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CKJ Review

CKJ REVIEW

Vertebral fractures in patients with CKD and the general population: a call for diagnosis and action

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ABSTRACT

Vertebral fractures (VFs) are the most common osteoporotic fractures in the general population, and they have been associated with high mortality, decreased quality of life, and high risk of subsequent fractures, especially when recent, multiple, or severe. Currently, VF diagnosis and classification determine fracture risk and the most appropriate anti-osteoporotic treatment. However, VFs are clearly underdiagnosed, especially in patients with chronic kidney disease (CKD), and CKD-associated osteoporosis has been disregarded until recently. VFs are associated with higher morbidity and mortality, and their prevalence and incidence differ depending on the grade of renal dysfunction (CKD G1–G5) and/or the type of renal replacement therapy (dialysis or transplantation). In addition to classical risk factors [such as higher age, female sex, reduced bone mineral density, diabetes and steroid use], various other factors have been associated with an increased risk of VFs in CKD, including CKD grade, haemodialysis vintage, time since renal transplantation, low or high intact parathyroid hormone and phosphate levels, and/or vitamin D and K_1 deficiencies. Importantly, several clinical societies have recently modified their algorithms according to the fracture risk classification (including the presence of VFs) and determined the most appropriate anti-osteoporotic treatment for the general

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population. However, there are no specific guidelines addressing this topic in patients with CKD despite an important paradigm shift regarding the prognostic value of bone mineral density in 2017 after the publication of the CKD-Mineral and Bone Disorder Kidney Disease: Improving Global Outcomes guidelines. A proactive attitude towards diagnosis, treatment, and research is proposed to avoid therapeutic nihilism.

Keywords: chronic kidney disease, dialysis, kidney transplant, risk factors, vertebral fracture

INTRODUCTION

Vertebral fractures (VFs) are the most common osteoporotic fractures [1]. These fragility fractures have been associated with a high morbidity (including decreased quality of life, chronic bone pain, and kyphosis), a high mortality, and a high risk of subsequent fractures [1–4], especially if they are recent, multiple, and/or severe [5–7]. Currently, VF diagnosis and classification determine the fracture risk and the most appropriate anti-osteoporotic treatment, at least in the general population [4]. However, VFs are clearly underdiagnosed, probably because most fractures are overlooked [1] and spinal radiographic imaging is not systematically performed [8]. Importantly, the lack of an adequate diagnostic and therapeutic approach is even more apparent in patients with chronic kidney disease (CKD), in whom the diagnosis and management of osteoporosis have been disregarded until recently. In 2014, it was pointed out that fractures in CKD patients are common, neglected and associated with sickness and death [9], and a call for action was published in 2016 [10]. The situation is, however, complicated by the coexistence of risk factors for classic osteoporosis and CKD-specific factors leading to 'renal osteodystrophy' [11].

In assessing bone metabolism and renal osteodystrophy, bone biopsy is still considered the gold standard for diagnosing the different forms of renal osteodystrophy (both high and low turnover bone disease). Although bone quantity and/or quality can be assessed by dual-energy X-ray absorptiometry (DXA) and other techniques such as Trabecular Bone Score (TBS), information on mineralization defects, bone metal deposition, and, of course, histomorphometric data are difficult to obtain by other techniques. Even when assessing cortical compartments, high-resolution peripheral quantitative computed-tomography (HR-pQCT) has not always correlated homogeneously with bone biopsy parameters [12, 13]. In addition, the potential utility of 18F-NaF PET/CT for non-invasive assessment of bone turnover and volume in CKD-MBD (with an area under the curve of 0.87 for discriminating adynamic bone disease) has recently been published [14]. Some authors recommend the use of bone turnover markers (or a combination thereof) as surrogate markers for bone turnover and/or fracture risk estimation [15–17]. In fact, the diagnostic performance of biochemical markers of bone turnover is considered acceptable, with clinical utility in ruling out both high and low turnover bone disease [17]. In fact, the 2017 Kidney Disease: Improving Global Outcomes (KDIGO) CKD-MBD guidelines suggested that measurements of serum PTH or bone ALP can be used to evaluate bone disease in patients with CKD G3a-G5D, because markedly high or low values predict underlying bone turnover (evidence 2B) [18]. It is also suggested that bone-derived turnover markers of collagen synthesis and breakdown should not be used in these patients [18].

Classically, bone fragility in patients with CKD was attributed to renal osteodystrophy, and the 2009 KDIGO guidelines did not recommend routine bone mineral density (BMD) testing in patients with CKD G3-5D. It was based on the rationale that 'BMD does not predict fracture risk as it does in the general population, and BMD does not predict the type of renal osteodystrophy' (evidence 2B) [19]. Nevertheless, few prospective studies subsequently demonstrated that low BMD is associated with increased fracture risk across the entire spectrum of CKD [20, 21]. Consequently, the 2017 KDIGO guidelines suggested BMD testing in patients with CKD G3-5D to assess fracture risk 'if results will impact treatment decisions' (evidence 2B) [18].

The primary motivations for this revision were the growing experience with anti-osteoporotic medications in patients with CKD, low BMD, and a high risk of fracture, and the recognition that although consideration of bone biopsy is plausible, the lack of ability to perform a bone biopsy may not justify withholding antiresorptive therapy from patients at high risk of fracture [18]. However, the 2017 KDIGO guideline update did not make any recommendations regarding treatment with anti-osteoporotic agents for patients with advanced CKD. The purpose of this narrative review is to particularly underline the importance of the diagnosis of VFs and to promote a proactive attitude towards diagnosis, treatment, and clinical research to avoid potentially deleterious therapeutic nihilism and its consequences (renalism) [22].

DIAGNOSTIC CRITERIA

Only up to one-third of VFs are clinical, with the remaining two-thirds (asymptomatic or morphometric) being overlooked [1]. Clinical signs of an acute VF include back (lumbar or dorsal) pain, which ranges from mild to severe and can lead to a marked decrease in independence and quality of life (even more so than a hip fracture). Physical examination shows increased pain over the palpated affected area, painful vertebral assessment (Lewin) and/or painful 'heel drop'. It is also recommended to search for VFs in patients with a suspicion of osteoporosis and back pain, age >70 years, treatment with osteopenic drugs such as glucocorticoids, frequent falls, kyphosis, and/or a significant loss of height (≥4 cm in comparison with historical height or ≥2 cm in comparison with previous measurements) [2, 23]. Indeed, in a series of postmenopausal women evaluated for osteoporosis treatment, nearly 50% of those >65 years presented VFs [24].

Both, symptomatic and morphometric VFs can be diagnosed using the Genant's semiquantitative method (Fig. 1) [5]. According to Genant's criteria, a visually estimated ≥20% decrease in vertebral height (anterior, mid, or posterior) is considered indicative of a VF [1, 5]. Genant's method can be used in CKD patients. Additionally, VFs can be diagnosed when there is a >3 SD difference in vertebral height as compared with adjacent vertebrae [1]. Other radiological signs associated with a VF are endplate depression, discontinuity of the endplate, and anterior cortex disruption. Therefore, it is important to engage radiologists to identify and report VFs when analysing any X-rays, and not only to perform a morphometric description [25].

Thus, patients with a high risk of fracture, including patients with CKD, especially those suffering from acute back pain potentially due to a VF should be evaluated by X-rays, and/or

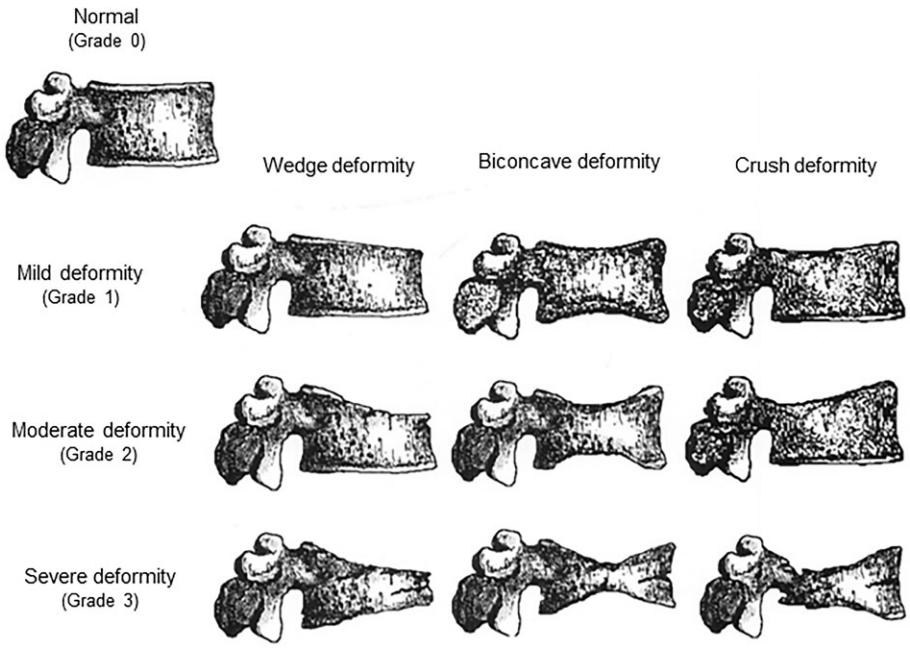

Figure 1: Classification of VFs according to Genant's radiological criteria [5].

other imaging modalities to diagnose VFs, such as computerized tomography, magnetic resonance imaging, radiofrequency echographic multi spectrometry, VF assessment (VFA) by DXA scans (Eastell and McCLoskey algorithms), or quantitative morphometry (software) [1, 9]. VFs are in the differential diagnosis of patients with a high risk of fracture, especially after an unusual stress, whereas osteoarthritis is the most common cause of chronic back pain. Physical examination and some imaging techniques also allow the clinician to differentiate between acute and chronic VFs. Note that magnetic resonance imaging, bone scintigraphy, and some types of computerized tomography can identify bone oedema and therefore an acute fracture. This diagnosis has important clinical and therapeutic implications in accordance with the above-mentioned concept of 'imminent risk of fracture', and patients with CKD should not be excluded from such evaluation. Figure 2 show a clinical approach to diagnosis and management of VFs.

In relation to BMD in CKD patients, it is also important to consider that lumbar BMD may be underestimated due to some artefacts including vascular calcification and osteoarthritis. The International Society for Clinical Densitometry recommends using all evaluable vertebrae and excluding only those affected by local artefacts. They also state that diagnostic classification based on BMD should not be based on a single vertebra. Although lateral spine radiographs should not be used to diagnose osteoporosis, they can help to exclude outliers by identifying vertebral artefacts [26]. On the other hand, the TBS is less affected by artefacts and provides additional information on bone quality.

EPIDEMIOLOGY

General population

Prevalence and incidence

The reported prevalence of VFs in the general population ranges widely, from 4.3% to 25.4%, depending on the study population, gender, age, and diagnostic criteria, as shown in Table 1 [27–30]. Additionally, the European Vertebral Osteoporosis Study (EVOS), that included males and females from 19 European countries, showed an increased prevalence of VFs with age and also a substantial geographical variation, with the highest rates present in Scandinavian countries [29]. The prevalence of VFs may also vary depending on the methodology and criteria used in the diagnosis, being higher with X-ray Genant criteria and lower in patients who underwent VFA by DXA [31, 32]. Thus, VFs identification with both, radiologic (X-ray) and densitometric (VFA) examination, may be useful to identify individuals at risk for developing fragility fractures [32].

On the other hand, the incidence of VFs also differs depending on the study population and diagnostic criteria as shown in Table 2 [27, 33–36], ranging from 4.45/1000 patient-years when using VFA to 19.3/1000 patient-years according to the medical history of general practitioners in Catalonia [32, 33]. The authors of the last study also recognize an underdiagnosis of morphometric VFs in clinical practice [33].

CKD

Prevalence

Very little evidence is available regarding the prevalence of VFs in CKD and with a large heterogeneity of VF risk, making a meta-analysis of VF studies unfeasible [37]. The few radiological assessments of the spine of these patients and the lack of reporting clearly entail a risk of overlooking asymptomatic fractures. Some authors described a similar VF prevalence in CKD patients and the general population [38], however, one should also differentiate the prevalence of VFs depending on the CKD stage as shown in Table 1. Thus, while one in four to five patients with CKD G3-G5 have morphometric VFs [38, 39], in patients undergoing haemodialysis the prevalence increases to between one- and two-thirds of patients [40–45], with the higher prevalence in patients with ≥1 years on haemodialysis and in those who do not receive oral calcitriol treatment [45]. Conversely, data on peritoneal dialysis are scarce.

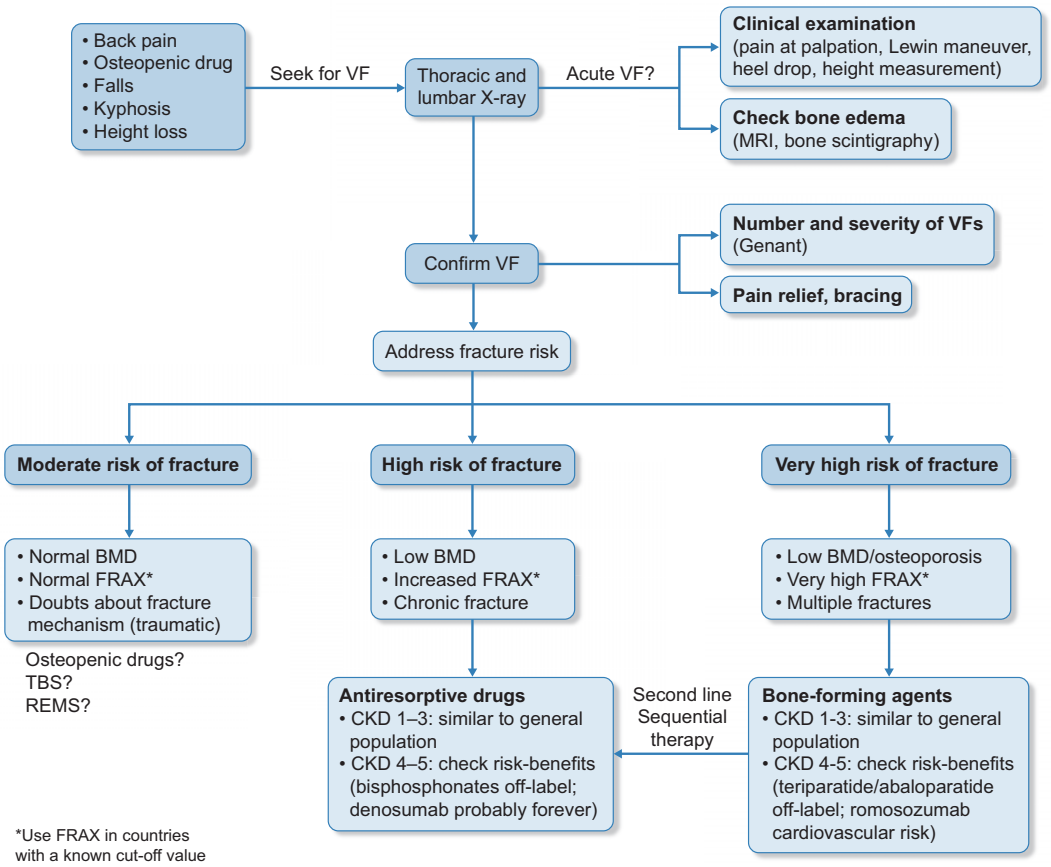

Figure 2: When and how to diagnose a VF: clinical approach and fracture risk classification. REMS, radiofrequency echographic multi spectrometry.

In patients undergoing kidney transplantation, a wider range of VFs has been [46–50]. The lowest value of 15% was observed in the Spanish EMITRAL study, which included 727 stable recipients from 28 Spanish clinics [46]; by contrast, according to Gianini *et al.* [50] more than half of patients with kidney transplantation have morphometric VFs.

It seems obvious that this variation in reported VF prevalence is probably not simply related to different stages of CKD or forms of renal replacement therapy, or to differences in age, sex, geography, patient numbers, or variation in CKD-mineral and bone disorder (CKD-MBD) care between countries. Rather, it probably also derives from the lack of a systematic approach and standardized diagnostic methods to assess VFs and from poor documentation in registries [8]. In fact, the diagnosis of any fragility fracture (especially VFs, usually with no or few symptoms) in CKD patients is typically delayed or absent. However, it is now very well known that fragility fractures can appear with a higher frequency and at a younger age in patients with CKD than in those without CKD, and that fractures (including VFs) increase morbidity and mortality not only in the general population but also in patients with CKD [8, 11, 18, 38, 51–53].

Incidence

In patients with CKD, the incidence of fragility fractures was reported to increase progressively from 15.0 to 46.3/1000 patient-years according to the CKD stage [54], however, VFs were unfortunately not included. In fact, only a few studies have addressed the incidence of VFs in patients with CKD, and most of these have reported odds ratios (OR) or risk ratios (RR) instead of incidence per 1000 patient-years [55, 56]. The limited and divergent evidence available does not support an increased incidence of VFs according to CKD stage [43, 55–57]. Also for patients undergoing dialysis or kidney transplant, recipient data assessing the incidence of VFs are scarce.

Incidence of VFs in CKD is shown in Table 2. Briefly, Elliott *et al.* [55] reported an overall VF incidence of 4.7/1000 patient-years with no difference among CKD stages, and a similar incidence has been reported in patients undergoing dialysis [58]. Other studies in haemodialysis patients have reported either a low incidence of VFs (8.57%) [57] or a moderate-to-high incidence (29%) [43]. Also for kidney transplant recipients data assessing the incidence of VFs are scarce [53, 59, 60], with only two studies reporting incidences of 7.2 and 15.4 per 1000 patient-years [60–62]. Nevertheless, the cumulative incidence of VFs after 15 years of follow-up after kidney transplantation, measured by a standardized incidence ratio, was 23.1 (12.3–39.6) [62].

Contrary to what might have been expected, a similar incidence of VFs has been reported in patients with advanced stages of CKD and kidney transplant patients as compared to the general population, whereas the prevalence of VFs in these clinical conditions is clearly increased (shown in Table 1). Accordingly, it may be concluded that VFs are underdiagnosed in CKD. Multiple explanations for this underdiagnosis have been suggested, including lack of awareness, lack of spinal X-rays (lumbar assessment being mostly overlooked), lack of description on radiologist reports, the presence of morphometric fractures (which are more frequent than clinical VFs), and a lack of

Table 1: Prevalence of VFs in the general population and patients with CKD.

		Prevalence	Definition of VFs
Prevalence of VFs in the general population			
Diaz-Lopez *et al*., Oviedo, Spain [29]		Women 25.4% Men 21.1%	Genant semiquantitative method
Melton *et al*., Rochester, USA [27]		Women 25.3%	>3 SD below any mean vertebral height
Jackson *et al*., CaMOS, Canada [28]		Women 23.5% Men 21.5%	>3 SD below the mean vertebral height of population
Schousbe *et al*., Study of Osteoporotic Fractures, USA [31]		21.8%	>3 SD height loss
Kwok *et al*., Mr OS and Ms OS, China [112]		Women 16.5% Men 14.9%	Genant semiquantitative method
O'Neill *et al*., EVOS, Europe [30]		Women 12% Men 12%	>3 SD below adjacent vertebrae
Kanterewicz *et al*., FRODOS, Spain [32]		Women 4.3%	VFA by DXA
Prevalence of VFs in patients with CKD			
CKD	Castro-Alonso *et al*., OSERCE, Spain [38]	18% in CKD G3–5	Genant semiquantitative method
	Mishima *et al*., Japan [39]	22.5% in CKD 3a[a]	Genant semiquantitative method
HD	Rodriguez-Garcia *et al*., Spain [41]	19.1%	Genant semiquantitative method
	Atsumi *et al*., Japan [42]	20.9%	Genant semiquantitative method
	Fusaro *et al*., EVERFRACT, Italy [40]	55.3%	Vertebral quantitative morphometry
	Fusaro *et al*., Italy [45]	61% in HD without oral calcitriol	Vertebral quantitative morphometry
Kidney transplantation	Torres *et al*., EMITRAL, Spain [46]	15%	Genant semiquantitative method
	Pérez-Sáez *et al*., Spain [48]	26.4%	Genant semiquantitative method
	Jansz *et al*., the Netherlands [43]	34% in transplantation-eligible patients	Genant semiquantitative method
	Velioglu *et al*., Turkey [47]	43.4%	Genant semiquantitative method
	Gogas Yavuz *et al*., Turkey [49]	56.4%	Genant semiquantitative method
	Giannini *et al*., Italy [50]	57%	Vertebral quantitative morphometry

HD: haemodialysis
[a]Patients with type 2 diabetes mellitus

codification on registries, among others [1, 3, 8, 11]. Therefore, it would be advisable to conduct a prospective study addressing the real incidence of VFs (both clinical and morphometric) in these patients.

Risk factors

Traditional. In the general population, traditional risk factors (with a RR ≥ 2) predisposing to fracture include: age (≥65 years), low body mass index (≤20 kg/m^2), previous fragility fracture, parental history of hip fracture, current glucocorticoid treatment (>5 mg for >3 months), and falls (≥2 per year) [63]. Other factors predisposing to fractures (with an RR between 1 and 2) include current smoking, alcohol consumption (>3 units per day), early menopause, hypogonadism, diseases associated with bone loss, medical treatment leading to bone loss, and risk factors for falls [63]. Patients with CKD may also have traditional risk factors for fractures and osteoporosis, as among the diseases and treatments associated with a higher risk of fracture development include organ transplantation, CKD with eGFR <60 ml/min/1.73 m^2, and hyperparathyroidism [15, 63]. Thus, patients with CKD, especially individuals with kidney transplantation, tend to have several causes of secondary osteoporosis [15].

CKD-related. Whereas in the general population a previous fracture, older age, and reduced BMD, as well as diabetes and glucocorticoid use, are well known risk factors for VFs [23, 64], other additional factors have been associated with the development of VFs in patients with CKD, and these may differ depending on the disease stage.

Table 3 summarizes the risk factors for VFs in CKD, patients undergoing haemodialysis, and kidney transplant recipients.

In patients with CKD, increasing age, low serum phosphate levels, creatinine clearance, low weight, and low BMD have all been associated with VF development [38, 56]. Renal function has not always been independently associated with risk of VFs in women with an eGFR <45 ml/min/1.73 m^2 [56]. Moreover, lumbar BMD does not seem to have the same predictive value as in the general population without CKD [8], indicating that reduced bone mass (evaluated with BMD) may not necessarily be a strong risk factor for VFs in CKD [8]. The overestimation of BMD at the lumbar spine in cases of osteoarthritis, spine deformity, and/or vascular calcifications could partly explain these findings. Nonetheless, data from a meta-analysis of 13 studies and four prospective cohort studies, which showed that BMD was significantly lower in patients with fractures and can predict fracture risk in CKD G3–5D, clearly influenced the recommendations of the 2017 KDIGO guidelines of BMD measurement

Table 2: Incidence of VFs in the general population and patients with CKD.

		Incidence	Definition of VF
Incidence of VFs in the general population			
Suris *et al.*, Catalonia, Spain [33]		19.3/1000 p-y	Database records
Van Der Klift *et al.*, Rotterdam, The Netherlands [34]		7.8/1000 p-y Women > 75 yr: 19.6/1000 p-y Men > 75 yr: 5.2/1000 p-y	Quantitative method
Melton 3rd, *et al.*, Rochester, Minnesota, USA. [27]		Women: 17.8/1000 p-y	>3 SD below any mean vertebral height
Felsenberg, *et al.*, EVOS (European Prospective Osteoporosis Study), Europe [35]		Women: 10.7/1000 p-y Men: 5.7/1000 p-y	>3 SD below adjacent vertebrae
Ferrar *et al.*, Osteoporosis and Ultrasound Study (OPUS), Sheffield, UK [36]		4.45/1000 p-y	VFA by DXA
Incidence of VFs in patients with CKD			
CKD	Elliott *et al.*, Canada [55]	4.7/1000 p-y in CKD G3b-4	From administrative data
HD	Danese *et al.*, CA, USA [58]	4.8/1000 p-y	From a clinical registry (US Renal Data System)
Kidney transplantation	O'Shaughnessy *et al.*, Minneapolis, USA [61]	7.2/1000 p-y[a]	Quantitative method, X-ray
	Vautour *et al.*, Minneapolis, USA [62]	15.4/1000 p-y	From medical records

[a]It only includes clinical VFs.
p-y, person-years

Table 3: Risk factors for VF development in CKD, haemodialysis, and kidney transplant patients.

Risk factors for VFs	CKD	Haemodialysis	Kidney recipients
General issues	– Age – ↓ Height	– Age – Gender – Previous fracture – Asian race	– Age – Gender
Kidney disease	– Duration of CKD	– Duration of haemodialysis	– Duration of transplant – Duration of previous haemodialysis – Cyclosporine A – Steroid use
Laboratory abnormalities	– ↑ Phosphate – ↓ eGFR – ↓ Creatinine Clearance	– ↑ ↓ intact PTH – ↓ Vitamin K_1 – ↑ Calcium – ↑ Ca × P product – ↓ Albumin – ↑ HbA1c	– ↑ PTH levels
BMD	– ↓ BMD – ↓ Cortical Thickness (Quantitative ultrasound)	– ↓ BMD lumbar – ↓ BMD total body	– ↓ BMD lumbar – ↓ BMD femoral neck
Comorbidities	– Peripheral vascular disease	– Prior cardiovascular events	– Diabetes – Aortic and iliac calcifications

to assess fracture risk in these subjects [18, 65]. When assessing bone using quantitative ultrasound, a decreased cortical thickness has been identified as a factor independently associated with VFs in patients with type 2 diabetes mellitus and low eGFR [39]. Additionally, peripheral vascular disease has been found to be associated with a higher VF risk [38]. Although the main conclusion is that decreased eGFR and longer duration of CKD are associated with a higher likelihood of VF development, some data also indicate that fracture incidence is increased in the early stages of CKD, especially among younger individuals and men [66].

In patients undergoing haemodialysis, the presence of VFs has been positively correlated with age, haemodialysis vintage, and female gender [40, 41, 57]. When assessing biochemical parameters as predictive factors for VFs, mean maximum calcium, mean maximum Ca × P product [41], low intact parathyroid

hormone (PTH) levels [42], and vitamin K_1 deficiency (including warfarin use) [44] have been associated with a greater risk of VFs. Previous fracture, Asian race, higher HbA1c, previous cardiovascular events, and lower serum albumin have also been related to VF development in patients with type 2 diabetes with CKD G3 [67]. In addition, BMD has been identified as a sensitive predictor of VFs in haemodialysis patients [42]. Thus, each decrease of 1 SD in lumbar BMD increased the age-adjusted odds ratio for VFs up to 2.0 times (1.4–2.0) while each SD decrease in total-body BMD increased it up to 1.6 times (1.1–1.6) [42]. Conversely, the TBS (which adds information on the bone trabecular microarchitecture) was not demonstrated to independently predict clinical fractures (or VFs) in prospective studies in patients with CKD who were undergoing haemodialysis [68, 69]. However, a lower TBS was found to be significantly associated with previous non-VFs. Additionally, a significantly lower prevalence of VFs has been reported in patients treated with calcitriol compared to those without this treatment (48.6% vs 61%), with an OR of 0.605 (0.404–0.907) [45]. Additionally, oral calcitriol was found to be associated with a reduction in the OR for VFs in both genders [45]. When the effects of cinacalcet on fracture events in patients receiving haemodialysis were evaluated in the EVOLVE trial [70], it was found that cinacalcet reduced the rate of clinical fractures by 16%–29% when accounting for differences in baseline characteristics, multiple fractures, and/or events prompting discontinuation of the study drug. However, VFs were recorded in only 1.2% of the total patient population, in a total of 51 fracture events, which almost certainly represents an underestimate because screening radiographs were not performed [70].

In kidney transplant recipients, risk factors for VFs have been reported to vary depending on gender [46, 61]. In male recipients, age and cyclosporine A (CsA) treatment were associated with a higher risk of VFs (OR 1.04, 1.01–1.06 and OR 3.2, 1.6–6.3, respectively), whereas in females, PTH values (OR per 100 pg/mL increase: 1.27; 1.043–1.542) and age (OR 1.07, 1.03–1.12) were the principal risk factors [46]. High PTH levels have been associated not only with an increased VF risk, but also with a greater number of VFs [50], confirming the need for strategies aimed at lowering serum PTH in kidney recipients as well. As would be expected, haemodialysis vintage and time since transplant have also been associated with VFs [49, 50, 61]. Additionally, Velioglu *et al.* [47] described higher steroid use (96.4% vs 80.8%, $P = .007$), more diabetes (76.7% vs 26.2%, $P = .039$) and lower BMD (1.052 ± 0.17 vs 1.12 ± 0.16 g/cm^2, $P = .023$) in kidney recipients with VFs compared to those without. However, in the multivariate analysis, only steroid use was found to be significantly associated with prevalent VFs (OR 0.121, 0.015–0.988), with lumbar BMD being marginally statistically significant ($P = .051$). Gogas Yavuz *et al.* [49] reported femoral neck BMD (Z-score) to be a risk factor for VF development in kidney recipients, while another study reported each lower −1 SD in femoral neck T-score to be associated with 48% higher odds of fracture (OR 1.48; 1.20–1.68, $P = .005$) [71]. Although an association has been reported between aortic and iliac calcifications and VFs, potentially due to the role of vitamin K deficiency in both bone and vascular pathology [44], other authors have not observed a significant association [46].

Vertebral and appendicular fractures in CKD: similarities and differences

Naylor *et al.* [54] reported an increased incidence of fragility fractures (including hip, forearm, pelvis, or proximal humerus), which increased progressively from 15.0/1000 patient-years in CKD G1 to 20.5, 24.2, 31.2, and 46.3/1000 patient-years in CKD G2, G3a, G3b, and G4, respectively; and an increasing incidence of appendicular fractures according to CKD stage. In addition, major fractures are common in incident dialysis patients (according to a study from the Swedish Renal Registry, 9% experienced a fracture within only 2.2 years of starting dialysis, of which 12% were VFs) [40]. In kidney allograft recipients up to 3.8% developed a fracture requiring hospitalization [72] with a fracture rate of 9.99 for any fracture and 1.54 for a hip fracture per 1000 patients-year [72].

With regard to hip fracture, several publications have shown a higher incidence of this fracture in patients with CKD compared with the general population. In women with CKD G3b, the higher incidence of hip fractures has been described in females >85 years of age compared with those aged 18–64 years (19.8 vs 1.26 per 1000 patients-year, respectively) [55]. In patients undergoing haemodialysis, the incidence of hip fracture is four times higher than in the general population after adjustment for age, gender, and ethnicity [73]; with an overall incidence of 7.45/1000 patients-year in men and 13.63/1000 patients-year in women [73]. Additionally, the incidence of hip fractures appears to be consistently higher in haemodialysis than in peritoneal dialysis patients. However, VFs were rarely addressed in these studies. In kidney transplantation, an incidence of hip fracture of ∼1.5 per 1000 patients-year has been reported [72, 74]. In addition, in these patients, hip fracture has been independently associated with an increased risk of death with a hazard ratio (HR) 3.288 [72].

Finally, in a recent meta-analysis that sought an association between CKD and fracture risk, the authors reported that the risk of VFs appeared to be lower than that of hip fractures and non-VFs [37], which were found to be clearly increased in CKD patients [75]. They suggested that a possible explanation is the fact that half of the studies of VFs in their meta-analysis used ICD codes or medical history to diagnose VFs, entailing a risk of overlooking asymptomatic fractures [37].

One potential reason for the discrepancy between risk of VFs and other fractures is the different effect of PTH and secondary hyperparathyroidism, which primarily impairs cortical bone whereas vertebrae are mainly constituted of trabecular bone [9]. However, data from bone biopsies, QCT, and TBS have also shown significant trabecular bone loss in CKD patients. In brief, Costa *et al.* [76], in 70 CKD G2 to G4 patients assessed by QCT, observed a similar average bone loss in the cortical and trabecular compartments (− 4.4%/year in cortical bone and −3.15%/year in trabecular bone) after 24 months of follow-up; although these changes did not occur simultaneously in all patients. PTH is not only associated with loss of cortical bone, but has also been associated with VFs risk [43]. Therefore, both trabecular and cortical bone contribute to the impairment of bone microarchitecture, poor bone quality, and increased fracture risk observed in CKD patients [77–80].

VERTEBRAL FRACTURE AS A RISK BIOMARKER

Subsequent fractures

It is extremely important to emphasize that a previous fragility fracture is probably the main risk factor for the development of a new fragility fracture. Thus, the relative risk of subsequent fracture within 1 year has been reported to be 5.3 [81], and there is a ∼50% incidence of subsequent fracture within the first 2 years after a sentinel fracture [82]. Such patients are accordingly referred to as being at ‘imminent risk of fracture’ [83]. In

addition to a recent fragility fracture, multiple fractures at baseline [HR 1.8 (1.2–2.7)] and the site of fracture are associated with a higher risk of subsequent fracture (with vertebral and hip fractures showing the higher rates for having further major osteoporotic fractures) [84]. Banefelt *et al.* [85] reported index VFs to be a strong independent risk factor for subsequent fracture, the HR being 2.72 (2.58–2.88) at 1 year and 2.25 (2.15–2.35) at 2 years. Other factors that have been associated with re-fracture are age (1.2-fold increase in HR per decade after the 60s), female gender (HR 1.5, 1.1–2.0), previous falls (OR 6.67, 6.03–7.37), glucocorticoid use (HR 1.16, 1.10–1.23), and femoral neck BMD lower than −3.5 SD (HR 3.7, 1.9–7.0) [2, 86–90].

A previous VF by itself constitutes the main risk factor for development of a new VF (RR 3.7, 2.8–4.9) [2]. Recent onset of a VF and the presence of multiple fractures carry an even higher risk of new VFs (RR 9.3, 1.2–71.6 and RR 7.3, 4.4–12.3, respectively). Additionally, those patients with lower BMD are at a higher risk of VF development [2, 7]. Each 1 SD decrease in baseline BMD value below the mean for a young person increases the risk of developing a new VF 1.6-fold (RR 1.6, 1.1–2.2) [2]. Lindsay *et al.* [2] described an up to 20% incidence of new VFs within the first year after a sentinel VF, emphasizing the need for clinicians to recognize the urgency in identifying and treating all patients who present with a VF. In postmenopausal osteoporosis with prevalent VFs, the incidence of new VFs differs according to the severity of the baseline VF [7]. Thus, after 3 years of follow-up the incidence of new VFs was reported to be 10.5%, 23.6%, and 38.1% in patients with mild, moderate, and severe prevalent VFs (placebo arm of the MORE trial). These data clearly indicate that the greater the severity and deformity of VFs, the higher the risk of new VF development [7]. Additionally, the severity of prevalent VFs has been identified as a predictor of non-VFs (including femoral fractures) [7].

Few studies have assessed imminent risk of fracture amongst patients with CKD. In the CREDENCE cohort, including patients with type 2 diabetes and CKD G2–G3, having a previous fragility fracture was associated with a higher risk for VFs [67]. However, the rate of incident fractures was low (only 3.1% over a median 2.35 years) and morphometric VFs were not assessed. In addition, CKD G4–G5 has been associated with a higher risk of subsequent fracture in a real-world evaluation from the Japan Medical Data Vision database [91]. Another study reported a higher incidence of fragility fractures in women and men with previous fractures, with the cumulative incidence at 3 years reaching 21.8% (13.0%–34.4%) among women aged 40–65 years with a previous fracture; however, the authors did not assess VFs and hypothesized that their inclusion would have further increased the incidence of fractures [21].

Morbidity

In the general population, significant utility loss has been described after a VF (0.92; 0.89–0.95) [64]. The utility loss has been described to be greater after a VF than after a hip (0.63; 0.61–0.65), humerus (0.51; 0.49–0.53), or forearm fracture (0.32; 0.31–0.33) [64]. Moreover, the mean utility loss after sustaining a VF decreases with age (the older the person, the less the utility loss), a finding explained by the increased mortality [64]. As expected, utility loss is higher in women than in men due to the higher risk of fractures in women [3, 64]. Nevertheless, no data are available on quality of life or utility loss in patients with CKD and VFs.

The important morbidity associated with VFs may include loss of independence, reduced quality of life, chronic back pain, and kyphosis [2], both in the general population and among patients with CKD. However, CKD patients have additional risk factors for other associated comorbidities, such as prolonged immobility (especially in haemodialysis patients), falls, tendency to bleeding, malnutrition, and higher rates of infection, and thus have higher hospitalization rates and longer hospital stays [51]. These aspects were analysed by Tentori *et al.* in haemodialysis patients with a hip fracture or other fragility fractures, but not specifically in patients with VFs [51]. The authors reported increasing frailty after a fracture to be a further contributor to the high incidence of adverse clinical outcomes [51].

Patients with CKD are at higher risk of cardiovascular events, and cardiovascular disease is known to be the most common cause of morbidity and mortality in those with fragility fracture [92]. In this context, VFs have been significantly associated with myocardial infarction in patients undergoing haemodialysis [93]. Given the high health and economic burden related to fragility fractures, strategies for fracture prevention should be identified, implemented, and probably underlined in patients with CKD.

Mortality

There are few data on long-term mortality following VFs [89]. In the Dubbo study, increased mortality was observed in patients who had sustained a fragility fracture compared to patients without fractures (women: 7.8 vs 4.3 per 100 patient-years; men: 11.3 vs 5.5 per 100 patient-years). Moreover, mortality rates were higher following a hip, vertebral, or major fracture than after minor fractures [89]. Thus, in women the mortality was 15.42 (12.88–18.52) and 8.97 (7.57–10.63) per 100 patient-years following a hip fracture and a VF, respectively, while in men it was 25.67 (19.46–33.87) and 15.16 (11.89–19.33), respectively. This mortality risk is clearly higher than that in the general population without fractures [89]. Similar data have been described by other authors, with higher mortality rates reported in men and after hip fractures, including also a markedly increased mortality compared to other major and minor fractures [88].

Not only has a higher fracture risk been described in patients with CKD, but CKD patients also have a higher mortality after sustaining a fragility fracture as compared to individuals with fragility fractures but without CKD [51]. Additionally, mortality varies depending on age. As previously mentioned, the most common cause of morbidity and mortality in patients with CKD (with or without fractures) is cardiovascular disease, which accounts for 45% of all deaths. The higher mortality observed after a VF in CKD patients has been at least partially associated with the known cross-talk between fractures and vascular calcification [94], and the presence of fractures may highlight an increased risk of cardiovascular disease and/or vascular calcification, an association that has been reported to be stronger in patients with CKD and VFs [9]. For instance, VFs have been associated with vascular calcification at both aortic (OR 1.77, 1.00–3.14) and iliac (OR 1.96, 1.27–3.04) locations [9].

Haemodialysis is the clinical procedure associated with the highest cardiovascular risk. It is well known that Tentori *et al.* [51] reported high rates of death and hospitalization following a bone fracture among haemodialysis patients from the DOPPS (Dialysis Outcomes and Practice Patterns) study. Post-fracture mortality rates exceeded 500/1000 patient-years and this increase in mortality was especially observed during the first month following the fracture, after which it declined [51]. However, in the DOPPS data set, fractures were coded as either 'hip' or 'other', and therefore specific information about VFs was not available.

Table 4: Criteria for fracture risk classification according to guidelines and corresponding anti-osteoporotic treatment recommendations.

	Classification of fracture risk:		
	Imminent	Very high	High
	AACE 2020 [4]		
Criteria	Not defined	Fractures: - recent (past 12 months) - multiple - while on antiOP therapy - while on osteopenic drugs BMD: very low T-score (<−3.0) High risk for falls Very high by FRAX®	Osteoporosis but not at very high fracture risk
Treatment recommendation		Abaloparatide Denosumab Romosozumab Teriparatide Zoledronate	Alendronate Denosumab Risedronate Zoledronate
	Swiss Association against Osteoporosis (SVGO), 2020 [95]		
Criteria	FRAX ≥ 10% within 2 years Recent fractures (<2 years): - vertebra or hip - humerus, radius, pelvis at ≥65 years	FRAX® ≥20% absolute risk above the intervention threshold Subjects on osteopenic drugs with T-score <−1.5 or FRAX above the intervention threshold	Past fractures (>2 years) FRAX above the intervention threshold but <20%
Treatment recommendation[a]	Teriparatide Zoledronate Denosumab Romosozumab	Teriparatide Bisphosphonates Denosumab	Bisphosphonates Denosumab
	SEIOMM, Spanish Guidelines, 2022 [23]		
Criteria	Not defined	Fractures: - ≥2 VFs - 1 vertebral or hip fracture with T-score <−3.0 Very low T-score (<−3.5)	Fracture (vertebra, humerus, radius, pelvis) + osteopenia T-score <−2.5 Osteopenia + risk factors for osteoporosis
Treatment recommendation[a]		Teriparatide Romosozumab	Alendronate Risedronate Denosumab Zoledronate
	Canadian Guidelines, 2023 [101]		
Criteria	Not defined	VF: - recent severe VF (within 2 years) and height loss of >40%) - multiple VFs (>1) AND T-score ≤−2.5	Fracture (hip, vertebra or ≥2 fragility fractures) Fracture risk ≥20% Age ≥70 years AND T-score ≤−2.5
Treatment recommendation		Teriparatide Romosozumab	Alendronate Risedronate Denosumab Zoledronate

[a]Published before EMA's authorization of romosozumab and abaloparatide in Europe
AntiOP, anti-osteoporotic

SCREENING STRATEGY AND FRACTURE RISK CLASSIFICATION

Most guidelines classify patients according to their fracture risk depending on age, previous fractures, BMD and other risk factors included in FRAX® (*Fracture Risk Assessment Tool*) [4, 95]. FRAXplus® was recently developed, allowing modifications of conventional FRAX estimates of probabilities of hip and major osteoporotic fractures based on knowledge of additional risk factors. Although the FRAX tool has predictive value for incident fractures in the general population and may provide useful information allowing identification of those CKD patients

most at risk of sustaining a fragility fracture [6, 100], it does not yet include kidney function, CKD stage, or renal replacement therapy modalities. Furthermore, VFs are not separately considered (FRAX only calculates the 10-year probability of a hip or major osteoporotic fracture with or without BMD).

Of note, there is not yet an international consensus on fracture risk classification and different clinical societies define fracture risk in different ways. However, all concur on the importance of identification of a VF. In this regard, the American Association of Clinical Endocrinology (AACE) includes a specific recommendation focused on seeking for morphometric VFs after the diagnosis of osteoporosis since VFs result in reclassification of the patient [4, 95]. Additionally, it should be noted that fracture risk specifically differs depending on the presence of VFs, their number [23], and the time since the fractures [95]. Table 4 summarizes the main criteria for fracture risk classification in the general population. The fracture risk classification determines the first anti-osteoporotic treatment; thus, in patients with imminent or very high fracture risk, a bone-forming agent is recommended as the first line of treatment; whereas antiresorptive treatment is the main recommendation in patients with high risk [4, 23, 95, 101] for the general population.

In this context, it should be noted that there are no specific guidelines for patients with CKD. In patients with CKD G1–G2 with osteoporosis and/or high risk of fracture, as identified by World Health Organization criteria, the 2017 KDIGO CKD-MBD guidelines recommend management as for the general population (evidence 1A) [18]. In patients with CKD G3a–G3b with PTH in the normal range and osteoporosis and/or high risk of fracture, treatment as for the general population is suggested (evidence 2B) [18]. In patients with CKD G3a–G5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, it is suggested that treatment choices take into account the magnitude and reversibility of the biochemical abnormalities and the progression of CKD, with consideration of a bone biopsy (evidence 2D) [18].

Both before and after these KDIGO guidelines, many algorithms have been proposed to guide nephrologists, rheumatologists and general practitioners on clinical decision-making in patients treated with glucocorticoids and patients with CKD plus osteoporosis and/or fractures [8, 23, 63, 102–106], including patients with CKD G4-5 [52, 104, 105]. Most anti-osteoporotic drugs (but ibandronate and teriparatide in primary prevention) have proven to be effective in preventing VFs in the general population [63], and data analyses from the pivotal trials of therapeutic agents used in osteoporosis show that these drugs can be considered in CKD G1–G3. Off-label drug use in patients with CKD and more severe renal impairment (CKD G4–G5) could offer significant benefits to subgroups of patients; however, the risks and benefits of available interventions need to be balanced at the individual level and discussed with the patient [52, 105]. An informed consent will probably be required before treatment [52, 105]. Treatments should be carefully tailored to each individual's bone turnover (bone turnover biomarkers not retained in the kidney, such as alkaline phosphatases and others, may be helpful) [107, 108], calcium/phosphate/VD balance and PTH levels, while we await for further evidence and/or new drugs [109, 110]. However, it must be taken into account that a more pragmatic and proactive approach to this serious complication, especially in secondary prevention, is currently advised for CKD patients although no algorithm has yet been validated by outcome data [52].

To summarize the therapeutic approach to osteoporosis in CKD, although most anti-osteoporotic treatments are still contraindicated or not recommended in patients with CKD-MBD with a creatinine clearance <35 or <30 ml/min, most therapeutic recommendations advocate the initiation of bone anabolic agents in patients with suspected adynamic bone disease or at imminent or very high risk of fracture; whereas antiresorptive treatment (including bisphosphonates and denosumab) is mostly recommended as first-line treatment in patients with high bone turnover disease, high risk of fracture, or in individuals with any contraindication to bone-forming agents [4, 23, 95, 111]. In any case, in patients with CKD G3a-G5D with biochemical abnormalities of CKD-MBD and low BMD and/or fragility fractures, it is suggested that the choice of treatment should take into account the magnitude and reversibility of the biochemical abnormalities (first) and the progression of CKD, with consideration of a bone biopsy (evidence 2D) [18]. However, the inability to perform a bone biopsy may not justify withholding therapy in patients at high risk of fracture [52, 106].

CONCLUSIONS

VFs are clearly underdiagnosed in patients with CKD. It should be noted that the importance of VFs as potent predictors of morbidity (including subsequent fractures) and mortality has been clearly demonstrated in the general population, and is probably underestimated in patients with CKD.

The available findings do demonstrate that the prevalence of VFs shown in patients with CKD is extremely variable but significant, while its real incidence is basically unknown. In addition to classical risk factors (such as age, sex, BMD, diabetes, and steroid use), CKD grade, haemodialysis vintage, time since transplant, CsA use, low or high intact parathyroid hormone and phosphate levels, and vitamin D and K_1 deficiencies, among other factors, have been occasionally associated with an increased risk of VFs in patients with CKD.

Considering all the information summarized in this article, it seems clear that there is a need to improve the identification of VFs (both clinical and morphometric) since VFs modify the fracture risk classification and may determine the most appropriate anti-osteoporotic treatment. VFs entail a high morbidity and mortality and may represent an imminent risk of a subsequent fracture, with a very high economic and social burden. The important paradigm shift reflected in the 2017 CKD-MBD guidelines not only evokes a more pragmatic approach to osteoporosis in patients with CKD, but probably also indicates the need for a multidisciplinary and homogeneous proactive attitude to diagnosis and treatment to avoid therapeutic nihilism.

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