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CKJ Review

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CKJ REVIEW

Management of fracture risk in CKD—traditional and novel approaches

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ABSTRACT

The coexistence of osteoporosis and chronic kidney disease (CKD) is an evolving healthcare challenge in the face of increasingly aging populations. Globally, accelerating fracture incidence causes disability, impaired quality of life and increased mortality. Consequently, several novel diagnostic and therapeutic tools have been introduced for treatment and prevention of fragility fractures. Despite an especially high fracture risk in CKD, these patients are commonly excluded from interventional trials and clinical guidelines. While management of fracture risk in CKD has been discussed in recent opinion-based reviews and consensus papers in the nephrology literature, many patients with CKD stages 3–5D and osteoporosis are still underdiagnosed and untreated. The current review addresses this potential treatment nihilism by discussing established and novel approaches to diagnosis and prevention of fracture risk in patients with CKD stages 3–5D. Skeletal disorders are common in CKD. A wide variety of underlying pathophysiological processes have been identified, including premature aging, chronic wasting, and disturbances in vitamin D and mineral metabolism, which may impact bone fragility beyond established osteoporosis. We discuss current and emerging concepts of CKD–mineral and bone disorders (CKD-MBD) and integrate management of osteoporosis in CKD with current recommendations for management of CKD-MBD. While many diagnostic and therapeutic approaches to osteoporosis can be applied to patients with CKD, some limitations and caveats need to be considered. Consequently, clinical trials are needed that specifically study fracture prevention strategies in patients with CKD stages 3–5D.

LAY SUMMARY

Patients with chronic kidney disease (CKD) are at increased risk of fractures, causing disability, impaired quality of life and increased risk of death. Osteoporosis is a common cause of fractures, and different medications have the potential to reduce fracture risk in osteoporosis. Several diagnostic criteria have been developed to identify patients at risk of fracture who would benefit from treatment. However, in CKD, the identification of patients with increased fracture risk is complicated by mineral metabolism disturbances due to reduced kidney function. Furthermore, patients with more advanced CKD are often excluded from clinical trials and treatment recommendations for fracture risk reduction. This review discusses diagnostic possibilities and treatment options to reduce fracture risk in patients with CKD, based on disease mechanisms, clinical experience, and clinical and experimental research. Although more research is needed, we conclude that many diagnostic and therapeutic approaches to osteoporosis can be applied in patients with CKD.

Keywords: biomarkers, bone mineral density, fracture risk, mineral metabolism, renal osteodystrophy

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INTRODUCTION

Large epidemiologic studies demonstrate an increasing fracture risk with more advanced stages of chronic kidney disease (CKD), compared with the general population. The simultaneous presence of traditional risk factors for bone fragility and CKD-specific mineral and bone disorders (CKD-MBD) poses a challenge to clinical evaluation, treatment and prevention. The 2017 update of the Kidney Disease: Improving Global Outcomes Initiative CKD-MBD guidelines recommend determination of bone mineral density (BMD) for fracture risk assessment in all stages of CKD, including dialysis patients, if results will impact treatment decisions [1]. Recent developments in diagnostic methodology and pathophysiologic understanding, and an increasing therapeutic armamentarium for the treatment and prevention of fragility fractures, open new possibilities for the clinician. Several systematic reviews of osteoporosis medication in CKD have been published recently, demonstrating an efficacy of different classes of bone-specific drugs for improvement of BMD and for fracture risk reduction [2, 3]. Thus, it may be time for a re-evaluation of the diagnostic and therapeutic strategies for fracture prevention in CKD.

This review summarizes current knowledge in the field, based on a recent on-line seminar on management of fracture risk in CKD, organized by the CKD-MBD Working Group of the European Renal Association (ERA), with inclusion of relevant literature published after that event. New and established methods for fracture risk prediction and prevention are discussed with focus on their relevance for patients with advanced CKD stages 4–5D.

EVALUATION OF FRACTURE RISK

FRAX for fracture risk prediction in CKD

FRAX is a computer-based fracture risk assessment tool, which can be found online at https://www.sheffield.ac.uk/FRAX. It has now been calibrated in 78 countries or territories, and 6 million calculations are performed annually in over 170 countries [4]. It calculates the 10-year probability of a major osteoporotic fracture as well as the 10-year probability of a hip fracture. The tool was developed based on specific risk factors, with or without femoral neck BMD as measured by dual-energy x-ray absorptiometry (DXA). FRAX includes the competing risk of death in the fracture risk assessment. This means that the risk of death, associated with other factors such as age, which precludes the occurrence of fracture, has been taken into account. However, FRAX currently does not include falls, which is another important and independent risk factor for fracture. Although there is a high prevalence of sarcopenia in CKD (up

to 70%) and an increasing incidence of falls with CKD severity, there is no direct evidence that sarcopenia in CKD is associated with increased risk of falls and fracture [5, 6].

Several studies have shown that the validity of risk prediction for people with CKD stages 3a and 3b is similar to those with estimated glomerular filtration rate (eGFR) >60 mL/min/1.73 m^2 [7–9]. However, these studies found that FRAX either under- or overestimates the fracture risk in both CKD and non-CKD. Possible reasons for these discrepancies are differences in methods used to identify fractures and the comparison of fracture risk in the study populations to the nationwide population risk used in FRAX. Overall, provided that these shortcomings are taken into account, FRAX can be used as a reliable fracture risk assessment tool in CKD stages 1–3.

There are few data on the role of FRAX in fracture risk prediction for CKD stages 4–5D, including dialysis patients [7, 8, 10, 11]. The next FRAX update may include risk factors such as recurrent falls, but the inclusion of CKD as a risk factor remains elusive. Renal osteodystrophy (ROD) impairs bone quality and is highly prevalent in CKD stages 4–5D [12]. However, important information on fracture risk relating to the type of ROD is unavailable, and a sufficiently powered study is unlikely to be achievable. Therefore, the question remains whether FRAX underestimates fracture risk in CKD patients who have ROD. Additionally, the increased mortality risk of CKD patients may require a re-adjustment to the competing risk of death. Furthermore, assessing 'imminent' fracture risk (within 1–2 years from an incident fracture) may appear clinically appropriate and is a current matter of research. Thus, development of new models or adjustment of the FRAX score with factors such as 'recent' fracture (rather than just fracture) or fracture site are currently being tested [13]. Such concern appears highly relevant in the context of CKD and should be evaluated in this population. Nonetheless, patients with any stage of CKD, including dialysis patients, who are currently identified as having high fracture risk by FRAX should be considered for treatment. Country-specific intervention thresholds for the general population are recommended, awaiting further evidence for specific thresholds in CKD [14].

DXA in CKD

The central role of bone mass in the operational definition of osteoporosis was recognized by the World Health Organization in 1994 with the publication of the BMD-derived T-score as a working definition of osteoporosis [15]. This did not ignore the contribution of other skeletal factors to fracture risk (e.g. high bone turnover, bone geometry, microarchitectural disruption, etc.), but simply recognized that BMD, measured by DXA, could capture about 70%–85% of bone strength in *ex vivo* studies and, more importantly, showed strong predictive ability for incident osteoporotic fractures in many studies [16]. Within the setting of CKD, it was initially assumed that a number of additional 'uraemic' factors might also influence skeletal strength and fracture risk and that the role for BMD measurements might be somewhat more limited [17]. This has proven not to be the case, with studies showing a similar gradient of risk for future fracture in CKD as in non-CKD populations [1, 18]. Nonetheless, the role of DXA-measured BMD in individual patient management is something that requires close collaboration and understanding between nephrologists and their local providers of BMD measurements, as a number of caveats in interpretation of BMD need to be considered. First, a T-score of –2.5 or less may not equal osteoporosis; impaired mineralization, e.g. osteomalacia, will also give rise to a low T-score, a situation in which some osteoporosis therapy might be potentially harmful. Secondly, many patients will be at high fracture risk despite having a T-score greater than –2.5, especially those with prior fractures. This has given rise to the development of tools for assessing absolute fracture risk such as FRAX, as discussed above [8]. Thirdly, the T-score definition of osteoporosis is inappropriate in certain clinical situations, particularly in children and young adults where the Z-score is more appropriate [19]. Finally, the finding of a low T-score or Z-score does not identify the cause, so that a comprehensive medical evaluation should be considered {e.g. to exclude malabsorption, the nature of an underlying ROD [hyperparathyroidism (HPT), adynamic bone] and/or senile osteoporosis, etc.}. The management of these, often complex, patients is enhanced by the development of multidisciplinary teams involving kidney and bone health expertise.

DXA scan derived Trabecular Bone Score

Trabecular Bone Score (TBS) is a grey-level textural parameter derived from DXA spine scans (other skeletal sites are becoming available) which provides information related to bone microarchitecture, with lower values indicating heterogenous or disrupted microarchitecture [20]. There is compelling evidence that TBS provides BMD- and FRAX-independent input to future fracture risk in the non-CKD population [21], and a FRAX-adjustment for TBS has been made available [22, 23]. More limited data suggest that the role of TBS in fracture risk prediction in the setting of CKD stage 5D and after kidney transplantation may be similar to that in non-CKD populations [24]. However, in patients with CKD stages 3–4, two large cohort studies found diverging results concerning the ability of TBS to predict fracture incidence: while Naylor *et al.* [25] found an association with incident fractures in patients with mostly CKD stage 3A, Rampersad *et al.* [26] found no association of TBS with fracture incidence in patients with CKD stages 3–4. These diverging findings may be due to differences in study design, e.g. severity of CKD and fracture identification. Thus, additional evidence is needed to further elucidate the role of TBS in CKD.

Novel bone imaging

HR-pQCT

Assessment of bone microstructure has traditionally relied on histomorphometry of bone biopsy specimens, as imaging modalities available for routine clinical use such as conventional computed tomography (CT) or DXA lack adequate resolution to study cortical or trabecular structure in detail. With the advent of new methods such as peripheral quantitative computed tomography (pQCT), high-resolution pQCT (HR-pQCT) and micro magnetic resonance imaging (μMRI) it is now possible to analyse bone microstructure non-invasively and thus more easily and longitudinally as well. However, it is important to note that all three techniques discussed here take images from the distal radius or distal tibia, anatomical locations where fractures do not have as serious clinical consequences as fractures of the vertebrae or the femoral neck. This limitation also applies to histomorphometry of bone biopsy samples, which are usually collected from the iliac crest. Furthermore, radius and tibia have different mechanical as well as metabolic properties and functions compared with the iliac crest, so comparisons between micro-imaging modalities (QCT, HR-pQCT and μMRI) and bone histomorphometry are bound to yield only modest correlations

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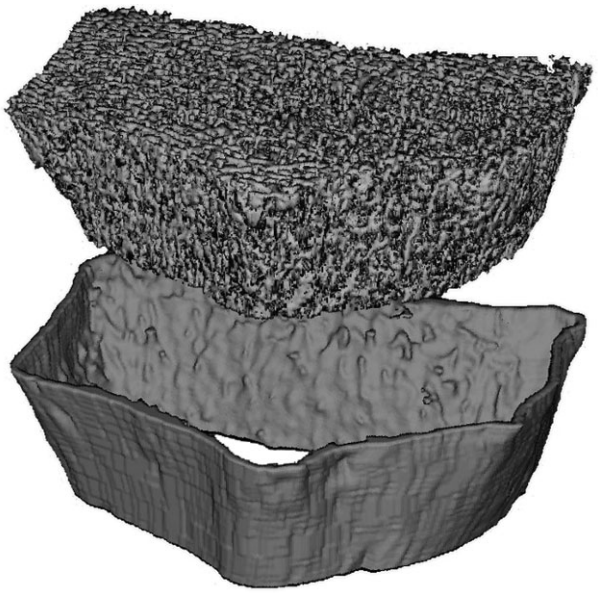

Figure 1: Three-dimensional (3D) reconstruction of the distal radius of a dialysis patient.
Source: Department of Radiology, Medical University Vienna, Austria.

for parameters of bone microstructure [27]. The majority of data on bone microstructure in CKD patients has been generated using HR-pQCT [27–35], which overcomes the shortcomings of pQCT and μMRI. While pQCT lacks the resolution to identify individual trabeculae and thus is more or less confined to structural studies of the cortex [36], the use of μMRI is currently limited by its availability at only a few specialized centres [37]. HR-pQCT has a resolution of approximately 80 μm, which allows for detailed examination of the trabecular compartment of bone (the typical trabecular width is 100–200 μm) as well as cortical porosity (Ct.Po). Generally speaking, increases in Ct.Po are expected to weaken mechanical bone strength. Interestingly, Ct.Po measured by HR-pQCT was found to increase over time in patients with CKD [38] and after kidney transplantation [34]. However, Ct.Po, measured by HR-pQCT, was not superior to BMD, determined by DXA, for identification of HD patients with prevalent fragility fractures [31]. Another cortical parameter associated with bone stability is the buckling ratio (BR), which is calculated by dividing the distance from the bone surface to the centre of the bone mass by the cortical thickness. Most studies describing BR are based on QCT data. A higher BR is associated with increased fracture risk [39, 40] and treatment with osteoporosis medication can improve the BR [41, 42]. Increased BRs compared with healthy controls have been described in dialysis patients [43] and after kidney transplantation [44]. HR-pQCT images can be reconstructed in 2D and 3D (Fig. 1) and can be used for virtual stress testing by estimating failure load using finite element analysis [45]. In a recent large international cohort, failure load outperformed individual parameters of microarchitecture, aBMD and FRAX as independent predictor of any incident fracture and incident major osteoporotic fractures in older men and women [46]. HR-pQCT studies have demonstrated that bone microarchitecture and failure load are significantly more compromised in patients with CKD [28, 35], including dialysis patients [29] with a history of bone fracture compared with patients without previous fracture, and that bone microstructure deteriorates rapidly in CKD patients [20]. However, in cross-sectional studies the power to discriminate patients according to fracture status was similar for HR-pQCT and conventional DXA [28, 29, 35].

Future research using HR-pQCT and μMRI could yield highly interesting insights into fracture prediction, pathophysiology of bone dynamics (e.g. spontaneous development and refilling of cortical porosity), effects of different treatments on bone microarchitecture, and, possibly, with the use of MRI-spectroscopy, also non-invasive analysis of bone composition and quality.

^{18}F-sodium fluoride positron emission tomography

Positron emission tomography (PET) is a non-invasive imaging method that enables measurement of the molecular function in tissues and organs by using short-lived radioactive isotopes. It monitors the movement of markers *in vivo*, without interfering with normal body functions. ^{18}F-sodium fluoride (^{18}F-NaF) PET allows assessment of regional bone turnover [47, 48]. The tracer ^{18}F-NaF is a sensitive bone-seeking compound with high and rapid bone uptake and plasma clearance [49], rendering a half-life of 110 min. ^{18}F-NaF reflects osteoblast activity and can therefore determine bone remodelling [50, 51].

^{18}F-NaF PET correlates with both dynamic and static histomorphometric parameters in bone biopsies [50, 51]. In a study of dialysis patients [50], ^{18}F-NaF PET had an area under the curve of 0.82 to discriminate histomorphometrically determined low turnover from non-low turnover bone disease, with a sensitivity of 76% and a specificity of 78%. ^{18}F-NaF PET is also a feasible method to follow the effect of both antiresorptive and anabolic treatment of osteoporosis in patients with normal kidney function longitudinally [52, 53]. The advantages of the method are that it is non-invasive, quick and reproducible, and enables assessment of regional bone turnover. Disadvantages are radiation exposure and its limited availability.

In the field of cardiovascular disease, ^{18}F-NaF PET has shown potential to broaden our understanding of the pathophysiological mechanisms underlying atherosclerosis and vascular calcification. The precise mechanism of vascular uptake of ^{18}F-NaF is unclear, but it seems to adsorb with high affinity to calcified deposits within plaques [54]. Indications of higher tracer uptake in culprit lesions after myocardial infarction have been presented [55]. Moreover, ^{18}F-NaF uptake in the arterial wall correlates with risk factors for atherosclerosis [56]. A recent study demonstrated independent positive associations between ^{18}F-NaF uptake in bone, histomorphometric parameters of bone turnover in bone biopsies and arterial calcification in end-stage renal disease patients [57], in line with a previous study of bone biopsy-based histomorphometric parameters of bone turnover and coronary calcification in dialysis patients [58].

In summary, ^{18}F-NaF PET seems to be a promising diagnostic tool when assessing bone turnover and treatment in patients with ROD. Future studies will determine ^{18}F-NaF PET's role in imaging of atherosclerosis and in exploring bone-vascular cross talk.

Bone biopsy

(Quantitative) histomorphometric analysis of bone is still the 'gold standard' for diagnosis and specific classification of the different types of ROD. Compared with other techniques for the evaluation of bone status, it also allows additional information on bone cell surface, number, and activity. Several (immuno-)histochemical stainings to evaluate cellular activity may be performed. Bone histomorphometry can be combined with other

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techniques such as μ-CT, for additional information on bone microarchitecture. However, a bone biopsy has several constraints. It is invasive, and as the histomorphometric analysis is laborious, time consuming, expensive (reimbursement is lacking in most countries), and requires specific expertise and complex diagnostic interpretation, it is only performed in a limited number of labs.

In the setting of CKD stages 4–5D, a bone biopsy is traditionally recommended in case of (i) suspected osteomalacia [persistent bone pain, multiple fractures, hypocalcemia, hypophosphatemia, elevated bone-specific alkaline phosphatase (BALP)], (ii) unexplained discordance between total ALP and/or BALP levels and parathyroid hormone (PTH), e.g. BALP >25–30 μg/L and PTH <100 pmol/L, in the presence of a normal liver function, (iii) unexplained persistent or severe hypo- or hypercalcemia/hypophosphatemia, and (iv) before prescription of anti-osteoporotic treatment (e.g. bisphosphonates, denosumab or teriparatide). However, a recent consensus statement by the ERA and the International Osteoporosis Foundation states that inability to perform a biopsy does not justify withholding treatment to CKD patients with high fracture risk [14]. Overall, the quantitative bone histomorphometric analysis, by providing information on bone turnover and mineralization, may help guide prevention and treatment of ROD. While the risk prediction of fractures can reasonably be based on BMD measurements in CKD stages 1–3, fracture risk evaluation is more complex in CKD stages 4–5D, as all subtypes of ROD may result in low BMD [59]. Additionally, subtypes of ROD can affect bone quality differently [12], thus, correct diagnosis of ROD may potentially improve fracture risk prediction in CKD stages 4–5D.

The iliac crest is the preferred site for a bone biopsy because it is easily accessible, only minimally affected by mechanical strain, and sampling from this site is associated with very low morbidity. Bone biopsies at the iliac crest can be obtained in a vertical or a horizontal direction. Whilst in the past, the great majority of bone biopsies were taken using a 7.5 mm Bordier–Meunier trephine, today up to 40% of biopsy procedures are performed with smaller, disposable, Jamshidi-type 4 mm trephines [60]. As demonstrated recently by Novel-Catin *et al.* [61], quantitative histomorphometric analysis of 3–3.5 mm hemi-biopsies fully matched with the whole-sample 7.5 mm biopsy (N = 68) in 91% of cases.

Quantitative bone histomorphometry encompasses the analysis of a series of both static (e.g. amount of osteoid, number of osteoblasts, bone area/volume, number of osteoclasts) and dynamic (e.g. bone formation rate, mineralization lag time, mineral apposition rate) parameters. In order to allow the analysis of dynamic parameters, double labelling with fluorochrome compounds such as demeclocycline or tetracycline is necessary prior to the bone biopsy procedure [61]. These compounds are incorporated into newly mineralized bone and emit a green-yellow colour under UV light (Fig. 2). Following sampling, the biopsy is directly fixed in 70% ethanol and may be stored at 4°C until shipping at environmental temperature (no refrigeration is necessary).

The classic description of the histologic abnormalities of ROD includes hyperparathyroid bone disease (osteitis fibrosa), adynamic bone, osteomalacia and mixed uraemic osteodystrophy. In 2006, the KDIGO consensus conference agreed on a new classification of ROD [62] that addresses the most important bone abnormalities, which include changes in bone turnover (T), mineralization (M) and volume (V) (Fig. 2). The TMV classification offers more precise information than the previously used classification system [63].

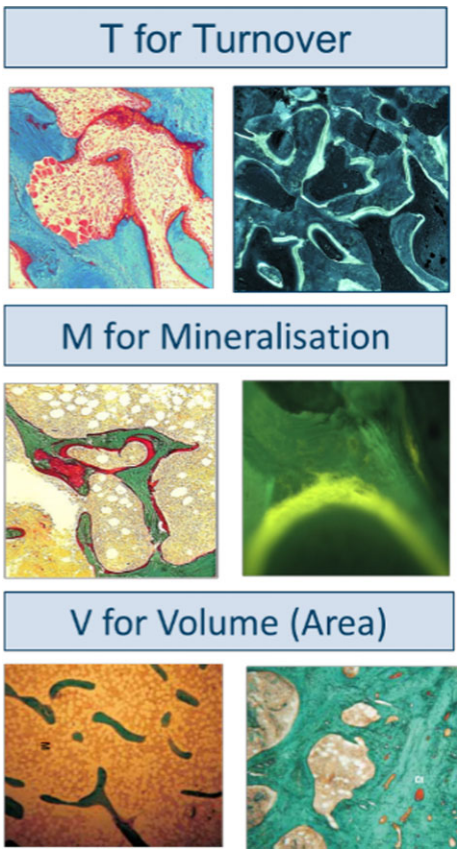

Figure 2: Representative Goldner stained and fluorescent tetracycline labelled sections (two upper right photographs) as examined for evaluation of turnover (T), mineralization (M) and volume (V).
Source: Laboratory of Pathophysiology, Department of Biomedical Sciences, University of Antwerp, Belgium.

Clinical evaluation of bone mechanical properties

Bone fragility is related to the mechanical properties of bone tissue, i.e. the bone's capacity to resist elastic deformation, plastic deformation and crack propagation. Determinants of bone material mechanical properties include matrix composition, microarchitecture, geometry, shape, remodelling dynamics, water content and occurrence of micro-damages. Disturbances in these parameters may contribute to increased bone fragility in the presence of normal bone mass [64, 65]. Standardized methods for the direct determination of mechanical bone properties comprise bending tests, and micro- and nanoindentation. Until recently, these methods were restricted to the use in *ex vivo* experimental studies or bone biopsies. The OsteoProbe® is a novel hand-held device for the *in vivo* determination of impact microindentation (IMI) of cortical bone, which in clinical studies was able to identify patients with prior fractures—both with and without CKD [66–69]. This device measures indentation depth in bone by IMI and calculates a bone material strength index (BMSi) by comparison with indentation depth in a standardized material [64]. Experimental studies have identified cortical material composition (e.g. the mineral-to-matrix ratio and the content of water or advanced glycation end-products), rather than microarchitecture or porosity as determinants of BMSi [70, 71]. Although BMSi is associated with BMD in postmenopausal osteoporosis [72] and in CKD (Johansson M, Qureshi AR, Jankowska M, Lindholm B, Haarhaus M. presentation at ERA-EDTA annual congress

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2021), the presence of a previous fracture is associated with lower BMSi, independent of BMD [67, 69]. Thus, IMI may evolve as a clinical tool to complement DXA in fracture risk evaluation. However, although the OsteoProbe® is approved for clinical use, evidence from large, prospective studies is still lacking.

Bone turnover markers in CKD

While imaging modalities to assess bone health perform reasonably well in assessing bone volume or mineral content, circulating markers derived from the formation or degradation of bone reflect bone turnover, and as such are complementary to imaging techniques currently used in clinical practice. Besides reflecting this different aspect of bone, these biomarkers have the advantage of being easily obtainable by a simple blood sample, rendering them suitable as screening tools for the diagnosis of bone turnover, and they can be followed longitudinally, to monitor effect of treatments that modulate bone turnover. General disadvantages of bone biomarkers are that many are not firmly associated with future fracture risk in general populations, unless at extreme values, and that several biomarkers have unpredictable kinetics in the setting of CKD. As disorders of bone turnover commonly found in CKD are more severe than in non-CKD populations and may impact bone fragility, the question remains whether bone biomarkers better reflect fracture risk in CKD. In fact, in a study on haemodialysis patients, BALP was a better predictor of fracture incidence than BMD at different sites or PTH [73].

PTH is the most frequently used biomarker for bone turnover in CKD. It is, however, important to realise, that, while PTH is a regulator of bone turnover, it does not reflect turnover *per se*. PTH may also reflect parathyroid disease, PTH molecules may be biologically inert, and PTH resistance on bone level can exist, all conditions in which PTH value fails as indicator of bone turnover. In contrast, circulating BALP is mainly derived from active osteoblasts and reflects turnover more directly. In the absence of liver disease, BALP comprises approximately 50% of total circulating ALP activity; thus, total ALP is commonly used as biomarker for routine control of bone formation in CKD. Clinically used target ranges for PTH [74] are derived from associations with mortality, not with bone histology or incidence rates of fractures. With these pitfalls in mind, a large study found that intact PTH had an area under the receiver operator characteristics curve (AUROC) of 0.701, with an optimal cut-off of 104 pg/mL for distinguishing low from non-low bone turnover, as assessed by bone histomorphometry in dialysis patients [75]. For the distinction between high and non-high turnover, an AUROC of 0.724 was found with an optimal intact PTH cut-off of 323 pg/mL [75]. The AUROCs for BALP were 0.757 and 0.711, with cut-off values of 33.1 U/L and 42.1 U/L for low and high turnover, respectively [75]. In that study, combining these two markers did not increase diagnostic performance. The most promising novel biomarkers in the CKD setting are procollagen type I N-terminal propeptide (PINP) and tartrate resistant acid phosphatase 5b (TRaP5b), reflecting bone formation and resorption, respectively [76]. PINP is cleaved from the N-terminal site of newly formed bone collagen as a triple helix polypeptide, the concentration of which is independent of kidney function. However, PINP also circulates as monomers, which do accumulate in CKD [77]. It is therefore of importance that the assay used detects intact PINP. TRaP5b is an osteoclast-derived enzyme, and its serum levels associate with the number and size of these cells [78]. Circulating levels are not influenced by kidney function or by dialysis [79]. Two recent studies indicate that osteoblast and osteoclast markers may outperform PTH as a biomarker of bone turnover in CKD [80, 81], especially when two markers are combined [81]. However, while the ability to discriminate high from non-high turnover was similar in CKD 4–5D and after kidney transplantation, the accuracy of biomarkers to distinguish between low and non-low turnover was lower in kidney transplant recipients [81].

TREATMENT OPTIONS

Non-pharmacological measures

Lifestyle and diet

Lifestyle factors influence fracture risk in osteoporosis, and patients with CKD are not exempt from these risks. Excessive alcohol intake and current smoking increase the risk of hip fractures in CKD [82], and a range of dietary factors have been linked to either low BMD or fractures, including a low protein intake [83], low fish intake [84] and lack of vitamin K [85]. A sufficient intake of calcium and vitamin D are crucial for maintenance of bone health (discussed in depth in a separate paragraph). More important than any single nutrient, however, is the overall nutritional status. There is a well-known direct relationship between body mass index and bone mass [86], and low body weight or weight loss are consistent risk factors for fracture in CKD patients, as well as in the general population [82, 87, 88].

Exercise

Loss of muscle mass and function, sarcopenia contributes to falls, fractures and overall mortality [89]. Evaluation of muscle function is simple and easy to perform in clinic by tests such as the short physical performance battery [90]. In CKD, both self-reported physical function [91] and low scores on tests such as the 6-minute walking test [92] associate with falls and fractures. Though no interventional trial has evaluated the effect of exercise on fracture risk in CKD, resistance training is capable of eliciting a normal, anabolic muscle-response even in CKD stage 5D [93], resulting in increased muscle strength and improved physical performance [93, 94].

Mechanical loading is also a key component in maintaining bone mass, and weight-bearing exercise has positive effects on the skeleton throughout life [95, 96]. A recent meta-analysis concluded that resistance training may also increase BMD in patients with CKD stages 3–5, mainly at the peripheral skeleton [97]. Progressive resistance training resulted in a small increase in whole-body bone mineral content after 12 weeks in patients receiving haemodialysis, when compared with sham (lightweight) exercise [93].

Falls

The propensity to fall is a strong, independent risk factor for fracture [98]. The fall risk is high in CKD, particularly in CKD stage 5D, with a recent fall reported in as many as 50% of elderly patients receiving haemodialysis [5, 99]. Reduced physical performance, malnutrition, depression and central nervous system-affecting drugs increase the risk of falls specifically in CKD [87, 100]. Very little has been published on initiatives aimed at reducing risk of falls in late-stage CKD. One single-centre study demonstrated a reduction in falls in the haemodialysis clinic—among patients, staff or visitors—by a pragmatic approach targeting factors involved in falls, such as slippery floors and poor lighting [101].

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Table 1: Non-pharmacological interventions to reduce fracture risk in CKD.

Lifestyle factor	Intervention
Drugs	Avoid long-term use of central nervous system–affecting drugs and proton pump inhibitors if possible
	The preference of low molecular weight heparin to unfractionated heparin may be advocated
	Glucocorticoid dose and duration should be reduced to a minimum, and fracture risk assessment must be considered mandatory for any patient initiating systemic steroid treatment
Diet and nutrition	Ensure sufficient nutrition, paying special attention to the calcium balance
	Promote cessation of smoking and moderation of alcohol intake
Physical function	Encourage exercise, to maintain physical function and reduce the risk of falls
	Resistance training may be particularly beneficial to skeletal health
Falls risk	Risk of falls should be evaluated—and acted upon

Drugs

CKD patients are treated with a multitude of drugs, many of which affect bone health. Loop-diuretics increase renal calcium excretion and increase the risk of fractures in the background population, likely due to induction of secondary HPT (SHPT) [102]. A similar effect was not seen in CKD stage 5D [103]. Thiazide diuretics increase tubular reabsorption of calcium, with small, positive effects on bone mass and fracture risk [104, 105]. As thiazides are considered ineffective with eGFR <30 mL/min/1.73 m^2 [106], there are currently no data available on the effect this class of diuretics may have on bone or mineral metabolism in CKD stages 3–5. This may change with the recent introduction of chlorthalidone as an efficient blood-pressure lowering thiazide in patients with CKD stage 4 [107].

The increased fracture risk seen with use of proton pump inhibitors (PPI) has received attention recently, although the precise mechanism is yet unknown [102, 108]. In a Danish registry-based study, PPI use increased the fracture risk for patients receiving haemodialysis to a similar level to that in the background population [103]. Treatment with PPI—but not with H2 receptor agonists—was also associated with increased risk of fractures in kidney transplant recipients [109].

Unfractionated heparin (UFH) use is associated with 5%–10% bone loss and increased risk of vertebral fractures in young, pregnant women [110]. Although these data are observational and have been criticized for the lack of appropriate controls [111], they are supported by experimental studies demonstrating inhibition of bone formation with rapid trabecular bone loss with the use of UFH [112]. A similar signal has not been found for low molecular weight heparin (LMWH) [113]. In a recent study, intradialytic UFH use was associated with greater bone loss at the spine over a 2-year period in patients receiving chronic intermittent haemodialysis, when compared with LMWH [114].

Bone loss and increased fracture risk are well-known side effects of systemic treatment with glucocorticoids. A daily dose of just 5 mg prednisolone increases the fracture risk by ~20%, with a dose-dependent increase in risk up to 60% with daily doses of 20 mg [115]. Cumulative glucocorticoid dose is a determinant of bone loss after kidney transplantation [116, 117], and steroid-sparing regimens are associated with reduced risk of fractures [118]. Glucocorticoids are also the cornerstone therapy for multiple glomerular disorders. Efforts to reduce glucocorticoid exposure through steroid-minimization, and/or combined immunosuppressive protocols are ongoing [119].

Conclusions regarding non-pharmacological interventions to lower fracture risk in CKD are summarized in Table 1 and Fig. 3.

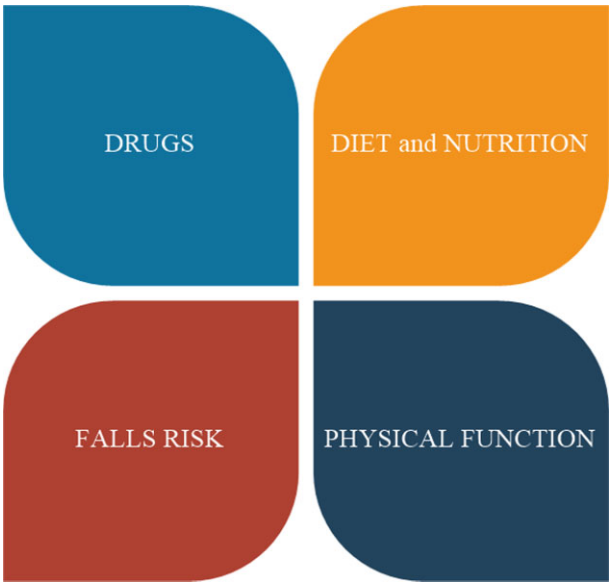

Figure 3: Targetable lifestyle factors associated with fracture risk in CKD.

Pharmacotherapy for fracture prevention in CKD

A range of pharmacological agents have been developed for fracture prevention in osteoporosis, which are generally safe and effective in CKD stages 1–3 [2, 3, 14]. Despite a sparsity of large clinical trials, specifically targeting fracture risk in CKD stages 4–5D, evidence from *post hoc* analyses of randomized and controlled trials (RCTs), moderately sized prospective clinical trials and observational studies supports pharmacological fracture risk reduction in all stages of CKD, although some caveats and limitations need to be considered, and we advise to obtain informed consent when considering off-label use of osteoporosis medication in CKD. Advantages and disadvantages of osteoporosis medications in CKD stages 4–5D are summarized in Table 2.

Calcium and vitamin D

Calcium and vitamin D are commonly used in pharmacological treatment strategies for fracture prevention in osteoporosis, and in the treatment and prevention of SHPT in CKD [120]. Early SHPT diagnosis and treatment is crucial for the management of patients with CKD [120]. Elevated PTH and abnormal calcium and phosphate levels are frequently observed from stage 3 CKD

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Table 2: Advantages and disadvantages of osteoporosis medications in CKD 4–5D.

	Advantages	Disadvantages
Calcium	Can reduce risk of sHPT and skeletal mineralization defects Lowers phosphorus load May improve BMD in combination with vitamin D	Excessive use may increase cardiovascular risk and risk for kidney stones
Vitamin D	Can reduce risk of sHPT and skeletal mineralization defects May improve BMD in combination with calcium Active vitamin D preferrable in CKD 5D Nutritional vitamin D preferable in CKD 4–5	Stimulates FGF23 Excessive use may increase cardiovascular risk Active vitamin D should be restricted to patients with SHPT and can in that case also be used as adjuvant therapy with bone-specific agents
Bisphosphonates	Can improve BMD in all stages of CKD Persistent effect after cessation No evidence for increased cardiovascular risk	Increased systemic retention May be associated with CKD progression in CKD 4–5 and reduced residual renal function in CKD 5D Occasional reports of AKI with intravenous use
Denosumab	Can improve BMD in all stages of CKD No evidence of increased cardiovascular or renal risk No dose adaptation needed in any stages of CKD, including CKD 5D	Risk for hypocalcemia (especially in severe HPT) Rapid BMD deterioration and increased fracture risk after cessation
PTH analogues	Can improve BMD in all stages of CKD May improve suppressed BFR	Safety uncertain Optimal dosing uncertain May aggravate existing hyperparathyroidism
Romosozumab	May improve BMD in all stages of CKD Anabolic and antiresorptive effect	May induce hypocalcaemia Cardiovascular safety uncertain Optimal dosing uncertain
HRT	Can improve BMD in all stages of CKD	Safety uncertain Limited to early menopause

AKI, acute kidney injury.

onwards [121], and it is estimated that 40%–82% of stage 3b/4 CKD patients have SHPT. Recently, Geng *et al.* [122] evaluated the relationship between baseline PTH levels and long-term risk of fractures, vascular events and death in a large cohort of stage 3–4 CKD patients. The study found that among these patients, high PTH was an independent risk factor in multivariable adjusted models predicting fracture, vascular events and death.

Furthermore, dysregulation of calcium and phosphorous homeostasis in CKD leads to decreased renal phosphate excretion, increased serum phosphate, elevated levels of fibroblast growth factor 23 (FGF-23) and reduced synthesis of $1,25(OH)_2$ vitamin D. Elevated FGF-23 expression downregulates residual renal 1-alpha-hydroxylase (CYP27B1), which further exacerbates deficiency of $1,25(OH)_2$ vitamin D, acting as an additional driver to SHPT. Continuous stimulation of the parathyroid glands by a combination of elevated serum phosphate, decreased serum calcium and markedly reduced serum $1,25(OH)_2$ vitamin D levels leads to increased PTH synthesis and release [123].

Vitamin D deficiency is common in patients with CKD, particularly in patients with proteinuria, due to loss of 25-hydroxy (25-OH) vitamin D with vitamin D binding protein [124], and is associated with fractures [125]. The advantage of native vitamin D is maintenance of feedback mechanisms in the synthesis of of $1,25(OH)_2$ vitamin D and possible effects due to extrarenal hydroxylation, yielding extrarenal production of $1,25(OH)_2$ vitamin D. Vitamin D supplementation should be prescribed early in the course of renal disease. For treatment and prevention of vitamin D deficiency in CKD patients, recommendations for the general population could be indicative. However, uncertainty exists with respect to optimal levels of 25-OH vitamin D and the dietary reference intake (DRI) for native vitamin D to achieve these levels. While the US Institute of Medicine recommends a DRI of 600 IU/day for ages 1 to 70 years, and 800 IU/day for 71 years and older to achieve serum 25-OH vitamin D levels of 16-20 ng/mL (40–50 nmol/L) [126], alternative algorithms result in somewhat higher DRIs for non-CKD populations [127–129]. For patients with CKD, an intake of 800 IU/day has been recommended [130], which may need to be modified to achieve the desired target level of 25-OH vitamin D. In postmenopausal osteoporosis, single therapy with calcium or vitamin D has little effect on fractures, while the combination of both may prevent incidence of non-vertebral fractures [131]. However, a negative feedback mechanism of active vitamin D on additional vitamin D activation may reduce the effect of native vitamin D treatment beyond vitamin D repletion on fracture risk [132]. The efficacy of native and active vitamin D substitution for fracture risk reduction in CKD stages 4–5D is not sufficiently studied and different indications may apply for management of osteoporosis and secondary hyperparathyroidism in this setting.

Long-term calcium deficiency may predispose to osteoporosis, but BMD loss related to age or menopause cannot be prevented and/or treated with calcium supplementation only [133, 134]. Furthermore, there may be negative effects associated with high doses of calcium on enhanced risk of nephrolithiasis, arrhythmias, and cardiovascular risk, although these results remain inconclusive [135]. This consumption of excessive amounts of calcium in adults can be especially harmful in patients with CKD [136], particularly in the presence of hypercalcemia, low PTH levels, adynamic bone, concurrent warfarin treatment and/or existing cardiovascular calcifications [137]. The intake of moderate doses (up to 1000 mg/day) of oral calcium in combination with antiresorptive treatment for 1 year

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improved BMD but did not increase the risk of cardiovascular calcifications or arterial stiffness [138]. However, high doses may be of potential harm, at least theoretically [139]. Therefore, a reasonable approach could be to encourage an appropriate intake of calcium primarily through the diet [126], and to complete with moderate pharmacologic calcium supplementation only if the nutritional intake is insufficient. The routine use of pharmacological supplementation of calcium or calcium-based phosphate binders for all patients with CKD stages 4–5D cannot be recommended [140].

Antiresorptive treatment

Antiresorptive agents are currently the most prescribed bone-specific drugs for fracture prevention in non-CKD populations. They comprise bisphosphonates and denosumab, the latter being a monoclonal antibody against receptor activator of nuclear factor kappa-B ligand. Antiresorptives improve BMD by slowing bone turnover and allowing for an increased mineralization of resorption cavities [141]. Whereas the positive effect of bisphosphonates on BMD may diminish with time [142], denosumab has a continued effect on BMD for up to 10 years, possibly due to sustained bone modelling [141, 143]. A robust body of evidence indicates a continuous fracture risk reduction by bisphosphonates, which persists for several years after treatment cessation [142], and fracture prevention by denosumab has been demonstrated for at least 10 years in postmenopausal women with normal kidney function [144] and CKD stages 1–3 [145]. It can be speculated that the persistent fracture risk reduction by bisphosphonates may be related to long skeletal retention times and a persistent suppressive effect on bone turnover for years after discontinuation. In contrast, bone turnover increases rapidly after discontinuation of denosumab, paralleled by a deterioration of BMD and an increased fracture risk [146]. Sequential treatment with an anabolic agent outperforms bisphosphonates in the ability to prevent this rapid decline of BMD following discontinuation of denosumab [147]. Due to impaired renal clearance of bisphosphonates with risk for systemic accumulation in the setting of CKD and occasional reports of acute kidney failure associated with intravenous administration, bisphosphonates are relatively contraindicated in CKD stages 4–5D, and their use is off-label in most countries when eGFR is <30 mL/min/1.73 m^2. Small studies in dialysis patients suggest a positive effect on BMD without increased risk for negative outcomes [148]. A recent observational study indicated similar effects of bisphosphonates on BMD gain in patients with CKD stages 1–3a and non-CKD patients, while the finding of a possible decreased effect in more advanced CKD was biased by very low patient numbers [149]. In addition, a moderate risk for CKD progression in patients with CKD stages 3b–5 was found in a large observational study, while bisphosphonate treatment was associated with improved survival, but only after propensity score matching [150]. Denosumab neither is cleared by the kidneys nor does it affect kidney function negatively, thus, it is not contraindicated in CKD stages 4–5D [14]. Several observational reports and some small RCTs indicate moderate to large effects on BMD without accelerated cardiovascular risk in end-stage renal disease [148]. A risk for hypocalcaemia exists following treatment with denosumab. This risk may be exaggerated by concomitant treatment with calcimimetics. Oral calcium and vitamin D can reduce the risk of severe or symptomatic hypocalcemia [151, 152]. Atypical femoral fractures and osteonecrosis of the jaw are rare complications of antiresorptive treatments, which do not occur more often in CKD than in other populations. Severe suppression of bone turnover has been discussed as an additional limitation, based on the concept that adynamic bone is a 'disease' and may contribute to negative bone and cardiovascular outcomes. The generalizability of this concept for any type of low bone turnover in CKD and, more specifically, to CKD patients on antiresorptive agents, has recently been challenged [148]. In summary, antiresorptive agents are safe and effective in CKD 1–3. Their use in CKD stages 4–5D can be beneficial, but should be based on individual evaluation, awaiting more direct evidence for fracture prevention in these patients.

Anabolic treatment

Currently, worldwide, two recombinant PTH analogues, teriparatide and abaloparatide, are available for the treatment of osteoporosis in postmenopausal women with high fracture risk. *Post hoc* analyses of pivotal trials demonstrated comparable efficacy on fracture risk reduction and BMD increases in patients with normal kidney function as compared with patients with CKD stage 1–3 and normal endogenous PTH levels [153, 154]. Regarding safety, in those with CKD, teriparatide more often induced hypercalcemia and hyperuricemia, but without accompanying increased incidence of clinical events such as nephrolithiasis or gout. Therefore, in CKD stage 1–3 patients with high fracture risk without elevated endogenous PTH, treatment with PTH analogues seems effective and safe, if adequately monitored.

For CKD stage 4–5 limited data are available. A small pilot study in haemodialysis patients with histomorphometrically proven adynamic bone demonstrated an increase in lumbar spine (but not femoral neck) BMD with daily-dosed teriparatide for 6 months [155]. Two small Japanese studies with weekly-dosed teriparatide demonstrated comparable effects in haemodialysis patients with biochemical signs of adynamic bone. In these studies, and in a Japanese post-marketing study in CKD stage 4–5 patients, teriparatide administration did not result in serious adverse events [156–158]. However, there are drawbacks to teriparatide administration in general. Consolidation therapy with antiresorptive treatment is needed after the use of PTH analogues and treatment duration is limited to 2 years because of an association of its long-term use with the development of osteosarcoma in rodent studies [159, 160]. In 2021, the United States Food and Drug Administration removed the time limit for treatment with teriparatide if a patient remains at or has returned to having a high risk for fracture [161].

To summarize, PTH analogues are effective and safe for fracture risk reduction in CKD stage 1–3 patients without metabolic derangements and with high fracture risk. In those with CKD stage 4–5 and signs of adynamic bone, PTH analogues can be considered for fracture risk reduction on an individual basis. Caution is needed because of a lack of data in this specific population, but identifying the CKD patient that may benefit from this form of anabolic treatment might be rewarding.

Romosozumab

Romosozumab is a fully human monoclonal antibody against sclerostin. Sclerostin, encoded by the gene *SOST*, is an osteocyte-secreted glycoprotein that has been identified as a pivotal regulator of bone formation. By inhibiting the Wnt and bone morphogenetic protein signalling pathways, sclerostin impedes osteoblast proliferation and function, thereby decreasing bone formation. In clinical trials, romosozumab resulted in an increase in BMD to a greater extent than alendronate and teriparatide with a decrease in risk of vertebral and nonvertebral

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fractures in postmenopausal women [162–164]. Romosozumab also increased the spine and hip BMD compared with placebo in men with osteoporosis [165]. Bone turnover marker data from these trials suggest an uncoupling of bone remodelling in favour of bone formation, which could be an asset in patients with CKD, acknowledging the high prevalence of low bone turnover in this patient population. Of equally great interest to CKD patients is the observation that BMD gains in postmenopausal women are accentuated in cortical bone [166], which is commonly affected in CKD. Unfortunately, clinical studies definitely proving the efficacy of romosozumab in the setting of CKD are neither available, nor currently scheduled. An observational report of 1 year of romosozumab treatment in haemodialysis patients demonstrated a positive effect on BMD without an increased incidence of cardiovascular events, compared with age- and gender-matched controls [167]. However, 61.5% of romosozumab-treated patients were pre-treated with bisphosphonates, which was stopped at initiation of romosozumab treatment. A recent *post hoc* analysis on data of two registration trials showed that the efficacy and safety of romosozumab versus alendronate or placebo among postmenopausal women with osteoporosis was similar at different levels of kidney function [168]. While these data on bone outcomes are reassuring, a numerically higher incidence of cardiovascular adverse events in the romosozumab group [164, 169] warrants caution and calls for additional safety data, especially in high-risk patients, which certainly includes patients with CKD. The putative higher cardiovascular risk may be explained by accentuated vascular calcification [170]. Furthermore, sclerostin may contribute to phosphate homeostasis by stimulating FGF23 expression in bone [171]. Of note, romosozumab therapy can induce profound hypocalcemia in patients with CKD stages 4–5D, which may be exaggerated by concomitant treatment with calcimimetics, necessitating close monitoring of serum calcium after initiation of romosozumab treatment in this population [172].

Menopausal hormone therapy and SERMs

The hypothalamic–pituitary–gonadal axis is disrupted in CKD [173]. Consequently, early menopause or hypogonadism are highly prevalent among CKD patients. Hormone replacement therapy (HRT) may be hypothesized to play a prominent role in the management of osteoporosis in CKD. Questions regarding the benefit–risk profile [174], lack of data from RCTs and availability of more potent alternatives has dampened the enthusiasm for post-menopausal HRT and selective oestrogen receptor modulators (SERMs) in the general population. However, current evidence reveals a benefit–risk profile that supports HRT treatment in women who have recently (<10 years) become menopausal, have menopausal symptoms and are <60 years old, with a low baseline risk for adverse events [175]. The limited data from RCTs precludes clear guidance with regard to HRT and SERMs in CKD patients [14, 176]. Acknowledging the increased cardiovascular risks (including a high risk for thromboembolic events) in patients with CKD, the benefit–risk profile may prove to be inferior.

Calcimimetics and parathyroidectomy

Hypo- and hypercalcaemia modulate PTH release and activation of its receptor (PTHR) in the kidneys, intestines, and bone, with the aim of restoring calcium equilibrium. Clinicians dealing with secondary hyperparathyroidism might be more attracted by the effects on the PTH/PTHR than on the calcium/Calcium sensing receptor (CaSR) system. However, the role of CaSR could be relevant since CaSR knockout animals die after birth, while the PTH-knockout and the double PTH-CaSR knockout animals survive. Therefore, distinct roles can be considered for the PTH/PTHR and Ca/CaSR systems when treating CKD patients.

Administration of high doses of PTH to PTH knockout and double PTH/CaSR knockout mice results in lower cortical and trabecular resorption in the latter, illustrating the complementary role of CaSR on PTH-induced bone effects [177]. In 5/6 nephrectomized rats developing ROD, PTH bone effects are mitigated by calcimimetics through PTH suppression, but direct bone effects are also possible as well, since bone cells express CaSR. Indeed, after parathyroidectomy and during PTH infusion to abolish treatment-related PTH declines, calcimimetics promoted bone formation rate and anabolic pathways in osteoblasts [178]. These results clearly demonstrate that, when treating ROD, direct effects of calcimimetics on bone may occur independently of PTH suppression and with potential effects on fracture rate [179]. In clinical practice, calcimimetics suppress PTH and can modify the bone phenotype [180]. Although there is a lack of high-quality evidence to support an effect of cinacalcet on fracture risk reduction in CKD stages 4–5D, *post hoc* analyses of placebo-controlled trials suggest that some effect may exist [181, 182]. Further subgroup analysis of the Evaluation of Cinacalcet Hydrochloride Therapy to Lower Cardiovascular Events (EVOLVE) trial indicates that it may be prudent to consider calcium balance when treating patients with high fracture risk with cinacalcet [181].

As for parathyroidectomy, in both primary [183] and secondary hyperparathyroidism [184], BMD increases after surgery in particular in patients with osteoporosis. In addition, a large study from US Renal Data System consistently shows that parathyroidectomy invariably diminishes fracture risk in haemodialysis patients [185]. However, as a trade-off, hospitalization rates may increase significantly early after and within 1 year of surgery [186].

As a whole, among the number of factors affecting bone strength [187], PTH reduction, either surgically or pharmacologically, is expected to reduce fracture rate in CKD patients with hyperparathyroidism, through different mechanisms and possibly according to the baseline bone status.

CONCLUSIONS

The increasing awareness of the high risk for fragility fractures among patients with CKD calls for improved guidance for evaluation, prevention, and treatment. The current review summarizes the evolving evidence in support of fracture risk evaluation and treatment in patients with all stages of CKD. We demonstrate that established diagnostic and therapeutic strategies may be safely and effectively applied also in patients with more advanced CKD and that risks, including suppression or stimulation of bone turnover, can be managed, based on individual patient evaluation. New diagnostic and therapeutic tools have the potential to improve tailoring of treatment strategies to individual patient needs. In spite of the current scarcity of evidence from randomized controlled trials for fracture prevention in CKD stages 4–5D, we advocate an active approach, based on the accumulating evidence, to close the treatment gap and meet the need of patients who are at risk for or suffer from fragility fractures. This approach has the potential to improve quality of life and reduce the increased mortality risk associated with fragility fractures.

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DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

CONFLICT OF INTEREST STATEMENT

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