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A consensus statement on the management of vertebral fractures in CKD stages G4–G5D

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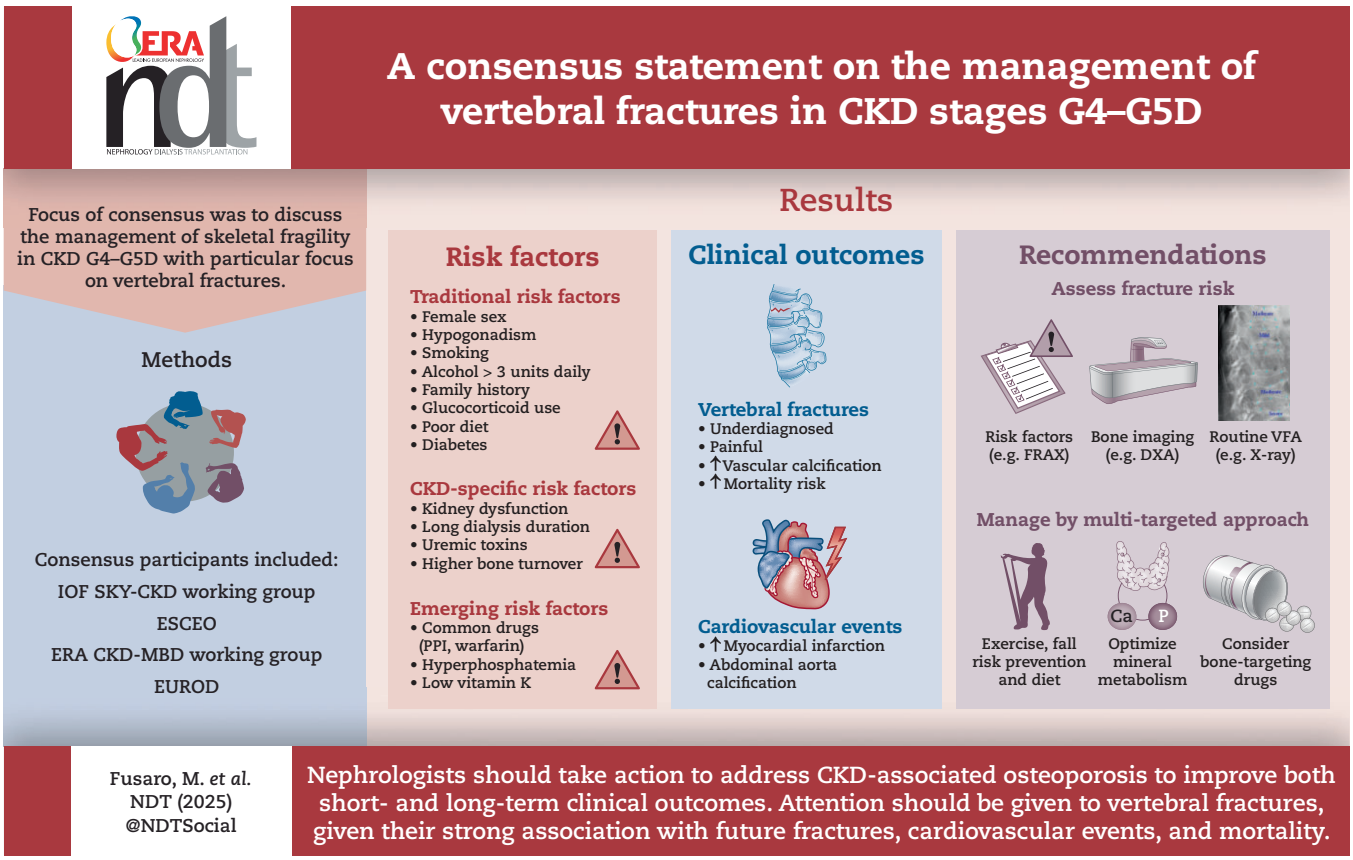
ABSTRACT

Skeletal fragility has long been overlooked by the nephrology community despite patients with chronic kidney disease (CKD) facing double the risk of hip fracture compared with the general population. Consequently, the term CKD-associated osteoporosis was recently coined to increase awareness. In this context, vertebral fractures are even less studied. Vertebral fractures predict increased fracture risk, and especially in advanced CKD, show a strong association with aortic and iliac vascular calcifications and cardiovascular events such as myocardial infarction. The scope of the present consensus paper is to comprehensively discuss the management of skeletal fragility in CKD patients, from diagnosis to treatment, with a particular focus on vertebral fractures in CKD G4–G5D.

Keywords: bone mineral density, chronic renal insufficiency, CKD-MBD, skeletal fragility, vertebral fractures

GRAPHICAL ABSTRACT



SUMMARY OF MAIN RECCOMANDATIONS FOR DIAGNOSIS AND TREATMENT OF VERTEBRAL FRACTURES IN PATIENTS WITH CKD G4–5D

Fracture risk in CKD

1. Patients with chronic kidney disease (CKD) are exposed to a variety of risk factors that increase the likelihood of developing vertebral fractures (VFs). Although CKD does not appear to increase the risk of VFs per se, VFs are a common complication of skeletal fragility in people with CKD, affecting up to 50% of patients.
2. VFs have been identified as a significant risk factor for myocardial infarction both in the general population and in haemodialysis (HD) patients, highlighting the association between skeletal fragility and cardiovascular complications in this population.
3. VFs are associated with higher mortality both in predialysis and dialysis patients.

Diagnosis of VFs in CKD

1. VFs can be defined as an alteration in the shape and size of the vertebral body arising from low-energy trauma or in the absence of any triggering factor.

2. The diagnosis of recent VFs is often based on clinical suspicion due to acute back pain. In addition to lateral thoracic and lumbar X-rays, magnetic resonance imaging should be useful to detect oedema, which is characteristic of symptomatic recent fractures.
3. Most VFs are asymptomatic. To evaluate the presence of such silent VFs, thoracic and lumbar (T4–L4) X-rays in a lateral projection or lateral dual-energy X-ray absorptiometry (DXA) is needed, with a semiquantitative method (using the Genant's visual assessment tool) or manual or computerized quantitative vertebral morphometry (QVM).
4. Thoracolumbar lateral spine X-rays also allow for evaluation of abdominal aortic calcification (AAC).

Assessment of bone health

1. DXA-based T-scores inform on reduced bone mass in the form of osteopenia (T-score of −1 and −2.5) or osteoporosis (T-score <−2.5). Given the increased fragility and comorbidities in CKD, a more conservative T-score threshold (−2.0 or −1.5) may be warranted.
2. FRAX (the Fracture Risk Assessment Tool) may predict the probability of fractures in CKD G3 but appears less reliable from G4 and further evidence is needed for CKD G5–5D.
3. The trabecular bone score, which measures grey-level textural variations of DXA images of the lumbar spine, shows promise for assessment of microarchitectural damage in CKD.
4. Radiofrequency echographic multispectrometry is a recent ultrasound technology that can assess both bone microarchitecture and bone density and may prove useful for rapid, bedside assessment of fracture risk.
5. Bone status indices are biomarkers released from bone during the process of skeletal remodelling, which may contribute to defining the status of the skeleton. Clearance by the kidney needs to be considered in the context of CKD.

Non-pharmacological interventions in VFs related to CKD

1. Routine physical exercise, especially aerobic (adapted to patients' clinical state), has been shown to improve the physical, cognitive and social well-being of patients, especially those receiving dialysis.
2. Lifestyle interventions such as smoking cessation, weight-bearing exercise, improved nutrition and limiting alcohol intake should be considered. Fall risk should be periodically monitored, for example, by tests of neuromuscular function (such as timed up-and-go and 6-minute walk tests).
3. Dietary balance is important for musculoskeletal health. Adequate intake of calcium (800–1000 mg/day), adequate serum concentrations of 25-hydroxyvitamin D (target serum value ≥30 ng/ml) and vitamin K1 (target serum value >0.4 nmol/l) may optimize musculoskeletal status of patients with CKD.

Osteoporosis treatment in CKD mineral and bone disorder–related VFs/skeletal fragility

1. Before initiating antiresorptive or anabolic therapy for CKD-associated osteoporosis, it is good clinical practice to first correct CKD-associated uraemic and mineral metabolism disturbances, including metabolic acidosis, vitamin D deficiency, vitamin K deficiency, hypocalcaemia, hyperphosphataemia and hyperparathyroidism.
2. The presence of VFs is an indication to consider bone-targeted treatment.
3. Not all available bone-targeted treatments are approved for use in patients with advanced CKD or those on dialysis. Thus their administration is considered off-label and formal informed consent may be required.
4. There is currently no available data on the effects of standard osteoporosis therapies on VFs in advanced CKD G4–5D.
5. Antiresorptive (bisphosphonates and denosumab), anabolic (teriparatide and abaloparatide) and mixed agents (romosozumab) can be utilized for osteoporosis therapy in CKD G1–3, as in the general population.
6. Antiresorptive drug administration for osteoporosis treatment in CKD G4–5D requires careful evaluation of risk:benefit ratios. Bisphosphonates are off-label (for patients with an estimated glomerular filtration rate (eGFR) <30 ml/min/1.73 m^2). Denosumab therapy should not be interrupted, as this may lead to a rebound effect with rapid bone loss and an increased risk of VFs. Further, the risk of hypocalcaemia after denosumab is high, particularly for patients receiving dialysis. However, its use in CKD G4–5D may be associated with hypocalcaemia that may be severe.
7. Anabolic drug administration for osteoporosis treatment in CKD G4–5D requires careful evaluation of the risk:benefit ratio. Teriparatide and abaloparatide are off-label (for patients with eGFR <30 ml/min/1.73 m^2) but may be considered for CKD patients at high fracture risk and low bone turnover. Treatment duration should not exceed 24 months.
8. Romosozumab, a mixed antiresorptive and osteoanabolic drug, is associated with increased cardiovascular risk and thus patients should be carefully evaluated and monitored if this therapy is considered in the setting of CKD.
9. No specific sequential treatment strategies tailored for the CKD population are currently available.

Monitoring of VFs

1. In patients with advanced CKD, it is recommended to perform regular (every 12 months) thoracolumbar (T4–L5) lateral X-rays to diagnose VFs and AAC.
2. DXA scans should be performed routinely for patients considered at high risk of fracture and should be repeated every 12–24 months to monitor the effects of therapy.
3. It is recommended to routinely monitor mineral metabolism parameters and optimize therapy for hyperparathyroidism, hyperphosphataemia and hypocalcaemia to lower VF risk.
4. In patients with CKD, it is recommended to prioritize monitoring non-kidney-retained bone turnover markers such as bone-specific alkaline phosphatase, intact procollagen type I N-propeptide and tartrate-resistant acid phosphatase 5b.

Systems of care: multidisciplinary

1. The implementation of a fracture liaison service (FLS) is a fundamental requirement of osteoporosis care. This FLS establishes a multidisciplinary team (from surgical to medical) within the hospital system for comprehensive care of patients following a fracture.

INTRODUCTION AND EPIDEMIOLOGY OF VERTEBRAL FRACTURES (VFs) IN CKD

Chronic kidney disease mineral and bone disorder (CKD-MBD) is a common complication of CKD that arises early in the course of the disease. The skeletal derangements associated with CKD-MBD are associated with bone loss, altered bone quality and

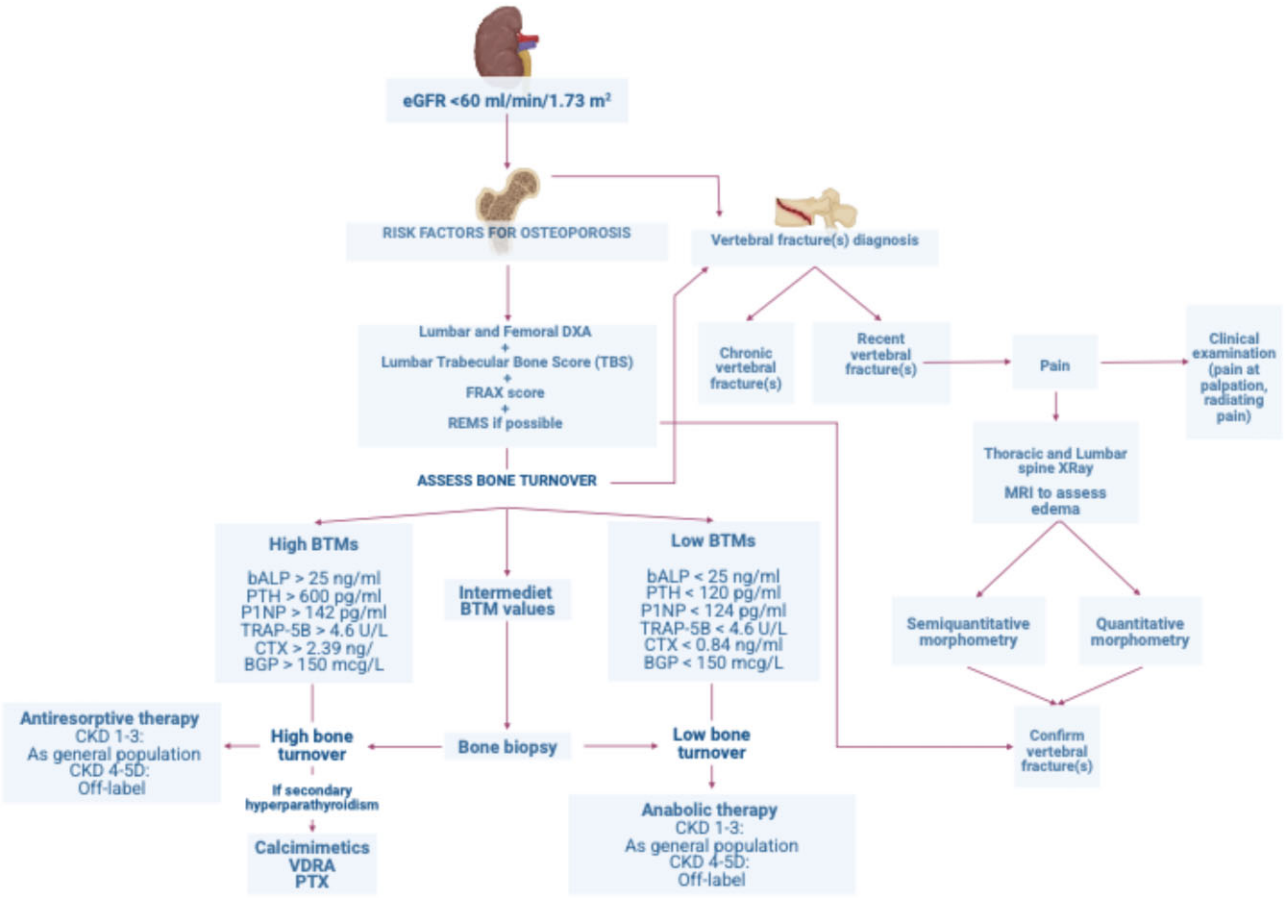


Figure 1: Skeletal fragility management algorithm for CKD patients. ALP: alkaline phosphatase; P1CP: procollagen type 1 C-terminal propeptide; CTX: C-terminal cross-linking telopeptide of type I collagen. Created in BioRender. Cossettini, A. (2025) https://BioRender.com/g50tsii.

increased risk of fractures. Fractures in CKD are not only common but also frequently neglected and associated with significant increased morbidity and mortality [1]. This has prompted a call to action, as bone and mineral disorders in CKD have been recognized for their important implications in cardiovascular health and aging [2]. Recently, the term CKD-associated osteoporosis was coined to increase awareness and prompt researchers and clinicians to focus on patient-relevant outcomes rather than biochemical abnormalities [3].

In advanced CKD, the hip is one of the most commonly affected fracture sites, likely due to cortical bone damage caused by secondary hyperparathyroidism [4]. The risk of hip fracture is four times greater for CKD patients than for people with normal kidney function [5]. VFs, on the other hand, are the consequence of reduced trabecular thickness [6]. Acute VFs are painful and characterized by lumbar and/or dorsal pain (depending on the location of the fracture), which worsens on palpation and may radiate anteriorly [1]. Furthermore, recent VFs, if investigated radiologically with computed tomography (CT) or magnetic resonance imaging (MRI), are generally surrounded by oedema (Fig. 1) [1]. However, many VFs are asymptomatic, which makes the diagnosis difficult without systematic screening.

The reported incidence and prevalence of VFs vary considerably, likely because of case mix (e.g. age, sex and CKD stage) and differences in diagnostic approach. The prevalence of VFs in CKD is comparable to that of the general population and has been estimated at 18–34% to >50%, as diagnosed by a semi-quantitative method or quantitative vertebral morphometry (QVM), respectively [7–9]. A similarly high prevalence of VFs has been demonstrated in kidney transplant recipients [10, 11].

Importantly, the presence of VFs is associated with increased mortality both in CKD and in the general population [7, 12].

The scope of the present consensus paper is to comprehensively discuss the management of skeletal fragility in CKD patients, from diagnosis to treatment, with a particular focus on VFs in CKD G4–5D.

METHODS

This consensus paper was prepared by requesting input on topics related to the management of VFs in CKD patients from members of the SKeletal fragilitY-Chronic Kidney Disease IOF Working Group (SKY-CKD IOF WG), the European Society for Clinical and Economic Aspects of Osteoporosis, Osteoarthritis and Musculoskeletal Diseases (ESCEO), the CKD-MBD Working Group of the ERA and the European Renal Osteodystrophy Working Group (EUROD). Opinion leaders were identified based on objective criteria (peer-reviewed publications in CKD-MBD and VFs, involvement in guideline development and recognized clinical expertise). The involvement of multiple experts from various worldwide scientific organizations did not allow for face-to-face interaction. However, the manuscript was developed through interaction by queries, replies and comments shared in the expert panel (Delphi-like), which was consequently prolonged for almost 2 years to obtain the best results set in this consensus statement.

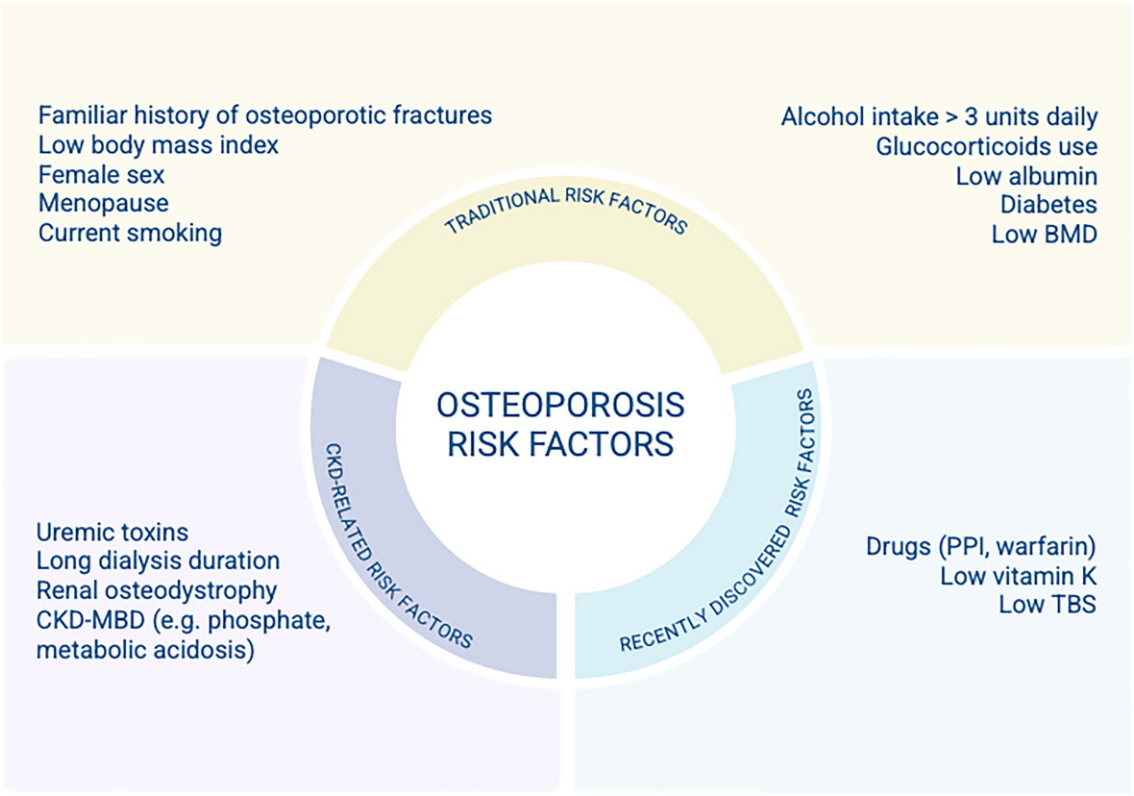


Figure 2: Osteoporosis risk factors in the general population and CKD patients. Created in BioRender. Cossettini, A. (2025) https://BioRender.com/dvkjq0q.

FRACTURE RISK IN CKD

A combination of traditional, recent and kidney-related risk factors contribute to the increased risk of fractures seen in CKD (Fig. 2). Unlike hip fractures, a decrease in the estimated glomerular filtration rate (eGFR; <45 ml/min/1.73 m^2) was not frequently associated with VFs [13].

Mineral metabolism disturbances are prominent in the pathogenesis of bone fragility and VFs in CKD patients. Elevated serum phosphate levels may contribute to skeletal deterioration through multiple mechanisms, including secondary hyperparathyroidism, impaired bone mineralization and vascular calcifications [14]. The association between hyperphosphataemia and skeletal fragility has been demonstrated in several studies, including analysis of the Dutch Rotterdam Study and the US Osteoporotic Fractures in Men Study (MrOS) [15]. Bone mineral density (BMD) was analysed in 12 216 participants. Higher phosphate levels were linked to an increased risk of fractures in men [15], while in women the association was weaker but still notable. A dose-dependent relationship was observed, indicating that phosphate levels are correlated with various types of fractures. The most pronounced connection was found between phosphate levels and VFs in men, particularly with kidney dysfunction [15].

The COSMOS (Current management Of Secondary hyperparathyroidism: a Multicentre Observational Study) is a 3-year, multicentre, prospective, observational cohort study involving 6797 haemodialysis (HD) patients across 227 centres in 20 European countries with a follow-up of 24 months. The study found that patients with baseline serum phosphate levels >6.1 mg/dl had a significantly higher fracture risk compared with those with levels between 4.3 and 6.1 mg/dl. Phosphate levels were particularly related to an increased risk of non-VFs, while no significant correlation was observed for VFs [16].

Thus, while higher phosphate levels are linked to increased fracture risk in CKD population, emerging evidence shows that even hypophosphataemia may be harmful, especially in kidney transplant recipients [6].

Moreover, hyperphosphataemia promotes arterial stiffness and microvascular damage [17]. The correlation between VFs and vascular calcifications (VCs) in CKD patients is increasingly recognized as a significant clinical concern. VCs may also contribute to skeletal disease through increased arterial stiffness, reducing blood flow to the bone and impairing its remodelling capacity [18].

Clinical studies have shown that the presence of aortic and coronary calcifications is independently associated with an increased risk of VFs in the general population and in CKD. A large meta-analysis by Gebre *et al.* [18] involving 86 articles and 61 553 patients found that abdominal aortic calcification (AAC) was associated with a greater risk of any fracture {relative risk [RR] 1.73 [95% confidence interval (CI) 1.48–2.02]} and VFs and non-VFs increased with increasing severity of AAC, with the highest values of AAC in case of VFs [18]. These data are confirmed by the EVOS (European Vertebra Osteoporosis Study) involving 624 men and women >50 years of age, which showed a strong association between VFs and severe AAC [19].

In CKD, the EVERFRACT (Epidemiological VERtebral FRACtures iTalian) study [9], a multicentre, observational study involving 387 patients receiving HD, provided important insights into the prevalence of VFs and VCs. One of the key findings of the EVERFRACT study was the strong association between VFs and both aortic and iliac artery calcifications [9]. Notably, when these calcifications were considered together, the odds ratio (OR) for VFs was almost 3, indicating a significantly higher risk. Importantly, spinal radiography allows for the simultaneous evaluation of VFs and AAC [20]. There are different methods to evaluate VCs, but the most widely

used is a semi-quantitative Kauppila score [21], which divides the severity of AAC into four grades (affected segments score, range 0–24) [21]. A recently proposed quantitative method, Calcify2D, precisely measures the extent of calcifications [22]. Improved reproducibility, both intra-and interobserver, has been suggested, with a higher intraclass correlation coefficient in the first series (0.78 versus 0.64), a 25% reduced minimum detectable difference and significantly higher values and an increasing trend with calcification severity compared with the Kauppila score [22]. Furthermore, the lateral image can provide insights into whether BMD measurements are biased upward due to overlaying calcified structures, although the contribution of AAC to bias the lumbar spine BMD has been recently challenged [23].

Conversely, the presence of VFs may predispose individuals to a higher risk of coronary artery disease and heart attacks. A study by Tankò *et al.* [24] involving 2576 women in the general population with a mean age of 66.5 years and a follow-up of 4 years found that the risk of cardiovascular events increased progressively with the increase in the number and severity of VFs. Another study from South Korea [25] analysed data from 38 935 patients with CKD, including 11 379 receiving HD and 27 556 with pre-dialysis CKD. A total of 5057 patients (13%) experienced a fracture, while 1431 (3.7%) had a myocardial infarction (MI) [25]. The study found that fractures were significantly associated with MI in patients on HD (OR 1.47, $P = .034$), whereas no significant correlation was observed in pre-dialysis CKD patients (OR 1.04, $P = .751$) [25]. Further subgroup analysis by fracture site revealed that VFs specifically were linked to an increased risk of MI in patients on HD (OR 2.11, $P = .024$), whereas femoral or other site fractures did not show a significant association [25]. This link between VFs and cardiovascular events may explain the higher mortality observed across CKD stages 3–5D [7, 26].

Both high and low circulating parathyroid hormone (PTH) levels have been shown to be associated with a high fracture rate [27, 28]. A U-shaped curve has been used to describe the relationship of PTH levels with fracture risk [27]. Jansz *et al.* [29] analysed lateral chest X-rays of 146 dialysis patients who were kidney transplant candidates to assess for the presence of VFs. The association with PTH also appeared in this case with a U-shaped curve and an RR of prevalence of VFs of 2.28 for the lowest tertile and 2.82 for the highest tertile compared with the middle tertile, where VFs were less present [29].

The VItamin K Italian (VIKI) study, which involved 387 HD patients (18 Italian units), found that low concentrations of vitamin K1 were the strongest predictor of VFs [OR 2.94 (95% CI 1.38–6.26), $P = .0053$] and that a deficiency in menaquinone 4 (MK4, a type of vitamin K2) was the most significant predictor of aortic calcification [OR 2.82 (CI 1.13–7.01), $P = .03$] [30].

DIAGNOSIS OF VFs IN CKD

None of the imaging approaches on their own have provided sufficient evidence to recommend their use in the clinical setting to identify CKD-associated osteoporosis. However, these techniques may be performed together to gain information on patients at high risk of (vertebral) fractures. How to use the tools at our disposal to evaluate the risk of fracture is provided in the algorithm in Fig. 1.

VFs refer to structural changes in the shape and size of the vertebral body, typically resulting from low-energy trauma or occurring spontaneously without any apparent triggering factor [31]. The diagnosis of acute VFs is primarily based on clinical suspicion, as patients often present with sudden and intense dorsal pain that can radiate anteriorly towards the hemicostal region [32]. This pain may be exacerbated by movement or changes in posture, significantly affecting the patient's mobility and quality of life [32]. However, as symptoms are sometimes non-specific or lacking, imaging studies are crucial to confirm the presence of a fracture and assess its severity.

Standard radiographic evaluation such as thoracic and lumbar (T4–L4) lateral X-rays or lateral dual-energy X-ray absorptiometry (DXA) should be performed, as recently suggested by the Kidney Disease: Improving Global Outcomes (KDIGO) group [3] to evaluate deformations in vertebral height, endplate irregularities or wedge-shaped deformities indicative of compression fractures [31]. While X-rays provide an initial assessment, they may not be able to differentiate between old, asymptomatic fractures and new, clinically relevant ones [32]. For this reason, MRI plays a critical role in the diagnostic process. MRI is particularly valuable in identifying bone marrow oedema, a hallmark of recent, symptomatic fractures, as it appears as increased signal intensity on T2-weighted and short tau inversion recovery sequences [32]. This distinction is essential for guiding appropriate treatment, as acute fractures may require different management strategies compared with chronic, stable fractures. VF assessment and/or lateral spine imaging is also recommended in patients with a history of height loss ≥4 cm [6].

Lateral radiographs are the most commonly used imaging approach to diagnose VFs. Thoracolumbar lateral radiography can be used to evaluate VFs both semi-quantitatively and quantitatively [33]. In the first case, VFs are classified according to Genant's classification into grade 1 (mild, reduction of the vertebral height of 20–25%), grade 2 (moderate, reduction of the vertebral height of 25–40%) and grade 3 (severe, reduction of vertebral height >40%) [33]. These fractures can have a wedge, biconcave or compression shape depending on whether they affect the anterior (a), middle (m) or posterior (p) height of the vertebra [33].

QVM defines VFs as a decrease in the vertebral height ≥20%, from T4 to L4, assessed using manual or computerized measurements of vertebral body height (H) with conventional radiographic methods, such as morphometric X-ray radiography [33]. Specifically, Ha/Hp indicates a wedge VF, Hm/Hp denotes a biconcave VF and Hp/Hp represents a crush VF. Both the number and grade of prevalent VFs represent strong predictors of future fragility fracture risk [33]. Furthermore, the type of VFs can allow a differential diagnosis of the disease: systemic involvement due to bone fragility (as in the case of osteoporotic fractures) typically presents as a wedge deformity while, for example, neoplastic fractures manifest themselves with involvement of the posterior border of the vertebral body (crush) [34]. The purpose of QVM is to measure vertebral body heights to increase the reproducibility of qualitative readings, particularly when evaluating atraumatic and asymptomatic vertebral deformities [33]. Of clinical importance is that the presence of one or more VFs at baseline increases the risk of sustaining a VF by 5-fold in the following year [35].

The key studies evaluating VFs in CKD patients are summarized in Table 1. Few studies have evaluated VFs using QVM; most have employed the semi-quantitative method, predominantly highlighting a wedge deformity and increased involvement of the T11, T12 and L1 vertebrae in both pre-dialysis and dialysis patients [7, 9]. As previously described, dorsolumbar lateral X-ray also allows for evaluation of AAC.

ASSESSMENT OF BONE HEALTH

Since the 2017 update of the KDIGO guidelines [36], which recommended the performance of DXA in patients with CKD if results would impact treatment decisions, several studies have

Table 1: Main studies on VFs in CKD patients.

Authors	Year	Stage of CKD	Prevalence of vertebral fractures, %	Assessment method
Mohini *et al.* [105]	1991	HD	8	Semi-quantitative
Atsumi *et al.* [106]	1999	HD	20.9	Semi-quantitative
Nam *et al.* [107]	2000	Transplanted	38.5	Semi-quantitative
Patel *et al.* [108]	2001	Transplanted	9.1	Semi-quantitative
Durieux *et al.* [109]	2002	Transplanted	44	Semi-quantitative
Rodriguez-Garcìa *et al.* [110]	2003	HD	19.1	Semi-quantitative
Mares *et al.* [111]	2009	HD	21	Semi-quantitative
Rodriguez-Garcìa *et al.* [8]	2009	HD	26.5	Semi-quantitative
Giannini *et al.* [10]	2010	Transplanted	57	Quantitative
Fusaro *et al.* [26]	2013	HD	55.3	Quantitative
Castro-Alonso *et al.* [7]	2020	3–5	18	Semi-quantitative
Jansz *et al.* [34]	2020	HD	34	Semi-quantitative
Jirasiririrak *et al.* [112]	2022	HD	27.5	Semi-quantitative
Bover *et al.* [113]	2024	3–5D	19.1	Semi-quantitative

demonstrated the importance of low BMD in predicting fracture risk across all stages of CKD [27]. In a study of 485 HD patients, Iimori *et al.* [27] demonstrated the importance of BMD in identifying prevalent VFs. Specifically, BMD of the total hip, femoral neck/trochanter and 1/3 distal radius (in this order) was found to be useful in predicting future fractures in female patients. In 2021, a European consensus manuscript highlighted the importance of adjusting the T-score value to the frailty of patients with CKD, suggesting that in this population an appropriate diagnostic and treatment threshold value could be a T-score <-2 or even <-1.5 [37].

However, DXA has limitations, including its inability to differentiate between types of renal osteodystrophy (ROD), its lack of distinction between cortical and trabecular microarchitecture and its relatively low resolution. [38]. Recently, novel software solutions like 3D DXA (3D-SHAPER; https://www.3d-shaper.com/en/index.html) have been developed to estimate cortical and trabecular bone compartments using three-dimensional statistical modelling, providing information on thickness and surface, trabecular volumetric BMD as well as geometric bone parameters [39]. Emerging studies are now reporting the use of 3D-DXA in CKD patients [40], although it remains to be seen if these measures will provide benefit in fracture prediction or prove superior to regular DXA in discriminating particular types of fractures, such as VFs.

FRAX (https://www.sheffield.ac.uk/FRAX) is the most widely used tool for assessing fracture risk. It uses 12 risk factors that, when combined, provide a score of probability of developing a bone fracture in the following 10 years adjusted for the competing risk of death [37]. Although CKD is not included as a cause of secondary osteoporosis in FRAX, the tool has been shown to preform reasonably well in patients with CKD who are not on dialysis, particularly in CKD G1–3, where CKD-MBD–related skeletal abnormalities are less probable [41–44]. However, in patients with CKD G4–5D the precision seems reduced [26], as FRAX does not account for reductions in bone quality, including microarchitectural and mechanical properties of the bone [6, 45]. It should also be considered that in the FRAX algorithm, VFs are not considered separately from other fractures [32]. Combining with BMD, the FRAX score may improve fracture risk prediction compared with FRAX alone, at least in the general population [46].

FRAXplus (https://www.fraxplus.org/frax-plus) allows for the modification of fracture risk prediction with additional risk factors such as higher-than-average exposure to glucocorticoids, information on trabecular bone score (TBS), number of falls in the previous year, duration of type 2 diabetes, concurrent information on lumbar spine BMD and high axis length; however, CKD is not yet accounted for in it. Other available risk assessment tools include QFracture (which accounts for CKD) and the Garvan model [34].

Another software solution available for the extraction of additional information from conventional DXA scans is TBS, which measures grey-level textural variations related to the microarchitecture from L1 to L4, thus providing an evaluation of the bone quality, namely the microarchitecture [6].

A recent meta-analysis [47] evaluated TBS as a marker of skeletal fragility across the spectrum of CKD. It found that lower TBS values were observed in CKD patients not on dialysis [−0.057 (95% CI −0.090 to −0.024), $P < .01$], in those on dialysis [−0.106 (95% CI −0.141 to −0.070), $P < .01$] and in kidney transplant recipients [−0.058 (95% CI −0.103 to −0.012), $P = .01$] compared with non-CKD [47]. Concerning fracture risk, TBS was not able to predict incident fractures in patients not yet on dialysis when fully adjusting the model for FRAX. However, in patients, those on dialysis with prevalent fractures had lower TBS values compared with those without fractures [47]. Among kidney transplant recipients, current evidence is insufficient to support a clear association between TBS and fracture risk [47].

REMS is a recent ultrasound technology that assesses bone health at the lumbar vertebrae and other axial sites [48]. From the image created, BMD, T-score, Z-score and Fragility Score can be calculated, allowing for evaluation of both bone quantity and quality [48]. REMS offers a detailed characterization of bone macro- and microarchitecture while minimizing interference from vascular calcifications, osteophytes and metallic implants, resulting in more precise measurements [48]. This technique has demonstrated good reliability in assessing bone health status in various studies on the general population. The literature on CKD patients remains limited. A study by Fassio *et al.* [49] from a real-life cohort of 41 patients receiving peritoneal dialysis therapy showed an agreement between REMS and lateral DXA (0.321, $P = .026$), while no significant agreement was revealed for REMS at

Table 2: Bone biomarkers classification.

Bone status indices	Renal clearance	HD clearance	High-turnover cut-off		Low-turnover cut-off		Hip fracture cut-off
			Salam [52]	Jørgensen [104]	Salam [52]	Jørgensen [104]	Imori [27], Maruyama [103]
Bone metabolism							
PTH (pg/ml)	Yes	Yes	>327	>143.5	< 83	<90.5	
Bone formation							
ALP (U/L)			>102	>97	<88	<87	>405
BALP (μg/L)	No	No	>31	>33.7	<21	<24.7	>27.4
PINP (μg/L)	No	No	>107	>120.7	<57	<49.8	
Bone resorption							
TRAP5b (U/L)	No	No	>4.6	>5.05	<4.6	<3.44	

P1CP: procollagen type 1 C-terminal propeptide.

the lumbar spine and anteroposterior DXA. At the femoral neck and at the total hip an agreement of 0.445 ($P < .01$) and 0.784 ($P < .001$) was found, respectively [49]. Furthermore, good performance of REMS compared with especially anteroposterior DXA in excluding artifacts from vascular calcifications was described [49].

Bone biopsy with histomorphometry remains the gold standard for the assessment of bone turnover, however, its widespread utility is limited by its invasive nature, expense and availability [50]. A quest for biomarkers that could achieve an acceptable diagnostic performance to predict the histomorphometric picture of a bone biopsy specimen has resulted in various studies that have explored the diagnostic utility of various biomarkers to differentiate between low, normal or high turnover in CKD-MBD.

Bone turnover markers (BTMs) are substances generated during bone metabolism that provide insights into bone health [51]. In CKD, BTMs are useful for assessing bone turnover and fracture risk, especially concerning skeletal fragility. Bone biomarkers can be classified as markers of bone metabolism, bone formation and bone resorption (Table 2) [52].

A study from Tamaki *et al.* [53] investigated the role of BTMs in predicting VFs in postmenopausal women. It found that elevated levels of both bone formation markers [such as bone alkaline phosphatase (BALP)] and bone resorption markers were associated with an increased risk of VFs over 10 years. This risk was independent of BMD in women who had been postmenopausal for ≥5 years. Specifically, high BALP levels were strong predictors of fractures, with an RR of 2.07 [53]. Unfortunately there are no data available on the use of BTMs as predictors of VFs in CKD.

NON-PHARMACOLOGICAL INTERVENTION IN SKELETAL FRAGILITY RELATED TO CKD

Sarcopenia is a major negative consequence of CKD. It decreases quality of life, contributing to falls, fractures and poor outcomes, thus increasing morbidity and mortality in the general and CKD population [54, 55]. Sarcopenia is almost universally present in older individuals and in patients with advanced CKD [54]. Whether the extent of muscle loss is related to renal disease progression is unclear, as most studies are cross-sectional and focused on dialysis populations. A recent study highlighted the various factors that accelerate muscle protein degradation and impair protein synthesis and repair pathways in individuals with CKD and sarcopenia [56–58]. These factors include a chronic catabolic state, metabolic acidosis, insulin and insulin-like growth factor 1 resistance, chronic inflammation, uraemic toxins, malnutrition, increased oxidative stress and impairment of muscle oxygen supply in dialysis patients [59]. Additionally, some antihypertensive drugs, such as beta blockers, have been shown to increase the rate of decline in muscle mass and function, while others, such as renin–angiotensin system inhibitors, have shown neutral effects [60]. Finally, low serum 25-hydroxyvitamin D [25(OH)D] concentrations are associated with severe sarcopenia in individuals with CKD G3–4 and those on HD [61].

Current prevention and treatment strategies for sarcopenia in CKD are limited due to the systemic nature of the initiating signals and the multifaceted catabolic mechanisms that accelerate muscle protein degradation while impairing protein synthesis and repair pathways [62]. Most interventional studies have focused on exercise in the dialysis population. Physical exercise has been used as a modulator of the purinergic system in CKD patients on HD, with beneficial effects on sarcopenia [62]. In a systematic review ($n = 64$ trials) and meta-analysis ($n = 19$ trials), intradialytic exercise has been shown to increase handgrip strength [standardized mean difference 0.58 (range 0.24–0.91); $P = .0007$; $I^2 = 40\%$] and 60-second sit-to-stand score [mean difference 3.74 repetitions (range 2.35–5.14); $P < .001$; $I^2 = 0\%$] [56].

Other non-pharmacologic strategies with proven antifracture efficacy should be utilized in all patients. For example, 60% of the observed reduction in fracture incidence in the general population has been attributed to lifestyle interventions, including smoking cessation, weight-bearing exercise, improved nutrition and moderating alcohol intake [37].

A history of falls is recognized as an independent risk factor for fractures in the general population and this association holds for CKD patients as well [63]. Furthermore, patients undergoing dialysis face an even greater fall risk than those with CKD who are not on dialysis [64–66]. Beyond pharmacological intervention, fall prevention strategies should also be prioritized to reduce fracture risk. Simple screening tools, such as fall risk questionnaires, provide useful estimates of an individual's susceptibility to falls. Additionally, neuromuscular function tests—including the timed up-and-go test and the 6-minute walk test—can help identify CKD patients with an increased fracture risk, likely due to reduced muscle strength and balance impairments [67].

Given the strong link between falls and fractures, physicians should not only assess fracture risk through traditional bone health parameters but also implement targeted interventions aimed at improving muscle function, optimizing medication regimens and addressing sensory deficits. A multifaceted approach that includes both medical management and fall prevention

strategies is crucial in reducing fracture incidence and improving the overall quality of life in CKD patients.

DIETARY CONSIDERATIONS

Calcium intake of 800–1000 mg/day (but not beyond 1500 mg/day) and vitamin D intake to keep levels of 25(OH)D above the recommended threshold of 30 ng/ml is a crucial intervention in the prevention and treatment of osteoporosis in CKD patients [3, 42].

As for vitamin K, several studies have demonstrated the importance to maintaining plasma concentrations >0.4 nmol/l. In particular, in a study conducted on 535 women hospitalized following a fall, better physical function and lower long-term injurious falls risk were observed with the intake of vitamin K1 [68]. Another study, this time conducted on 523 patients on HD, evaluated the effect of vitamin K on muscle cramps. A beneficial effect of vitamin K2 (MK) emerged, which reduced the frequency, duration and severity of muscle cramps [69]

CKD-MBD TREATMENT TO PREVENT VFs

In the most recent KDIGO guidelines [3], ROD has been incorporated into the broader definition of CKD-associated osteoporosis, emphasizing its role in disorders of bone strength. By integrating ROD into the definition of CKD-associated osteoporosis, the guidelines provide a more comprehensive framework for understanding and managing bone health in CKD patients [3]. This new concept enhances treatment approaches by encouraging a more holistic management of skeletal fragility, incorporating CKD-MBD therapy alongside traditional osteoporosis treatments [3].

Before initiating an antiresorptive or anabolic agent to treat CKD-associated osteoporosis, we stress the importance of optimizing the management of uraemia and mineral metabolism disturbances of CKD, including rectification of imbalances as metabolic acidosis, vitamin D deficiency, vitamin K deficiency, hyperphosphataemia and hyperparathyroidism. Correction of 25(OH)D deficiency can at least partially correct elevated PTH levels in patients with mild to severe CKD [37]. Furthermore, data in patients with CKD G5D suggest that 25(OH)D >30 ng/ml optimizes bone mineralization [70]. Studies have suggested that in addition to vitamin D analogues, the use of calcimimetics such as cinacalcet may reduce the risk of fractures in CKD patients with secondary hyperparathyroidism, as observed in a secondary analysis of the EVOLVE trial (NCT00345839) [71].

In a secondary analysis of the VIKI study, 177 of 387 (45.7%) patients on HD were treated with oral calcitriol. In multivariable logistic regression analysis, oral calcitriol was associated with 40.2% reduced odds of VFs (OR 0.598, $P = .043$) without an increase in VF compared with untreated patients [72].

In another secondary analysis of the VIKI study [73] it was highlighted by multivariate logistic regression that MK4 deficiency was associated with sevelamer use (OR 2.64, $P = .011$) and aortic calcification [OR 8.04 (95% CI 1.07–60.26), $P = .04$]. In the same logistic model, in patients treated with sevelamer, total oral calcitriol levels <150 μg/l compared with those with total oral calcitriol ≥150 μg/l were associated with a higher VF risk (OR 3.15, $P = .003$) [73].

Although data on vitamin K supplementation related to skeletal fragility in CKD are few and inconsistent, there are encouraging data on the general population, especially vitamin K1 and MK4, highlighting a significant reduction of bone/vertebral fractures [74]. The beneficial effects of vitamin K on vascular calcifications are still a matter of debate.

OSTEOPOROSIS TREATMENT IN CKD-MBD–RELATED VFs/SKELETAL FRAGILITY

Bone biopsy remains the gold standard for evaluating skeletal health, providing crucial insights into bone turnover and mineralization defects. This has proved essential in understanding that it is best to start therapy in patients with CKD-associated osteoporosis [75]. However, a major challenge in managing osteoporosis in advanced CKD and dialysis patients is the lack of approved therapies specifically tailored to this population. Most current osteoporosis treatments are not officially approved for use in individuals with severe CKD or those undergoing dialysis, causing their administration to be off-label and often necessitating formal informed consent [37]. Additionally, there is a significant lack of clinical data on the efficacy and safety of standard osteoporosis treatments for preventing or managing VFs in advanced CKD (stages 4–5D), as most research focuses on hip fractures. This is particularly noteworthy since identifying VFs is crucial for initiating osteoporosis treatment in these patients, making VF assessment a key component of their management [3].

Treatment may involve the use of different drugs depending on the type of underlying metabolic bone disorder [5]. The drugs used are generally antiresorptive (bisphosphonates and denosumab), anabolic steroids and dual-action drugs [5]. The characteristics of the various drug classes are described in Table 3. All types of osteoporosis drugs can be administered until CKD G3.

Bisphosphonates have not been recommended in patients with an eGFR <30 ml/min/1.73 m^2 due to concern for excessive accumulation of bisphosphonate in the skeleton, resulting in a potential oversuppression of bone remodelling [76–79].

However, some studies on CKD patients seem to encourage administration of these drugs even in the most advanced stages of kidney disease. Recently a retrospective Danish study of 71 patients with CKD stage 3b–5 compared alendronate with placebo and found increases in femoral, lumbar and hip BMD in the treated group compared with untreated patients [77]. In a 6-month, double-blind, controlled study in 42 renal transplant recipients with an eGFR >30 ml/min/1.73 m^2 within 2 weeks of transplantation who received 4 mg of zoledronate [80], there was a significant increase in lumbar and whole-body BMD and a significant increase in femoral neck bone strength parameters with no significant differences in mean changes in serum creatinine and other biochemical parameters between the two groups. However, there was no significant difference in the development of new VFs between the treated and untreated groups [80]. Furthermore, several studies have proven that patients treated with bisphosphonates experience a reduction in the risk of hospitalization for cardiovascular events [81, 82].

Finally, a moderate risk for CKD progression in patients with CKD stages 3b–5 treated with oral bisphosphonates was found in a large observational study [83]. However, in one cohort this treatment was associated with improved survival, but only after propensity score matching [83, 84].

Denosumab is a monoclonal antibody used in the treatment of osteoporosis. It inhibits osteoclastogenesis by binding to the ligand receptor of nuclear factor kappa-B (RANKL) [5]. It does not require dose reductions to maintain its tolerability and safety profile and its efficacy in patients with CKD is not compromised, as the drug is not renally metabolized [85]. The role of denosumab in managing osteoporosis in patients with age-related kidney disease was explored in a post hoc analysis of the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months

Table 3: Osteoporosis drugs in CKD patients.

Drug	Mechanism of action	Dose adjustment with CKD	Therapeutic indications	Adverse effect
Antiresorptive agents				
Bisphosphonates	Bind to bone hydroxyapatite sites and inhibit osteoclast-mediated bone resorption	eGFR ≥30 ml/min/1.73 m^2: no dose adjustment recommended; eGFR <30 ml/min/1.73 m^2: use not recommended	High bone turnover states	Osteonecrosis, adynamic bone disease, AKI, eGFR decline, hypocalcaemia
Denosumab	Human immunoglobulin G monoclonal antibody against RANKL, binds RANKL and prevents osteoclast activity	No dose adjustment	High bone turnover states	Osteonecrosis, adynamic bone disease, urinary infections, severe hypocalcaemia, rebound osteoclast activity
Raloxifene	Selective oestrogen receptor modulator, acts as oestrogen agonist in bone	No dose adjustment	Osteoporosis, high bone turnover states	Risk of thrombosis
Anabolic agents				
Teriparatide, abaloparatide	Recombinant human PTH. Similar activity of PTH, stimulates osteoblast activity	No dose adjustment; use not recommended in severe kidney failure	Low bone turnover states	Hypercalcaemia, nausea, worsening of cutaneous calcifications or calciphylaxis
Mixed agent				
Romosozumab	Humanized monoclonal antibody against sclerostin, promotes osteoblast differentiation and activity, transient uncoupling of bone resorption and formation	No dose adjustment	Osteoporosis	Cardiovascular disease or events, hypocalcaemia, arthralgias

(FREEDOM) trial [86]. It analysed denosumab administration in 73 and 2817 women with a creatinine clearance of 15–29 and 30–59 ml/min, respectively, using the Cockroft–Gault formula. There was no interaction between treatment effect and kidney function, and adverse events did not differ by kidney function. Denosumab increased BMD at the spine and hip and resulted in 68% lower odds of VFs in subjects with an eGFR of 30–59 ml/min/1.73 m^2. Iseri *et al.* [40], in a retrospective study of 124 CKD patients on dialysis, highlighted, with DXA 3D, a significant increase in BMD, cortical thickness and strength indices in the hip region for the first 3.5 years. After 3.5 years, a plateau was reached, in contrast with what happens in populations with primary osteoporosis, which instead report a continuous increase in bone parameters even up to 8 years [87]. The discontinuation of denosumab led to a progressive loss of the improvements acquired, as is known to happen, which prevents suspension of the drug in the CKD population, since it would expose them to an increased risk of fractures. For this reason, long-term administration must be considered in advanced CKD patients who start denosumab therapy [88]. Mild to severe and life-threatening hypocalcaemia is a serious concern with denosumab administration in patients with CKD [85, 89]. However, clinical data suggest that denosumab can be safely administered to patients with advanced CKD-associated osteoporosis as long as patients are supplemented with active vitamin D and have an adequate calcium intake with the necessary adjustment of dialysate [90].

The use of osteoanabolic agents, i.e. forms of recombinant PTH or PTH-related peptide (teriparatide and abaloparatide, respectively) and a slow-release molecule recently developed (palopegteriparatide), is still controversial and limited in patients with CKD [5]. If used in CKD G4–5D, they require a careful evaluation of risk/benefit, as they are off-label for eGFR <30 ml/min/1.73 m^2. However, these drugs seem to be especially useful in patients with a very high risk of fracture (i.e. ≥2 VFs, 1 VF or hip fracture + BMD <−3.0 T-score or BMD <−3.5 T-score) due to their ability to decrease fracture risk much more rapidly in the general population. Data on the anti-fracture efficacy of these agents in CKD exist from the Fracture Prevention [91] and ACTIVE (NCT01343004) trials [92] for patients with age-related kidney function decline without CKD-MBD. The Fracture Prevention Trial analysed 1637 patients with renal impairment (CKD G1–3) who were given teriparatide versus placebo. A significant increase in procollagen type 1 N-terminal propeptide (P1NP) and BMD at the lumbar and femoral levels was observed in all stages of CKD, with a similar risk reduction for vertebral and non-vertebral fractures [91]. The ACTIVE trial [92] is a controlled phase 3 study of 2463 postmenopausal female patients with osteoporosis, of whom 627 had an eGFR <60 ml/min/1.73 m^2, who were administered either abaloparatide or teriparatide. What emerged was a statistically significant reduction in VFs in the groups of patients treated with teriparatide and abaloparatide compared with placebo for an eGFR >60 ml/min/1.73 m^2, while in patients with an eGFR <60 ml/min/1.73 m^2, a non-significant reduction in VFs was observed. In the treated arm, a significant increase in BMD was observed at the lumbar and femoral sites in patients with an eGFR <60 ml/min/1.73 m^2 compared with patients with a higher eGFR. Osteoanabolic agents are considered suitable for CKD patients with a high risk of fragility fractures and low bone turnover, or adynamic bone disease [93], which represents the most common bone phenotype in the CKD cohort [94].

Romosozumab is a humanized monoclonal antibody that binds to sclerostin, with inhibitory action and promotion of osteoblast

differentiation and activity [95]. Romosozumab acts as an anabolic and an antiresorptive drug concurrently and leads to a temporary increase in bone formation markers alongside a reduction in bone resorption. This causes a transient uncoupling of bone resorption and formation, making this drug a unique pharmacological agent in the potential treatment of CKD-MBD [95].

Romosozumab has shown promising data in patients with mild to moderate CKD; from the post hoc analysis of the FRAME (NCT01575834) and ARCH (NCT01631214) phase 3 clinical trials, an increase in BMD at the lumbar spine and femoral neck and a reduction of relative risk of new VFs at month 12 are reported across all kidney function categories [95]. Nevertheless, in a study by Saag *et al.* [96], patients given 12 months of romosozumab followed by 12 months of alendronate, compared with 24 continuous months of alendronate, had an increase in serious cardiovascular adverse events [OR 1.31 (95% CI 0.85–2.00)], i.e. ischaemic cardiac and cerebrovascular events. A few small trials have also evaluated the role of romosozumab in patients in advanced CKD [97, 98].

A Japanese prospective, observational, single-centre cohort study included 13 prior osteoporosis patients on HD who first received romosozumab once a month for 12 months (210 mg subcutaneously once every month). They then received denosumab for an additional 12 months (60 mg subcutaneously once every 6 months). After 1 year, an increase in BMD (both in the total hip and femoral neck) and no new VFs were observed during the study period. The same study highlighted a progression in the coronary artery calcium score and thoracic aorta calcium score, especially from 6 months of treatment [97, 98]. Thus a careful balance between the very high risk of fracture and its consequences versus the cardiovascular risk is mandatory when considering the use of romosozumab. Indeed, the current safety warning from the US Food and Drug Administration and the European Medicines Agency is to avoid use in high cardiovascular risk patients [99].

MONITORING OF VFs/SKELETAL FRAGILITY

In managing patients with advanced CKD, it is suggested to perform lateral X-rays of the thoracic and lumbar spine (T4–L5) to assess VFs and AAC [3]. For example, for patients initiating renal replacement therapy, such as HD or peritoneal dialysis, X-rays are advised to monitor for VFs and AAC (every 12 months) [22]. DXA scans should be repeated every 12–24 months to monitor BMD changes and evaluate bone health status or the effectiveness of osteoporosis treatments [37]. In CKD patients, it is advisable to monitor non-kidney-retained BTMs, such as BALP, P1NP, and tartrate-resistant acid phosphatase 5b (TRAP-5b). These markers provide valuable insights into bone turnover rates and help guide therapeutic interventions, as they are less influenced by renal function compared with other markers [100]. Implementing these recommendations can enhance the early detection and management of bone and vascular complications in CKD patients, ultimately improving their quality of life and clinical outcomes. Prospective studies are needed to better understand the association between BTMs and VFs.

SYSTEMS OF CARE: MULTIDISCIPLINARITY

A fracture liaison service (FLS) is a multidisciplinary, system-level approach designed to reduce the risk of subsequent fractures in patients who have recently sustained fragility fractures [101]. Research indicates that the risk of a second fracture is time-dependent, with the highest likelihood occurring within the first 2 years after an initial fracture [37]. FLS programs systematically identify patients presenting with fragility fractures, assess their risk of future fractures, including their falls risk, and ensure timely osteoporosis management. These services facilitate access to osteoporosis care through referrals for bone health evaluation, fracture risk assessment and the initiation or recommendation of treatment [101]. Furthermore, given the already underdiagnosis rate of VFs in both the general population and even more in the CKD population, it would be desirable to have an expert on them in the FLS network [102].

Given the high prevalence of osteoporosis among patients with advanced CKD, a nephrologist should be included in the FLS multidisciplinary team to ensure optimal osteoporosis care in this population. While FLS has proven highly effective in managing osteoporosis in patients without advanced CKD, further integration of nephrology expertise is essential to address the unique bone health challenges in those with severe kidney disease [37].

In conclusion, nephrologists must take action to address the longstanding and complex issue of bone disease in CKD patients to enhance both their short- and long-term clinical outcome. More attention should be given to VFs, given the strong association with cardiovascular events that distinguishes it from hip fracture in which the association is weak if not null. Another major challenge in treating CKD patients is the need for patient-centric therapies. Collaborations with pharmaceutical companies to develop agents specifically designed for CKD-associated osteoporosis is essential. We need prospective studies on VFs to strengthen and expand the recommendations of this consensus statement.

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