drüeke TB, Massy ZA. Changing bone patterns with progression of chronic kidney disease. *Kidney Int* 2016; **89:** 289–302.

31 Paneni F, Diaz Cañestro C, Libby P, Lüscher TF, Camici GG. The aging cardiovascular system: understanding it at the cellular and clinical levels. *J Am Coll Cardiol* 2017; **69:** 1952–67.

32 Shanahan CM, Crouthamel MH, Kapustin A, Giachelli CM, Towler DA. Arterial calcification in chronic kidney disease: key roles for calcium and phosphate. *Circ Res* 2011; **109:** 697–711.

33 Laouari D, Friedlander G, Burtin M, et al. Subtotal nephrectomy alters tubular function: effect of phosphorus restriction. *Kidney Int* 1997; **52:** 1550–60.

34 Block GA, Spiegel DM, Ehrlich J, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. *Kidney Int* 2005; **68:** 1815–24.

35 Suki WN, Zabaneh R, Cangiano JL, et al. Effects of sevelamer and calcium-based phosphate binders on mortality in hemodialysis patients. *Kidney Int* 2007; **72:** 1130–37.

36 McGovern AP, de Lusignan S, van Vlymen J, et al. Serum phosphate as a risk factor for cardiovascular events in people with and without chronic kidney disease: a large community based cohort study. *PLoS One* 2013; **8:** e74996.

37 Yoon CY, Park JT, Jhee JH, et al. High dietary phosphorus density is a risk factor for incident chronic kidney disease development in diabetic subjects: a community-based prospective cohort study. *Am J Clin Nutr* 2017; **106:** 311–21.

38 Tonelli M, Sacks F, Pfeffer M, Gao Z, Curhan G. Relation between serum phosphate level and cardiovascular event rate in people with coronary disease. *Circulation* 2005; **112:** 2627–33.

39 Palomino HL, Rifkin DE, Anderson C, Criqui MH, Whooley MA, Ix JH. 24-hour urine phosphorus excretion and mortality and cardiovascular events. *Clin J Am Soc Nephrol* 2013; **8:** 1202–10.

40 Chang AR, Lazo M, Appel LJ, Gutiérrez OM, Grams ME. High dietary phosphorus intake is associated with all-cause mortality: results from NHANES III. *Am J Clin Nutr* 2014; **99:** 320–27.

41 Rufino M, de Bonis E, Martín M, et al. Is it possible to control hyperphosphataemia with diet, without inducing protein malnutrition? *Nephrol Dial Transplant* 1998; **13** (suppl 3)**:** 65–67.

42 Hill KM, Martin BR, Wastney ME, et al. Oral calcium carbonate affects calcium but not phosphorus balance in stage 3-4 chronic kidney disease. *Kidney Int* 2013; **83:** 959–66.

43 Gutiérrez OM, Anderson C, Isakova T, et al. Low socioeconomic status associates with higher serum phosphate irrespective of race. *J Am Soc Nephrol* 2010; **21:** 1953–60.

44 Sullivan C, Sayre SS, Leon JB et al. Effect of food additives on hyperphosphatemia among patients with end-stage renal disease: a randomized controlled trial. *JAMA* 2009; **301:** 629–35.

45 Karavetian M, de Vries N, Elzein H, Rizk R, Bechwty F. Effect of behavioral stage-based nutrition education on management of osteodystrophy among hemodialysis patients, Lebanon. *Patient Educ Couns* 2015; **98**: 1116–1122.

46 Lou LM, Caverni A, Gimeno JA, et al. Dietary intervention focused on phosphate intake in hemodialysis patients with hyperphosphoremia. *Clin Nephrol* 2012; **77:** 476–83.

47 Uribarri J. Phosphorus homeostasis in normal health and in chronic kidney disease patients with special emphasis on dietary phosphorus intake. *Semin Dial* 2007; **20:** 295–301.

48 Stenvinkel P, Larsson TE. Chronic kidney disease: a clinical model of premature aging. *Am J Kidney Dis* 2013; **62:** 339–51.

49 John GB, Cheng CY, Kuro-o M. Role of klotho in aging, phosphate metabolism, and CKD. *Am J Kidney Dis* 2011; **58:** 127–34.

50 Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011; **121:** 4393–408.

51 Olauson H, Lindberg K, Amin R, et al. Parathyroid-specific deletion of klotho unravels a novel calcineurin-dependent FGF23 signaling pathway that regulates PTH secretion. *PLoS Genet* 2013; **9:** e1003975.

52 Galassi A, Cupisti A, Santoro A, Cozzolino M. Phosphate balance in ESRD: diet, dialysis and binders against the low evident masked pool. *J Nephrol* 2015; **28:** 415–29.

53 Hu MC, Shi M, Zhang J, et al. Klotho: a novel phosphaturic substance acting as an autocrine enzyme in the renal proximal tubule. *FASEB J* 2010; **24:** 3438–50.

54 Shimada T, Hasegawa H, Yamazaki Y, et al. FGF-23 is a potent regulator of vitamin D metabolism and phosphate homeostasis. *J Bone Miner Res* 2004; **19:** 429–35.

55 Isakova T, Wahl P, Vargas GS, et al. Fibroblast growth factor 23 is elevated before parathyroid hormone and phosphate in chronic kidney disease. *Kidney Int* 2011; **79:** 1370–78.

56 Hu MC, Kuro-o M, Moe OW. The emerging role of klotho in clinical nephrology. *Nephrol Dial Transplant* 2012; **27:** 2650–57.

57 Gutiérrez OM, Mannstadt M, Isakova T, et al. Fibroblast growth factor 23 and mortality among patients undergoing hemodialysis. *N Engl J Med* 2008; **359:** 584–92.

58 Isakova T, Xie H, Yang W, et al. Fibroblast growth factor 23 and risks of mortality and end-stage renal disease in patients with chronic kidney disease. *JAMA* 2011; **305:** 2432–39.

59 Moe SM, Chertow GM, Parfrey PS. Cinacalcet, fibroblast growth factor-23, and cardiovascular disease in hemodialysis: the Evaluation of Cinacalcet HCl Therapy to Lower Cardiovascular Events (EVOLVE) Trial. *Circulation* 2015; **132:** 27–39.

60 Ix JH, Katz R, Kestenbaum BR, et al. Fibroblast growth factor-23 and death, heart failure, and cardiovascular events in community-living individuals: CHS (Cardiovascular Health Study). *J Am Coll Cardiol* 2012; **60:** 200–07.

61 Lutsey PL, Alonso A, Selvin E, et al. Fibroblast growth factor-23 and incident coronary heart disease, heart failure, and cardiovascular mortality: the Atherosclerosis Risk in Communities study. *J Am Heart Assoc* 2014; **3:** e000936.

62 Ärnlöv J, Carlsson AC, Sundström J, et al. Higher fibroblast growth factor-23 increases the risk of all-cause and cardiovascular mortality in the community. *Kidney Int* 2013; **83:** 160–66.

63 Kestenbaum B, Sachs MC, Hoofnagle AN, et al. Fibroblast growth factor-23 and cardiovascular disease in the general population: the Multi-Ethnic Study of Atherosclerosis. *Circ Heart Fail* 2014; **7:** 409–17.

64 Souma N, Isakova T, Lipiszko D, et al. Fibroblast growth factor 23 and cause-specific mortality in the general population: The Northern Manhattan Study. *J Clin Endocrinol Metab* 2016; **101:** 3779–86.

65 Lindberg K, Amin R, Moe OW, et al. The kidney is the principal organ mediating klotho effects. *J Am Soc Nephrol* 2014; **25:** 2169–75.

66 Haring R, Enserro D, Xanthakis V, et al. Plasma fibroblast growth factor 23: clinical correlates and association with cardiovascular disease and mortality in the Framingham Heart Study. *J Am Heart Assoc* 2016; **5:** e003486.

67 Udell JA, Morrow DA, Jarolim P, et al. Fibroblast growth factor-23, cardiovascular prognosis, and benefit of angiotensin-converting enzyme inhibition in stable ischemic heart disease. *J Am Soc Coll Cardiol* 2014; **63:** 2421–28.

68 Faul C, Amaral AP, Oskouei B, et al. FGF23 induces left ventricular hypertrophy. *J Clin Invest* 2011; **121:** 4393–408.

69 Mirza MA, Hansen T, Johansson L, et al. Relationship between circulating FGF23 and total body atherosclerosis in the community. *Nephrol Dial Transplant* 2009; **24:** 3125–31.

70 Mirza MA, Larsson A, Lind L, Larsson TE. Circulating fibroblast growth factor-23 is associated with vascular dysfunction in the community. *Atherosclerosis* 2009; **205:** 385–90.

71 Farrow EG, Davis SI, Summers LJ, White KE. Initial FGF23-mediated signaling occurs in the distal convoluted tubule. *J Am Soc Nephrol* 2009; **20:** 955–60.

72 Duce JA, Podvin S, Hollander W, Kipling D, Rosene DL, Abraham CR. Gene profile analysis implicates klotho as an important contributor to aging changes in brain white matter of the rhesus monkey. *Glia* 2008; **56:** 106–17.

73 King GD, Rosene DL, Abraham CR. Promoter methylation and age-related downregulation of Klotho in rhesus monkey. *Age (Dordr)* 2012; **34:** 1405–19.

74 Sun CY, Chang SC, Wu MS. Suppression of klotho expression by protein-bound uremic toxins is associated with increased DNA methyltransferase expression and DNA hypermethylation. *Kidney Int* 2012; **81:** 640–50.

75 Alem AM, Sherrard DJ, Gillen DL, et al. Increased risk of hip fracture among patients with end-stage renal disease. *Kidney Int* 2000; **58:** 396–99.

76 Ball AM, Gillen DL, Sherrard D, et al. Risk of hip fracture among dialysis and renal transplant recipients. *JAMA* 2002; **288:** 3014–18.

77 Nickolas TL, McMahon DJ, Shane E. Relationship between moderate to severe kidney disease and hip fracture in the United States. *J Am Soc Nephrol* 2006; **17:** 3223–32.

78 Wakasugi M, Kazama JJ, Taniguchi M, et al. Increased risk of hip fracture among Japanese hemodialysis patients. *J Bone Miner Metab* 2013; **31:** 315–21.

79 Jadoul M, Albert JM, Akiba T, et al. Incidence and risk factors for hip or other bone fractures among hemodialysis patients in the Dialysis Outcomes and Practice Patterns Study. *Kidney Int* 2006; **70:** 1358–66.

80 Vautour LM, Melton LJ, 3rd, Clarke BL, Achenbach SJ, Oberg AL, McCarthy JT. Long-term fracture risk following renal transplantation: a population-based study. *Osteoporos Int* 2004; **15:** 160–67.

81 Chang CY, Tang CH, Chen KC, Huang KC, Huang KC. The mortality and direct medical costs of osteoporotic fractures among postmenopausal women in Taiwan. *Osteoporos Int* 2016; **27:** 665–76.

82 Center JR, Nguyen TV, Schneider D, Sambrook PN, Eisman JA. Mortality after all major types of osteoporotic fracture in men and women: an observational study. *Lancet* 1999; **353:** 878–82.

83 Naves M, Rodríguez-García M, Díaz-López JB, Gómez-Alonso C, Cannata-Andía JB. Progression of vascular calcifications is associated with greater bone loss and increased bone fractures. *Osteoporos Int* 2008; **19:** 1161–66.

84 Moe S, Drüeke T, Cunningham J, et al. Definition, evaluation, and classification of renal osteodystrophy: a position statement from Kidney Disease: Improving Global Outcomes (KDIGO). *Kidney Int* 2006; **69:** 1945–53.

85 Kazama JJ, Iwasaki Y, Fukagawa M. Uremic osteoporosis. *Kidney Int Suppl (2011)* 2013; **3:** 446–50.

86 Torres PU, Bover J, Mazzaferro S, de Vernejoul MC, Cohen-Solal M. When, how, and why a bone biopsy should be performed in patients with chronic kidney disease. *Semin Nephrol* 2014; **34:** 612–25.

87 Piraino B, Chen T, Cooperstein L, Segre G, Puschett J. Fractures and vertebral bone mineral density in patients with renal osteodystrophy. *Clin Nephrol* 1988; **30:** 57–62.

88 Iimori S, Mori Y, Akita W, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients—a single-center cohort study. *Nephrol Dial Transplant* 2012; **27:** 345–51.

89 Bover J, Ureña P, Brandenburg V, et al. Adynamic bone disease: from bone to vessels in chronic kidney disease. *Semin Nephrol* 2014; **34:** 626–40.

90 Brandenburg VM, Floege J. Adynamic bone disease-bone and beyond. *NDT Plus* 2008; **1:** 135–47.

91 Evenepoel P, Bover J, Ureña Torres P. Parathyroid hormone metabolism and signaling in health and chronic kidney disease. *Kidney Int* 2016; **90:** 1184–90.

92 Ng AH, Omelon S, Variola F, et al. Adynamic bone decreases bone toughness during aging by affecting mineral and matrix. *J Bone Miner Res* 2016; **31:** 369–79.

93 Kurz P, Monier-Faugere MC, Bognar B, et al. Evidence for abnormal calcium homeostasis in patients with adynamic bone disease. *Kidney Int* 1994; **46:** 855–61.

94 London GM, Marty C, Marchais SJ, Guerin AP, Metivier F, de Vernejoul MC. Arterial calcifications and bone histomorphometry in end-stage renal disease. *J Am Soc Nephrol* 2004; **15:** 1943–51.

95 Denburg MR, Tsampalieros AK, de Boer IH, et al. Mineral metabolism and cortical volumetric bone mineral density in childhood chronic kidney disease. *J Clin Endocrinol Metab* 2013; **98:** 1930–38.

96 West SL, Lok CE, Langsetmo L, et al. Bone mineral density predicts fractures in chronic kidney disease. *J Bone Miner Res* 2014; **30:** 913–19.

97 Yenchek RH, Ix JH, Shlipak MG, et al. Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol* 2012; **7:** 1130–36.

98 Iimori S, Mori Y, Akita W, et al. Diagnostic usefulness of bone mineral density and biochemical markers of bone turnover in predicting fracture in CKD stage 5D patients—a single-center cohort study. *Nephrol Dial Transplant* 2012; **27:** 345–51.

99 Naylor KL, Garg AX, Zou G, et al. Comparison of fracture risk prediction among individuals with reduced and normal kidney function. *Clin J Am Soc Nephrol* 2015; **10:** 646–53.

100 Ketteler M, Block GA, Evenepoel P, et al. Executive summary of the 2017 KDIGO Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD) Guideline Update: what's changed and why it matters. *Kidney Int* 2017; **92:** 26–36.

101 Naylor KL, Garg AX, Zou G, et al. Comparison of fracture risk prediction among individuals with reduced and normal kidney function. *Clin J Am Soc Nephrol* 2015; **10:** 646–53.

102 West SL, Lok CE, Langsetmo L, et al. Bone mineral density predicts fractures in chronic kidney disease. *J Bone Miner Res* 2015; **30:** 913–19.

103 Yenchek RH, Ix JH, Shlipak MG, et al. Bone mineral density and fracture risk in older individuals with CKD. *Clin J Am Soc Nephrol* 2012; **7:** 1130–36.

104 Akaberi S, Simonsen O, Lindergård B, Nyberg G. Can DXA predict fractures in renal transplant patients? *Am J Transplant* 2008; **8:** 2647–51.

105 Jamal SA, West SL, Nickolas TL. The clinical utility of FRAX to discriminate fracture status in men and women with chronic kidney disease. *Osteoporos Int* 2014; **25:** 71–76.

106 Naylor KL, Leslie WD, Hodsman AB, Rush DN, Garg AX. FRAX predicts fracture risk in kidney transplant recipients. *Transplantation* 2014; **97:** 940–45.

107 Malluche HH, Davenport DL, Cantor T, Monier-Faugere MC. Bone mineral density and serum biochemical predictors of bone loss in patients with CKD on dialysis. *Clin J Am Soc Nephrol* 2014; **9:** 1254–62.

108 Hoerger TJ, Simpson SA, Yarnoff BO, et al. The future burden of CKD in the United States: a simulation model for the CDC CKD Initiative. *Am J Kindey Dis* 2015; **65:** 403–11.

109 Wright NC, Looker AC, Saag KG, et al. The recent prevalence of osteoporosis and low bone mass in the United States based on bone mineral density at the femoral neck or lumbar spine. *J Bone Miner Res* 2014; **29:** 2520–26.

110 Bauer DC. Clinical practice. Calcium supplements and fracture prevention. *N Engl J Med* 2013; **369:** 1537–43.

111 Jackson RD, LaCroix AZ, Gass M, et al. Calcium plus vitamin D supplementation and the risk of fractures. *N Engl J Med* 2006; **354:** 669–83.

112 Bolland MJ, Leung W, Tai V, et al. Calcium intake and risk of fracture: systematic review. *BMJ* 2015; **351:** h4580.

113 Bischoff-Ferrari HA, Dawson-Hughes B, Baron JA, et al. Calcium intake and hip fracture risk in men and women: a meta-analysis of prospective cohort studies and randomized controlled trials. *Am J Clin Nutr* 2007; **86:** 1780–90.

114 Bolland MJ, Avenell A, Baron JA, et al. Effect of calcium supplements on risk of myocardial infarction and cardiovascular events: meta-analysis. *BMJ* 2010; **341:** c3691.

115 Lewis JR, Radavelli-Bagatini S, Rejnmark L, et al. The effects of calcium supplementation on verified coronary heart disease hospitalization and death in postmenopausal women: a collaborative meta-analysis of randomized controlled trials. *J Bone Miner Res* 2015; **30:** 165–75.

116 Genovesi S, Gallieni M. Cardiovascular complications of calcium supplementation in chronic kidney disease: are there arrhythmic risks? *Expert Opin Drug Saf* 2014; **13:** 1143–48.

117 Hill KM, Martin BR, Wastney ME, et al. Oral calcium carbonate affects calcium but not phosphorus balance in stage 3–4 chronic kidney disease. *Kidney Int* 2013; **83:** 959–66.

118 Spiegel DM, Brady K. Calcium balance in normal individuals and in patients with chronic kidney disease on low- and high-calcium diets. *Kidney Int* 2012; **81:** 1116–22.

119 Moe SM, Drüeke TB, Block GA et al. KDIGO clinical practice guideline for the diagnosis, evaluation, prevention, and treatment of Chronic Kidney Disease–Mineral and Bone Disorder (CKD–MBD). *Kidney Int Suppl* 2009; **76** (suppl 113)**:** S1–130.

120 Eckardt KU, Coresh J, Devuyst O, et al. Evolving importance of kidney disease: from subspecialty to global health burden. *Lancet* 2013; **382:** 158–69.

121 Ross AC, Taylor CL, Yaktine AL, Del Valle HB, for the Institute of Medicine Committee to Review Dietary Reference Intakes for Vitamin D, Calcium. Chapter 2. In: Ross AC, Taylor CL, Yaktine AL, Del Valle HB, eds. Dietary reference intakes for calcium and vitamin D. Washington DC: National Academies Press (US), 2011: 35–74.

122 Ketteler M, Elder GJ, Evenepoel P, et al. Revisiting KDIGO clinical practice guideline on chronic kidney disease–mineral and bone disorder: a commentary from a Kidney Disease: Improving Global Outcomes controversies conference. *Kidney Int* 2015; **87:** 502–28.

123 Ishani A, Blackwell T, Jamal SA, Cummings SR, Ensrud KE, for the MORE Investigators. The effect of raloxifene treatment in postmenopausal women with CKD. *J Am Soc Nephrol* 2008; **19:** 1430–38.

124 Jamal SA, Bauer DC, Ensrud KE, et al. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. *J Bone Miner Res* 2007; **22:** 503–08.

125 Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res* 2005; **20:** 2105–15.

126 Miller PD, Schwartz EN, Chen P, Misurski DA, Krege JH. Teriparatide in postmenopausal women with osteoporosis and mild or moderate renal impairment. *Osteoporos Int* 2007; **18:** 59–68.

127 Hernández E, Valera R, Alonzo E, et al. Effects of raloxifene on bone metabolism and serum lipids in postmenopausal women on chronic hemodialysis. *Kidney Int* 2003; **63:** 2269–74.

128 Tanaka M, Itoh K, Matsushita K, et al. Effects of raloxifene on bone mineral metabolism in postmenopausal Japanese women on hemodialysis. *Ther Apher Dial* 2011; **15** (suppl 1)**:** 62–66.

129 Bergner R. Bisphosphonate therapy in renal osteodystrophy—a review. *J Nephrol* 2013; **26:** 450–55.

130 Wilson LM, Rebholz CM, Jirru E, et al. Benefits and harms of osteoporosis medications in patients with chronic kidney disease: a systematic review and meta-analysis. *Ann Intern Med* 2017; **166:** 649–58.

131 Jamal SA, Bauer DC, Ensrud KE, et al. Alendronate treatment in women with normal to severely impaired renal function: an analysis of the fracture intervention trial. *J Bone Miner Res* 2007; **22:** 503–08.

132 Miller PD, Roux C, Boonen S, Barton IP, Dunlap LE, Burgio DE. Safety and efficacy of risedronate in patients with age-related reduced renal function as estimated by the Cockcroft and Gault method: a pooled analysis of nine clinical trials. *J Bone Miner Res* 2005; **20:** 2105–15.

133 U.S. Food and Drug Administration. FDA drug safety communication: new contraindication and updated warning on kidney impairment for Reclast (zoledronic acid). 2011. https://www.fda.gov/Drugs/DrugSafety/ucm270199.htm (accessed Oct 5, 2017).

134 Amerling R, Harbord NB, Pullman J, Feinfeld DA. Bisphosphonate use in chronic kidney disease: association with adynamic bone disease in a bone histology series. *Blood Purif* 2010; **29:** 293–99.

135 Ma S, Goh EL, Jin A, et al. Long-term effects of bisphosphonate therapy: perforations, microcracks and mechanical properties. *Sci Rep* 2017; **7:** 43399.

136 West SL, Patel P, Jamal SA. How to predict and treat increased fracture risk in chronic kidney disease. *J Intern Med* 2015; **278:** 19–28.

137 Jamal SA, Ljunggren O, Stehman-Breen C, et al. Effects of denosumab on fracture and bone mineral density by level of kidney function. *J Bone Miner Res* 2011; **26:** 1829–35.

138 Launay-Vacher V, Aapro M, De Castro G Jr, et al. Renal effects of molecular targeted therapies in oncology: a review by the Cancer and the Kidney International Network (C-KIN). *Ann Oncol* 2015; **26:** 1677–84.

139 Block GA, Bone HG, Fang L, Lee E, Padhi D. A single-dose study of denosumab in patients with various degrees of renal impairment. *J Bone Miner Res* 2012; **27:** 1471–79.

140 Cejka D, Kodras K, Bader T, Haas M. Treatment of hemodialysis-associated adynamic bone disease with teriparatide (PTH1-34): a pilot study. *Kidney Blood Press Res* 2010; **33:** 221–26.

141 Sumida K, Ubara Y, Hoshino J, et al. Once-weekly teriparatide in hemodialysis patients with hypoparathyroidism and low bone mass: a prospective study. *Osteoporos Int* 2016; **27:** 1441–50.

142 Strippoli GF, Craig JC, Schena FP. The number, quality, and coverage of randomized controlled trials in nephrology. *J Am Soc Nephrol* 2004; **15:** 411–19.

143 Moe SM, Nickolas TL. Fractures in patients with CKD: time for action. *Clin J Am Soc Nephrol* 2016; **11:** 1929–31.