


European Consensus Statement on the diagnosis and management of osteoporosis in chronic kidney disease stages G4–G5D

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ABSTRACT

Controlling the excessive fracture burden in patients with chronic kidney disease (CKD) Stages G4–G5D remains an impressive challenge. The reasons are 2-fold. First, the pathophysiology of bone fragility in patients with CKD G4–G5D is complex and multifaceted, comprising a mixture of age-related (primary male/postmenopausal), drug-induced and CKD-related bone abnormalities. Second, our current armamentarium of osteoporosis medications has not been developed for, or adequately studied in patients with CKD G4–G5D, partly related to difficulties in diagnosing osteoporosis in this specific setting and fear of complications. Doubts about the optimal diagnostic and therapeutic approach fuel inertia in daily clinical practice. The scope of the present consensus paper is to review and update the assessment and diagnosis of osteoporosis in patients with CKD G4–G5D and to discuss the therapeutic interventions available and the manner in which these can be

used to develop management strategies for the prevention of fragility fracture. As such, it aims to stimulate a cohesive approach to the management of osteoporosis in patients with CKD G4–G5D to replace current variations in care and treatment nihilism.

Keywords: bone mineral density, chronic renal insufficiency, CKD-MBD, mineral metabolism, renal osteodystrophy

SUMMARY OF MAIN RECOMMENDATIONS ON THE DIAGNOSIS AND MANAGEMENT OF OSTEOPOROSIS IN CHRONIC KIDNEY DISEASE G4–G5D

Diagnosis of osteoporosis in chronic kidney disease

1. Osteoporosis is a condition characterized by low bone mass and microarchitectural and qualitative bone deterioration that leads to bone fragility and fracture susceptibility.
2. The operational definition of osteoporosis is based on an areal bone mineral density (BMD) assessed by dual-energy X-ray absorptiometry (DXA) at the spine or hip < -2.5 standard deviation from the BMD in young female adults (T-score).

Risk factors for fragility fractures

1. Clinical risk factors for osteoporosis in chronic kidney disease (CKD) patients comprise traditional risk factors including older age, female sex, low body mass index, fragility fracture history, glucocorticoid treatment and CKD-specific risk factors such as long dialysis duration.
2. BMD as assessed by DXA predicts fractures in patients with CKD G4–G5D. However, DXA probably underestimates the actual fracture risk in patients with CKD G4–G5D, as it does not account for impaired bone quality. The consistency of the risk prediction across stages of disease and degree of parathyroid hormone (PTH) control remains to be documented.

Assessment of fracture risk

1. In patients with CKD G4–G5D, DXA may be considered in postmenopausal women, or men >50 years of age. Routine DXA testing (screening) in all CKD G4–G5D patients is not supported by current evidence.
2. The hip and the lumbar spine are the primary skeletal site to evaluate BMD by DXA.
3. The forearm may be included in the DXA evaluation of the skeletal site panel, but one should be aware of operator-dependent variability and potential bias by arteriovenous fistula.
4. Trabecular bone score and alternative imaging techniques need further clinical evaluation pending clinical implementation.
5. Vertebral fracture assessment (VFA) and/or lateral spine imaging is recommended in all patients undergoing DXA evaluation and in patients with a history of ≥ 4 cm height loss, kyphosis, or recent or current long-term oral glucocorticoid therapy. Imaging should include the abdominal aorta for determination of vascular calcification.
6. FRAX predicts fracture probability in all CKD stages. Additional evidence is required to define whether further arithmetic adjustments to conventional FRAX estimates have to be made with knowledge of advanced CKD.
7. Non-kidney-retained bone turnover markers (BTMs), especially bone-specific alkaline phosphatase, may be useful for fracture risk prediction in CKD G4–G5D, awaiting further confirmation.

Intervention thresholds for pharmacological therapy

1. CKD patients >50 years of age with a prior fragility fracture [(major osteoporotic fracture (MOF))] may be considered for treatment without the need for further BMD assessment.
2. In the absence of MOF, a DXA T-score threshold ≤ -2.5 at the lumbar spine or hip is recommended, recognizing that a higher threshold of -2.0 or -1.5 may be more appropriate.
3. FRAX country-specific intervention thresholds are appropriate in CKD patients.

Non-pharmacological intervention

1. A sufficient supply of calcium should be guaranteed (800–1200 mg/day, preferentially through diet) and vitamin D stores should be repleted according to osteoporosis and CKD-MBD guidelines.
2. Regular weight-bearing exercise should be advised, tailored to the needs and abilities of the individual patient.
3. The falls risk needs to be evaluated regularly and acted upon.

Pharmacological intervention

1. CKD-MBD therapy should be optimized according to current guidelines before considering specific osteoporosis management.
2. Metabolic disturbances linked to bone fragility (acid–base, uraemic toxicity) should be controlled at all times.
3. Risks and benefits of available pharmacological interventions need to be balanced at the individual level and discussed with the patient. Formal informed consent may be required when considering off-label use.
4. Evolving evidence indicates that antiresorptive agents may be effective in advanced CKD and that vascular and skeletal risks are not excessively high.
5. Renal risks of bisphosphonates are poorly explored in patients with CKD G4–G5D, which calls for caution.
6. Denosumab confers no risk of kidney function decline, but the risk of severe hypocalcaemia with denosumab is increased in CKD and needs to be addressed by concomitant vitamin D and calcium supplementation.
7. Withdrawal of denosumab therapy may be associated with an increased risk of vertebral fracture.

Monitoring

1. Non-kidney-retained BTMs, such as bone-specific alkaline phosphatase, intact procollagen type I N-propeptide and tartrate-resistant acid phosphatase 5b, should be preferentially monitored in CKD patients.
2. Monitoring of BTMs may inform on the early therapeutic response.
3. Monitoring of BTMs after therapy withdrawal (offset of effect) may inform on the need for reintroduction.
4. Repeat DXA informs on the long-term treatment effect on BMD. The time interval when treatment effect can be detected may vary depending on the treatment modality and underlying type of renal osteodystrophy.

Systems of care

1. Coordinator-based fracture liaison services (FLSs) should be considered to systematically identify and guide CKD patients with fragility fractures, in close collaboration with nephrologists. The (cost-)effectiveness of FLSs has been established in the general population.

INTRODUCTION

Chronic kidney disease (CKD) is defined by the Kidney Disease: Improving Global Outcomes (KDIGO) CKD guideline as abnormalities of kidney structure or function, present for >3 months, with implications for health. As much as 10–15% of the adult population is affected worldwide. The National Kidney Foundation/Kidney Disease Outcomes Quality Initiative (NKF/KDOQI) classifies CKD into five stages using thresholds of estimated glomerular filtration rate (eGFR). The prevalence of advanced CKD, defined as CKD G4–G5D (corresponding to an eGFR <30 mL/min/1.73 m²), is estimated at 0.5–1% [1, 2]. In 2010, 284 individuals per million population were estimated to be undergoing maintenance dialysis (CKD G5D) throughout the world. This number is expected to increase, paralleling the rapid global increase in chronic cardio-metabolic diseases [3]. Disturbances in mineral and bone metabolism occur early in the course of CKD to become almost universal in patients with advanced disease. The term CKD–mineral and bone disorder (CKD-MBD) is currently used to describe a broader clinical syndrome which is manifested by abnormalities in bone and mineral metabolism and/or extraskelatal calcification. CKD-MBD associates with fractures and cardiovascular morbidity and mortality [4].

Osteoporosis is a condition characterized by low bone mass and/or qualitative bone deterioration that leads to bone fragility and fracture susceptibility [5]. The economic and societal burden of fragility fractures is massive, previously estimated at 37 billion € per year in 27 European countries alone, and is set to rise owing to an increasing skew towards an older population. Over the last three decades, the ability to predict those at risk has developed enormously through the use of fracture prediction tools and an increasing understanding of scanning modalities, such as dual-energy X-ray absorptiometry (DXA). Also, the armamentarium to tackle osteoporosis has continued to expand. Against this background, the observation of a huge treatment gap between those at risk of fracture and those receiving treatment for the prevention of fragility fractures is large and quite remarkable [6].

Both CKD and osteoporosis may evolve subclinically over years, with renal failure (imminent need for dialysis) and fracture, respectively, often being the presenting scenario. CKD and osteoporosis are common diseases of the elderly and often go hand in hand. Incorporated in CKD G4–G5D is a state of impaired bone quantity [7–13] and quality [14] that associates with increased fracture risk [15]. For example, patients with CKD G5D show a non-vertebral fracture risk that is 4- to 6-fold higher than the fracture risk of age- and gender-matched controls [16, 17]. Fractures are a major cause of morbidity, and compared to CKD patients without fractures, patients with fractures experience a multifold increased risk of mortality [18, 19].

While osteoporosis care in patients with CKD G1–G3 is not different from the general population, as long as there are no biochemical abnormalities suggesting the presence of CKD-MBD, osteoporosis care in patients with CKD G4–G5D remains a major challenge. The complexity of the pathophysiology of bone fragility in these patients, as well as the lack of data

on the efficacy and safety of osteoporosis medications in patients with CKD G4–G5D [20] fuel diagnostic and therapeutic inertia [21, 22]. The above-mentioned treatment gap may thus be hypothesized to be even wider in patients with CKD G4–G5D.

The scope of the present consensus paper is to review and update the assessment and diagnosis of osteoporosis in patients with CKD G4–G5D and to discuss the therapeutic interventions available and how these can be used to develop management strategies for the prevention of fragility fracture. As such, it aims to stimulate a cohesive approach to the management of osteoporosis in patients with CKD G4–G5D, to replace current variations in care and treatment nihilism. This consensus paper builds on guidance issued for the diagnosis and management of osteoporosis in postmenopausal women [23, 24]. Given the paucity of systematic reviews, meta-analyses and randomized controlled trials specifically dealing with the topic of osteoporosis in CKD G4–G5D, mainly original manuscripts have been used to provide the evidence base. In the preparation of this consensus paper, a survey on the topic was sent to members of the Committee of Scientific Advisors (CSA) and the Committee of National Societies (CNS) of the International Osteoporosis Foundation (IOF) and to members of the European Renal Association–European Dialysis and Transplant Association (ERA-EDTA) CKD-MBD working group. Results of the survey were discussed in a face-to-face meeting comprising an expert panel of nephrologists and metabolic bone specialists. This consensus paper was endorsed by the CSA and the CNS of the IOF and by the European Renal Osteodystrophy (EUROD) workgroup [25].

PATHOPHYSIOLOGY OF BONE FRAGILITY IN CKD G4–G5D

A proper understanding of the pathophysiology of bone fragility in the setting of CKD G4–G5D may help to define the optimal diagnostic and therapeutic approach. However, a detailed discussion of this topic is beyond the scope of this consensus paper and can be found in excellent reviews elsewhere [26, 27]. It is important to acknowledge that bone fragility in CKD G4–G5D is the composite of primary osteoporosis and drug-induced and CKD-related bone abnormalities. First, primary age-related and postmenopausal osteoporosis may manifest itself at a younger chronological age in CKD patients, consistent with the notion that in bone as well as other tissues, CKD is a state of accelerated/premature ageing. Second, CKD patients are often treated with a multitude of drugs, many of them with proven or putative detrimental bone effects. Examples include corticosteroids, loop diuretics, heparin, proton pump inhibitors [28] and vitamin K antagonists [29]. Third, the uraemic environment, characterized by (micro)inflammation, metabolic acidosis, accumulation of uraemic toxins [27, 30] and disturbances in calcium, phosphate, parathyroid hormone (PTH) and vitamin D metabolism, causes renal bone disease, commonly referred to as renal osteodystrophy (ROD). ROD encompasses abnormalities in bone turnover (remodelling), mineralization and volume, which alone or in combination may impair bone

strength. High turnover bone disease, which is essentially the histological expression of secondary hyperparathyroidism (SHPT), has long been the predominant type of ROD, but in the last two decades, low turnover bone disease, mostly of the adynamic type, has become increasingly prominent in dialysis patients [31–33]. Mineralization defects have waned over time and are rather uncommon in contemporary adult dialysis patients [31–33]. The uraemic milieu contributes to alterations of the biochemical composition of bone, including matrix composition, mineral:matrix ratio and crystallinity, thereby negatively affecting bone quality [30]. In addition, systemic diseases that can affect kidney function (e.g. diabetes [34], systemic lupus erythematosus [35]) and primary renal diseases (e.g. autosomal dominant polycystic kidney disease [36]) may be associated with a specific bone phenotype that may predispose to fractures.

Various paracrine and endocrine signals participate in bone remodelling, with the Wnt/ β -catenin pathway and PTH playing a central role [37, 38]. Direct effects of PTH on osteoblasts and osteocytes, and indirect actions on osteoclasts, promote both bone formation and bone resorption. The final effect on bone mass, either anabolic or catabolic, depend on the duration, intensity and periodicity of PTH exposure. Bone resorption predominates in response to continuous exposure to high circulating PTH levels, whereas intermittent PTH administration leads to a net increase in bone mass. Continuous as compared with intermittent PTH exposure regulates different sets of genes in bone cells, or alternatively, affects the same genes in a sustained versus transient manner, first favouring bone resorption and second, bone formation. PTH receptor type 1 signalling in osteoblasts and osteocytes can increase the receptor activator of nuclear factor B ligand:osteoprotegerin (RANKL:OPG) ratio. The OPG–RANKL–RANK pathway appears to be the main mediator of the catabolic actions of PTH. Moreover, continuous exposure to PTH causes a sustained upregulation of monocyte chemoattractant protein-1, another mediator of bone resorption. The anabolic effect of PTH on bone, conversely, seems to be mediated largely through canonical Wnt/ β -catenin signalling. PTH may increase Wnt/ β -catenin signalling both directly and indirectly, e.g. by repressing the osteocytic expression of secreted Wnt antagonist sclerostin [39]. Conversely, increased expression of Wnt inhibitors can oppose PTH actions in early CKD [38, 40]. It is increasingly acknowledged that PTH hyporesponsiveness is as much an integral component of CKD-MBD as elevated circulating PTH levels [41].

Signals to the bone, either mechanical or chemical (including therapeutics), can differentially affect the cortical and trabecular bone compartments [42]. Experimental and clinical evidence indicate that high PTH signalling predominantly causes cortical bone loss through increases in cortical porosity and thinning due to endocortical trabecularization [43, 44]. This may also explain why peripheral fractures are especially common in CKD patients.

DIAGNOSIS OF OSTEOPOROSIS IN CKD G4–G5D

Osteoporosis, as described by the World Health Organization (WHO) since 1994, and then by the National Institute of Health (NIH), is a condition characterized by low bone mass

and microarchitectural bone deterioration that leads to bone fragility and fracture susceptibility [5]. Its operational definition is based on an areal bone mineral density (BMD) assessed by DXA at the spine or hip ≤ -2.5 standard deviation (SD) from the BMD in young female adults. CKD G4–G5D is often considered one of the exclusions for this definition. We stand for an inclusive definition of osteoporosis, including patients with CKD G4–G5D, in spite of the contributions of ROD to the decreased bone strength in this population. Since CKD is a state of accelerated ageing, primary osteoporosis may also play a more prominent role in bone fragility in CKD G4–G5D patients than previously recognized and may eventually overcome the impact of ROD itself.

RISK FACTORS FOR FRAGILITY FRACTURES IN CKD G4–G5D

Clinical risk factors

Clinical risk factors contribute to fracture risk over and above that provided by BMD. Classic clinical risk factors for fracture include age, sex, low body mass index (BMI), parental history of hip fracture, current smoking, alcohol intake of ≥ 3 units daily and causes of secondary osteoporosis (e.g. type 2 diabetes), and probably most importantly, a previous fragility fracture. These risk factors also apply to patients with CKD G4–G5D [45]. In addition, a long dialysis duration has been identified as a risk factor for fracture in CKD G5D patients [16].

BMD

Assessment of BMD has provided a pivotal determinant of fracture risk in the non-CKD population. In general, all densitometric techniques have high specificity, but low sensitivity. DXA is widely available and is the clinical standard to measure BMD and estimate fracture risk. DXA does not have sufficient resolution to discriminate between cortical and trabecular bone or between deficits in bone volume vs. mineralization. Several sources of bias may hamper the interpretation of DXA data at the lumbar spine. These include compression fractures, calcification of the abdominal aorta, orthopaedic deformities (scoliosis, hypertrophic degenerative disease, focal sclerotic bone disease) and calcium, barium, or lanthanum within the gastrointestinal tract. Many cross-sectional and prospective population studies indicate that the risk of fracture increases by a factor of 1.5–3.0 for each 1 SD decrease in BMD. The association between BMD and fracture risk is continuous. Hence, given that osteopenia is much more common than osteoporosis, most fragility fractures occur in individuals with osteopenia. Furthermore, increases in BMD with treatment account for up to 80% of the fracture risk reduction [46, 47], confirming the critical role of reduced BMD as a risk factor for fractures and a treatment target in the non-CKD population.

An increasing body of evidence indicates that DXA may predict fractures in CKD as well as in the non-CKD population [10, 48–51], although some doubt remains as to the consistency of the fracture risk prediction by DXA across stages of CKD and the degree of PTH control [10, 48]. Accounting for these data, the KDIGO now supports BMD testing in patients with

CKD G3a–G5D with evidence of CKD-MBD and/or risk factors for osteoporosis. An important qualifier is that BMD testing should be performed only ‘if results will impact treatment decisions’ (guideline 3.2.1. 2017 update) [52]. Importantly, since DXA does not inform on bone quality, which is commonly impaired in advanced CKD, it likely underestimates the actual fracture risk in these patients. The implementation of BMD testing in clinical CKD practice raises the following practical questions: who to test, which skeletal site(s) to select and what time interval to adopt for repeat testing?

ASSESSMENT OF FRACTURE RISK

BMD as assessed by DXA

The role of BMD measurement for the assessment of fracture risk depends on the ease of access to densitometry and the overall fracture risk profile, and should not be different in individuals with and without (advanced) CKD. At present, there is no universally accepted policy for population screening (routine testing) in Europe to identify patients with osteoporosis or at high risk of fracture. Patients overall are identified opportunistically using a case-finding strategy, that is, on the finding of a previous fragility fracture or the presence of significant risk factors [23]. With the increasing development of effective agents and price reductions and improving access to densitometry, the screening policy may change, particularly for populations at high risk, including CKD patients. Reviewing guidelines for the general population, several bone societies recommend BMD screening in women and men >65 and >70 years, respectively. In younger patients, BMD screening is recommended if either postmenopausal or >50 years and considered high risk [53, 54] (International Society of Clinical Densitometry, ‘2015 ISCD official positions—adult’ 2015, <http://www.iscd.org/official-positions/2015-iscd-official-positions-adult/>). Considering CKD patients at high risk, DXA testing in patients with CKD G4–G5D may thus be considered in postmenopausal women and patients >50 years of age. This recommendation is opinion based and needs to be confirmed by large-scale screening studies. We also acknowledge the difficulty in clinically distinguishing menopause from the commonly occurring amenorrhoea in premenopausal women with advanced kidney disease.

Which skeletal site(s) to select? As in the general population, the hip and the lumbar spine are the primary skeletal sites to evaluate BMD by DXA in patients with CKD G4–G5D. Since SHPT primarily affects cortical bone, DXA data at cortical-rich skeletal sites (e.g. mid-shaft radius, 90% cortical bone; femoral neck, 75% cortical bone) may be hypothesized to allow better fracture discrimination, although clinical studies so far have largely failed to support this hypothesis [10, 55, 56]. A relatively low prevalence of hyperparathyroid bone disease in contemporary patients with CKD G4–G5D [31, 32], a high operator variability for forearm (radius) measurements and bias by a functioning arteriovenous fistula [57, 58] may have contributed to limited statistical power.

What time interval to adopt for a repeat DXA? The optimal interval for repeating DXA scans is uncertain, but because changes in BMD over short intervals are often smaller than the measurement error of most DXA scanners, at least in the general population, frequent testing (e.g. <2 years) is unnecessary in most patients, unless the rate of loss is expected to exceed the least significant change for that DXA machine (i.e. >2–3%). Even in high-risk patients receiving drug therapy for osteoporosis, DXA BMD changes at the individual level are small compared to measurement error, and changes may take >3 years to be significant [59]. Therefore, DXA should only be repeated if the result will influence clinical management or if rapid changes in BMD are expected. There is a paucity of information regarding long-term changes in (cortical and trabecular) bone mass in patients with CKD G4–G5D. Compared to individuals with normal kidney function, the decline of BMD is accelerated in elderly women with CKD [13, 60]. A recent 2-year prospective study in 89 haemodialysis (HD) patients reported a 1.2% and 3.1% decline of BMD at the total hip after 1 and 2 years, respectively; BMD at the spine was unchanged during the study period [61].

Vertebral fracture assessment

Vertebral fractures are common in patients with CKD, as in the general population [17, 62]. The majority of vertebral fractures do not come to medical attention and thus remain undiagnosed. Many guidelines for the diagnosis and management of osteoporosis in postmenopausal women emphasize the importance of identifying vertebral fractures and promote more frequent use of vertebral imaging for fracture risk assessment and determining the need for pharmacotherapy [63]. It is reasonable to adopt the International Society for Clinical Densitometry (ISCD) guidelines with regard to vertebral fracture assessment (VFA) in patients with CKD G4–G5D. The ISCD recommends lateral spine imaging with standard radiography or densitometric VFA when the T-score is <−1.0 and if one or more of the following is present: women ≥70 years or men ≥80 years of age, historical height loss >4 cm (>1.5 inches), self-reported but undocumented prior vertebral fracture, or glucocorticoid therapy equivalent to ≥5 mg of prednisone or equivalent per day for ≥3 months.

Lateral X-ray or DXA of the (lumbar) spine also allows assessment of abdominal aortic calcification [64] and thus may be useful in concomitantly stratifying cardiovascular risk [65].

Trabecular bone score (TBS) and alternative imaging techniques

The TBS is a recently developed analytical tool that performs novel grey-level texture measurements on lumbar spine DXA images, thereby capturing information relating to trabecular microarchitecture. In the general population, TBS has been shown to be a predictor of fracture independent of BMD and clinical risk factors (e.g. FRAX score) [66]. Recent evidence indicates that TBS may also represent a useful adjunct to BMD to discriminate non-vertebral fracture status in the dialysis population [67] and to predict fractures in patients with mild renal impairment and after kidney transplantation [68]. However,

TBS as well as other DXA-based bone texture measurements need further evaluation before their implementation in clinical practice can be advocated.

Alternative imaging techniques, able to distinguish between cortical and trabecular bone, such as high-resolution peripheral quantitative computed tomography (HR-pQCT) and magnetic resonance imaging, have been postulated to be superior to DXA in discriminating fractures in CKD, but so far have yielded conflicting results [43, 69–72]. QCT may be more sensitive than DXA for monitoring bone loss at the hip in CKD [61].

Falls risk

Falls history is an independent risk factor for fracture in the general population [73]. In CKD patients as well, a history of falls associates with fractures [74]. The falls risk should be taken into consideration when assessing whether to commence medication for osteoporosis, and should also alert the physician to the opportunity to target falls risk directly (see below). According to a secondary analysis of data collected in the 2014 Behavioral Risk Factor Surveillance System, adults ≥ 65 years of age with CKD are at increased risk of falling and of suffering an injury as a result of a fall compared with adults in the same age range without CKD [75]. Dialysis patients also have a higher falls risk than non-CKD counterparts [76–78]. Key to minimizing falls risk is an evaluation of secondary causes, including (orthostatic) hypotension, bradycardia, psychotropic drugs, sarcopenia, neuropathy and decreased vision. Various simple questionnaires allow estimates of the falls risk to be made. Poor performance on tests of neuromuscular function (including timed up-and-go and 6-min walk tests) also may identify those at higher risk of fracture in CKD [74]. This likely reflects their higher risk of falls due to impaired muscle strength.

Fracture risk assessment tools

The limitations of DXA BMD for risk assessment have stimulated the development of risk prediction algorithms that integrate several risk factors for fracture. These include the Garvan fracture risk calculator, QFracture and FRAX. Of these, FRAX (<https://www.sheffield.ac.uk/FRAX/tool.aspx>) has been the most extensively used [23]. FRAX is a computer-based algorithm that calculates the 10-year probability of a major fracture (hip, clinical spine, humerus or wrist fracture) and 10-year probability of a hip fracture. A unique feature of FRAX is that it considers competing mortality in the fracture risk estimation procedure. The various FRAX tools have been refined in different countries to take into account the genetics of bone fracture risk. There are many risk factors for fractures used in FRAX, including age, sex, BMI, family history, alcohol use, smoking, glucocorticoids and rheumatoid arthritis. There is also an option to say yes or no to secondary osteoporosis, including diabetes, osteogenesis imperfecta, long-standing hyperthyroidism, hypogonadism, premature menopause, chronic malnutrition or malabsorption and chronic liver disease. FRAX is an easy and well-validated tool, but it also has some limitations, e.g. it does not account for dose responses or time dependency of several key risk factors or incorporate falls risk. Noticeably absent in the list

of secondary causes of osteoporosis is the presence of CKD. Despite this limitation, mounting evidence confirms that FRAX performs as well in patients with CKD as in the general population for fracture discrimination and fracture risk prediction [50, 76, 79, 80]. Intuitively, one would expect FRAX to underestimate fracture risk in CKD as it does in diabetes mellitus. However, both under- and overestimation of the absolute fracture risk have been reported [50, 80]. As previously mentioned, the FRAX risk engine considers competing mortality in the fracture risk estimation procedure. CKD patients not only have an increased fracture risk, but also a limited life expectancy. The impact of CKD on the FRAX score thus may prove to be neutral. Additional large epidemiological studies are required to define whether further arithmetic adjustments to conventional FRAX estimates have to be made with knowledge of CKD G4–G5D. At least in the general population, FRAX with BMD can identify fractures better than FRAX alone [81].

Biochemical markers of bone turnover

In the general population, bone-specific alkaline phosphatase (BALP), procollagen type I N propeptide (PINP) and C-terminal cross-linking telopeptide of type I collagen (CTX) associate with future risk of fractures, although modestly at best [82–84]; and the ability of CTX and PINP to predict incident hip fractures in postmenopausal women has recently been challenged [85]. The association of BTMs with fracture risk in individuals with CKD is even less clear. To avoid bias related to renal retention, BTMs that are not cleared by the kidneys, such as BALP, trimeric PINP and tartrate-resistant acid phosphatase-5b (TRAP-5b), should be considered in the setting of CKD. Total alkaline phosphatase, which is routinely monitored in CKD patients, is a valid surrogate for BALP in the absence of liver dysfunction. Epidemiological data suggest a simple, linear relationship between total alkaline phosphatase levels and fracture risk in CKD patients [86]. In HD patients, BALP outperformed DXA and PTH for the prediction of fracture incidence [48]. After kidney transplantation, the association of BALP, PINP and TRAP5b with fracture risk is less clear [10]. Studies investigating the association between PTH and fracture risk show a complex J- or U-shaped relationship, with both very high and very low PTH levels conferring an increased fracture risk [16, 87, 88]. This observation aligns with clinical and experimental data indicating that both low and high PTH levels with the corresponding low or high bone turnover may impair bone quality [14].

INTERVENTION THRESHOLDS FOR PHARMACOLOGICAL THERAPY

BMD as assessed by DXA

Whereas BMD provides the cornerstone for the diagnosis of osteoporosis, the use of a fixed BMD cut-off is less than optimal as an intervention threshold. Fracture probability may indeed differ according to the country of origin and age category [23]. A T-score ≤ -2.5 at the hip or lumbar spine has been used as an inclusion criterion in most registration studies evaluating

antiosteoporotic drugs for postmenopausal osteoporosis and is widely adopted as an intervention threshold in the osteoporosis literature. It should be acknowledged that the choice of this intervention threshold is purely arbitrary. Intervention thresholds have ranged from T-scores of -3.0 to -1.5 depending on the clinical context, the country or health economic factors. In diabetics, the intervention threshold has been set as -2.0 , accounting for the fact that fracture risk at -2.0 in diabetics is similar to risk at -2.5 in nondiabetics [89]. Unfortunately, comparable data for CKD patients are lacking. Therefore, a T-score intervention threshold ≤ -2.5 at the lumbar spine or hip is recommended, recognizing that a higher threshold of -2.0 or -1.5 may be more appropriate.

Fracture risk as assessed by FRAX

Awaiting the results of additional large epidemiological studies defining whether arithmetic adjustments to conventional FRAX estimates have to be made with knowledge of CKD G4–G5D, conventional country-specific intervention thresholds as defined for postmenopausal women may be used as rough guides for patients with CKD G4–G5D [23]. The intervention threshold is most commonly set at the age-specific fracture probability equivalent to individuals with a prior fragility fracture and therefore rises with age. In other words, the intervention threshold is set at the ‘fracture threshold’. The thresholds used have varied since they depend critically on local factors such as reimbursement issues, health economic assessment and willingness to pay for health care in osteoporosis and access to DXA.

History of fragility fracture

As previously emphasized, fragility fractures of the long bones (arms, legs), spine and pelvis are associated with an increased risk of future fractures [19, 90], especially in the 12 months following the event [91]. Individuals >50 years of age with a history of fragility fracture may be considered for intervention without the necessity of a BMD test (other than to monitor treatment).

MANAGEMENT

The management of osteoporosis in patients with CKD G1–G3 is the same as for the general population, as long as there are no biochemical abnormalities suggesting the presence of CKD-MBD. Clinicians dealing with such patients are referred to guidance and guidelines as issued by several bone and endocrine societies [23]. The management of osteoporosis in patients with CKD G4–G5D is more challenging. Concerns with regard to efficacy and safety of available non-pharmacological and pharmacological approaches in the setting of CKD G4–G5D cause hesitancy and inertia among clinicians. A recent systematic review, updating evidence on the efficacy and safety of common osteoporosis medications (including bisphosphonates, teriparatide, raloxifene and denosumab) among CKD patients concluded that effects on BMD, fracture risk and safety are not clearly established [20]. That being said, the absence of evidence does not equate to evidence of an absence of effect. Many large registration trials of new osteoporosis drugs excluded patients

with overt renal failure (CKD G4–G5D), mainly for two reasons: renal safety concerns and unpredictable bias by ROD. This consensus paper aims to provide some guidance on the management of osteoporosis in patients with advanced CKD, but we are awaiting further high-quality data [92]. Reflecting the complex pathophysiology, therapy of osteoporosis in CKD G4–G5D should be multifaceted and include control of CKD-MBD, control of uraemia and specific osteoporosis management.

Control of CKD-MBD

A first step in controlling the fracture risk in CKD G4–G5D patients is optimizing CKD-MBD treatment. A detailed discussion of the optimal treatment of CKD-MBD is beyond the scope of this position paper and can be found in recent guidelines and review papers [52]. We herein briefly elaborate on the role of a bone biopsy and BTMs in the workup of a patient with osteoporosis and advanced CKD.

Histomorphometric analysis of a tetracycline double-labelled iliac crest bone biopsy remains the gold standard for the diagnosis of disturbances of bone turnover and mineralization in CKD, both of which may affect bone strength independent of bone mass. Bone biopsies are underused by clinicians, largely because of the invasive character of the procedure, but also because worldwide only a few centres are able to perform histologic and histomorphometric analyses of bone biopsies and the expertise is progressively vanishing. Current procedures using Yamshidi-type needles with an inner diameter <4 mm, local anaesthesia and light sedation (midazolam) are better tolerated and can easily be performed in an outpatient setting [25]. Further, there is considerable variability between biopsies taken from different sites at the same time in the same patient [93].

Several circulating biomarkers have been suggested for the clinical differentiation between high and low bone turnover in CKD, the most well established being PTH and BALP (see above). The quest for the optimal BTM (panel) is ongoing, but so far no single biomarker, or combination of biomarkers has approached the diagnostic accuracy of a bone biopsy [94]. The association of fibroblast growth factor 23, sclerostin and circulating microRNA signatures with bone health in patients with CKD remains a topic of ongoing research [95–97]. Individual treatment decisions should be based on trends of BTMs rather than on single time point levels [52].

Importantly, although a bone biopsy may still be relevant in the workup, the KDIGO emphasizes that the inability to perform a bone biopsy may not justify withholding osteoporosis therapy from patients with a high risk of fracture [52].

Control of uraemia

Efforts should be made to correct metabolic acidosis [98], to avoid chronic mild hyponatraemia [99], to reduce CKD- and age-related inflammation [100] and to clear uraemic toxins with proven or putative skeletal toxicity [27, 30].

Non-pharmacological osteoporosis management

Mobility and falls. Immobilization causes bone loss. Immobilized patients may lose as much bone in a week as they would otherwise lose in a year. Weight-bearing exercise forms

an integral component of osteoporosis management. This may be highly relevant in HD patients, as these patients commonly show a poor and rapidly deteriorating physical performance. Studies investigating the relationship between physical activity and BMD in HD are few, and so far have been negative [28]. Exercises to improve muscle strength and balance may reduce the likelihood of falls and may prove effective in reducing fracture rates.

Nutrition. Adequate dietary intakes of key bone nutrients, such as calcium and vitamin D, contribute to bone health and reduce the risk of osteoporosis and fracture. The Recommended Nutrient Intakes (RNIs) are 1000–1200 mg of calcium and 600–800 IU of vitamin D per day in men and women >50 years of age [101, 102]. The validity of these figures in CKD G4–G5D patients is unclear, given the complexity of calcium homeostasis in this specific setting.

Data from small cohort studies indicate that dietary calcium intake falls below the RNI in a substantial proportion of CKD patients, both in the USA [103, 104] and Europe [28, 105]. Regional variability may be anticipated, reflecting dietary heterogeneity [106, 107]. In general, CKD patients free of calcium supplements should be considered at risk of a negative calcium balance [103, 108], which in turn may be a neglected culprit of a low bone mass [28, 109]. It is recommended to estimate calcium intake in CKD patients at risk of osteoporosis and fracture (e.g. through user-friendly online calculators) and to adjust dietary intake and/or calcium supplements accordingly. Acknowledging potential cardiovascular risks, the total exogenous elemental calcium supply should not exceed 1200 mg/day. In patients on dialysis, calcium transfers from the dialysate should additionally be accounted for when estimating dietary calcium needs [108].

Acknowledging that patients with CKD G4–G5D are often vitamin D depleted, the KDIGO recommends monitoring 25-hydroxyvitamin D [25(OH)D; calcidiol] levels and correcting vitamin D insufficiency and deficiency using treatment regimens with nutritional vitamin D as recommended for the general population [110]. The optimal supplementation regimen remains to be defined, but the goal should at least be the same as for non-CKD patients, namely an optimal 25(OH)D level of 20–30 ng/mL (50–75 nmol/L) [102]. Large intermittent doses of nutritional vitamin D should be avoided, as such regimens have been associated with an increased risk of fractures and falls.

Vitamin K deficiency is common among patients with CKD G4–G5D [29, 111]. Mounting epidemiological evidence shows an association between vitamin K status and fracture risk in patients with CKD G4–G5D [29, 112]. However, it is too premature to support the routine monitoring of vitamin K status or supplementation with vitamin K in these patients.

Lifestyle modifications. Evidence is limited, but multimodal exercise programs, moderation of alcohol consumption and cessation of smoking have been associated with improved bone health in the general population [113] and therefore their implementation should also be considered in patients with CKD G4–G5D.

Pharmacological osteoporosis management

The most commonly used osteoporosis drugs in Europe are bisphosphonates, denosumab and agents derived from PTH. Recently, romososumab has been approved for the treatment of osteoporosis. These have all been shown to reduce the risk of vertebral and non-vertebral fracture in postmenopausal women and, in some cases, agents have been shown specifically to decrease the fracture risk at the hip. In studies of men, most outcome measures have included BMD and BTMs as surrogates for efficacy, with no fracture endpoints [114].

Fracture prevention trials for osteoporotic treatment agents included some patients with creatinine in the normal laboratory range, but with decreased kidney function as determined by eGFR. Registration studies thus enabled evaluation of the efficacy and safety of common osteoporosis medication in (female) patients with impaired kidney function as low as CKD G4. It is important to note that all these studies were *post hoc* analyses of otherwise healthy individuals with no significant aberrations in markers of mineral metabolism and that the follow-up time was rather short (at most 3 years). Treatment recommendations in this consensus paper (Table 2) are focused on postmenopausal women and men >50 years of age. Evaluation and treatment of younger patients with advanced CKD at increased fracture risk are complex and should be individualized.

Bisphosphonates. *Mode of action.* Bisphosphonates are stable analogues of the inorganic compound pyrophosphate. They have a strong affinity for bone apatite, both *in vitro* and *in vivo*, which is the basis for their clinical use. Bisphosphonates are potent inhibitors of bone resorption and produce their effect by reducing the recruitment and activity of osteoclasts. The potency and mechanism of action vary depending on the length and structure of the side chain. The nitrogen-containing bisphosphonates alendronate, ibandronate, risedronate and zoledronic acid are currently most commonly used [115, 116].

Pharmacokinetics and pharmacodynamics. Oral bioavailability of bisphosphonates is low, ~1% of the dose ingested, and is impaired by food, calcium, iron, coffee, tea and orange juice. Bisphosphonates are not metabolized. Between 27% and 62% of the drug binds to bone mineral and the rest is excreted via the kidneys, predominantly within hours after administration. Of note, the concentration of bisphosphonates is lower in cortical than trabecular bone [117]. The role of bone turnover on skeletal accumulation of bisphosphonates remains unclear; recent preclinical data challenge the hypotheses that skeletal accumulation is increased in high bone turnover states [117]. Bisphosphonates persist in bone for a long time, are slowly released during cycles of bone remodelling and can re-enter the systemic circulation, and also the kidney, with no change observed in their molecular structure or metabolic activity. Renal excretion occurs by both passive glomerular filtration and active transport in renal proximal tubular cells. Experimental and clinical evidence show increased serum half-life and renal accumulation in the setting of CKD [118]. Bisphosphonates are cleared by dialysis [119]. The efficacy of dialytic clearance varies between bisphosphonates, probably owing to variable protein binding. Alternative dosing regimens in CKD (lower dose,

lower frequency), though theoretically logical, have so far not been validated using clinical endpoints.

Efficacy. *Post hoc* analyses of pivotal clinical trials evaluating bisphosphonates found that these drugs had similar efficacy, improved BMD and reduced fractures, in subjects with mild or moderately reduced eGFR (up to CKD G4) compared to those with normal eGFR [120–122]. Studies investigating the efficacy of bisphosphonates in patients with CKD G5, including those on dialysis, or in patients with earlier stage CKD presenting with biochemical disturbances of mineral metabolism are scarce, limited by small sample size and yielded inconsistent findings [123–127]. Patients with high bone turnover at baseline may be anticipated to show the highest BMD gains [128].

Safety. Bisphosphonates have been suggested to compromise skeletal, vascular and renal health. These risks call for caution, but need some nuance.

Suppression of bone turnover is inherent to bisphosphonates and most osteoporosis patients who are treated with bisphosphonates develop a low bone formation rate. However, there is no evidence that the level of remodelling suppression in CKD is more than that in non-CKD counterparts [129]. Implications of drug-induced suppression of bone turnover towards bone strength are intensely debated. Decreased bone resorption and formation lead to more secondary mineralization in the bone, so that the bone becomes harder. This may contribute to improving bone strength and reduced fracture risk [130]. Bone remodelling suppression, on the other hand, may also increase collagen cross-linking by advanced glycation end products and thus impair bone quality. Furthermore, according to a recent bone biopsy study, overmineralization (often referred to as brittle bone) may impair toughening mechanisms in cortical bone, which in turn may confer an increased risk of atypical fractures [131]. Data from a 2015 study of alendronate in postmenopausal women, conversely, suggest that even a prolonged reduction in bone turnover is unlikely to be associated with adverse effects on bone material properties [132]. In CKD patients, low PTH levels, as a proxy of low bone turnover, have been associated with increased fracture risk [87, 133]. These findings remain to be confirmed by formal bone biopsy studies. Furthermore, it remains a matter of debate whether low bone turnover *per se* or the disease causing low bone turnover is accountable for the perceived increased fracture risk. Of note, the 2017 KDIGO update no longer considers a bone biopsy mandatory prior to initiating bisphosphonate therapy [52].

Theoretically, bisphosphonates may both accelerate and attenuate vascular calcification. On the one hand, bisphosphonates reduce bone formation and thereby reduce the ability of bone to buffer exogenous calcium influx. A decreased buffering capacity may increase the risk of transient hypercalcaemia and as such promote vascular calcification. In postmenopausal women treated with antiresorptive therapy, however, accelerated vascular calcification has not been reported [134]. On the other hand, bisphosphonates may be hypothesized to suppress vascular calcification. The mechanism may be multifactorial. First, bisphosphonates are analogues of pyrophosphate, which is a potent vascular calcification inhibitor. However, at least in patients with good renal function, conventional doses of

nitrogen-containing bisphosphonates fail to yield circulating concentrations that are sufficient to exert direct anticalcifying effects. Second, by reducing bone turnover, bisphosphonates reduce the bone efflux of phosphate and calcium. In clinical studies, the first-generation drug etidronate markedly reduced progression of vascular calcification in CKD patients [135], while recent-generation nitrogen-containing bisphosphonates (alendronate, ibandronate) yielded inconsistent vascular outcomes [124, 126, 134].

Bisphosphonates have historically been associated with a risk of acute kidney injury (acute tubular necrosis, focal segmental glomerulosclerosis). According to a 2003 review, however, these agents can be administered to patients with various degrees of renal impairment, with no long-term decline in renal function if used with care and in accordance with the prescribing information. This applies to both oral and intravenous (IV) bisphosphonates. Nevertheless, the low incidence of renal adverse events has led to the inclusion of warnings on the prescribing information of all bisphosphonates regarding the use of these agents in patients with severe renal impairment (creatinine clearance < 30 or < 35 mL/min). For IV zoledronic acid, this warning constitutes a contraindication in the registration labels for patients with eGFR < 35 mL/min [136]. Renal risks should be considered when defining the individual risk:benefit ratio in patients with osteoporosis and CKD, even in patients with CKD G5D, as long as there is residual renal function. There is no need for supplementary renal function testing following the initiation of bisphosphonates in patients with CKD G4–G5D.

Other safety concerns with bisphosphonates include an acute phase reaction (IV bisphosphonates only), oesophagitis, atrial fibrillation, hypocalcaemia, osteonecrosis of the jaw (ONJ) and atypical subtrochanteric fractures. The incidence of ONJ and atypical fractures in the osteoporosis patient population is very low and is estimated at 1–90 and 7–9 per 100 000 patient-years of exposure, respectively [137–139]. Otherwise stated, for each atypical femur fracture, >1200 fractures, including 135 hip fractures, are prevented [137]. For ONJ and atypical subtrochanteric fractures, the risk is reported to be higher with a longer duration of bisphosphonate therapy. Pre-existing dental disease and prior dental extraction are the highest risk factors for ONJ. Any dental disease that requires intervention and poor oral hygiene should be addressed prior to proceeding with antiresorptive therapy [138, 139].

In aggregate, the efficacy and safety of bisphosphonates in patients with CKD G4–G5D need further clarification. However, at present there is no clear reason to assume that the overall risk:benefit ratio of therapy with bisphosphonates is less favourable in patients with CKD G4–G5D than in the general population. When considering off-label use, patients should be properly informed about potential risks, benefits and alternatives and notes should be included in the patients' files [140]. Whether a different dosing regimen is required and whether the duration of therapy should be shorter in patients with CKD G4–G5D remains to be investigated. Awaiting this evidence, classical dosing regimens may be used in patients with CKD

G4–G5D, although regimens using lower doses or longer intervals may be equally valid. In patients without residual renal function (no renal risks), intravenous formulations may be preferred in order to limit pill burden, to avoid interference with phosphate binders (lower bioavailability) and to exclude non-adherence. As in the general population, it is reasonable to reassess CKD patients after 3 years of therapy or after a new fracture using FRAX with femoral neck BMD.

Denosumab. *Mode of action.* Denosumab is a fully human monoclonal antibody against RANKL, a cytokine that is essential for the formation, function and survival of osteoclasts. By binding RANKL, denosumab prevents the interaction of RANKL with its receptor, RANK, on osteoclasts and osteoclast precursors and reversibly inhibits osteoclast-mediated bone resorption [115, 116].

Pharmacokinetics and pharmacodynamics. In contrast with bisphosphonates, renal function does not have a significant effect on denosumab pharmacokinetics and pharmacodynamics [141].

Efficacy. Administration of IV denosumab every 6 months has been shown to improve BMD in CKD G4–G5D in a *post hoc* analysis of the large Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM) registration trial [142] and in small open-label pilot studies [126, 143, 144]. As for bisphosphonates, it can be speculated that BMD gain will be less in patients with low bone turnover at baseline, although there is no hard evidence to support this view. Animal data indicate that denosumab may impact on bone not only by suppressing bone resorption, but also by maintaining, and perhaps slightly stimulating (periosteal), modelling-based bone formation [145]. The contribution of periosteal modelling-based bone formation to the overall BMD gains in denosumab-treated patients remains to be defined. Periosteal modelling-based bone formation may explain why steady BMD gains are observed during prolonged remodelling inhibition in the general population [146], and may also have contributed to the up to 5% increase in lumbar spine bone mass reported in denosumab-treated *de novo* renal transplant recipients [147], many of which may have had low–normal bone turnover at baseline.

Safety. A major concern with the use of denosumab in CKD is the increased risk of severe and symptomatic hypocalcaemia. The risk of denosumab-induced hypocalcaemia seems to be highest in patients with increased bone turnover at baseline. According to a recent meta-analysis, calcium levels reach a nadir in the first 2 weeks to 2 months after dosing [143]. This complication resembles hungry bone syndrome, observed following potent PTH suppression therapy [148]. Hypocalcaemia can be alleviated by preemptive calcium and vitamin D supplementation and using a high-calcium bath in dialysed subjects [143, 149].

Another major concern is the offset of effect. While bisphosphonates are retained by the skeleton and treatment cessation is associated with slow bone release, for denosumab the bone loss is rapid. All the bone gain on therapy at the hip is lost within 6 months, and cessation of therapy is associated with a 30% increase in vertebral fractures (4.2% versus 3.2%) [150]. Hence denosumab should either be administered continuously or followed by some alternative antiresorptive therapy. BTMs

may be useful to monitor the offset of effect in patients (see below) [151].

From a nephrological perspective, similar concerns as for bisphosphonates exist for denosumab with regard to potential implications of decreased bone turnover on bone strength. As previously mentioned, steady BMD gains are observed during prolonged remodelling inhibition with denosumab in the general population, while bone strength is preserved [146]. It needs to be re-emphasized that (iatrogenic) low bone turnover does not equal low bone turnover disease/dynamic bone disease. The mechanisms contributing to the latter, rather than the low bone turnover *per se*, may underlie the association of low bone turnover disease/dynamic bone disease with poor outcomes. An association between low bone turnover disease/dynamic bone disease (as determined by histomorphometry) and incident fractures remains to be demonstrated.

Whereas in the bone compartment the role of RANKL and OPG is well defined, in the vascular compartment it is more controversial, as preclinical findings [152] are not consistent with human epidemiological observations [153, 154]. It is reassuring that in a *post hoc* analysis of the FREEDOM trial, the frequency of aortic calcification (AC) progression >3 years did not differ between postmenopausal women in the placebo (22%) and denosumab (22%) groups ($P = 0.98$). Of note, AC progression also did not differ between treatment groups when analysed by baseline eGFR or by baseline AC scores [155]. Along with these findings, therapy with either alendronate or denosumab up to 1 year did not affect vascular health indices (including vascular calcification scores) in dialysis patients [126, 156].

As with bisphosphonates, denosumab therapy associates with ONJ and atypical fractures, but absolute risks are very low [138]. Whereas bone turnover is permanently suppressed for the duration of bisphosphonate therapy and even thereafter (long skeletal $t_{1/2}$), bone turnover in denosumab-treated patients shows an early profound decrease and thereafter partly recovers up to the next administration. Whether these differences in pharmacodynamics translate into different risks of atypical fractures remains to be seen.

Evidence from recent trials suggests that the risk of new clinical and vertebral fractures increases when treatment with bisphosphonates or denosumab is stopped. These data question the view that patients on long-term treatment with bisphosphonates or denosumab should always be offered a drug holiday. Different pharmacokinetic properties for different therapies and target populations require different strategies to manage drug intermission [139].

Finally, it is important to note that antiresorptive agents do not impair fracture healing.

PTH analogues. *Mode of action.* Teriparatide (PTH1–34) is a recombinant peptide consisting of the first 34 amino acids of human PTH. Teriparatide regulates both bone formation and resorption, whereby intermittent exposure results in the restoration of bone microarchitecture through an increase in the number and thickness of trabeculae and accelerated mineralization. It may also increase cortical thickness, mainly by endocortical apposition; however, cortical bone density decreases

due to intracortical remodelling and an increase in cortical porosity. Abaloparatide is an analogue of PTH-related peptide designed to have relatively greater affinity for the transient state of PTH1 receptor, thus potentially being more anabolic [116].

Pharmacokinetics and pharmacodynamics. Giving PTH to patients with CKD-MBD, in whom hyperparathyroidism is a prominent feature, seems counterintuitive. However, high levels of circulating PTH does not equal high PTH signalling. PTH hyporesponsiveness or resistance is a major issue in CKD G4–G5D [41] and may explain why bone turnover is low–normal in the majority of dialysis patients, despite these patients presenting with high PTH levels [31, 32]. Intermittent PTH boluses in patients with absolute or relative hypoparathyroidism may be hypothesized to elicit an anabolic bone response and improve bone strength. The impact of CKD on the pharmacokinetics and pharmacodynamics of PTH analogues remains to be investigated. Recent animal data suggest that intermittent teriparatide therapy may elicit an anabolic response in bone even in the presence of secondary hyperparathyroidism [157].

Efficacy. Data proving the efficacy of teriparatide in CKD are scarce. One double-blind trial of 1637 ambulatory postmenopausal women treated with teriparatide found that reductions in the risk of vertebral and non-vertebral fractures, as well as treatment-emergent and renal-related adverse events, were similar among patients with mild to moderate vs. without renal impairment [158]. A *post hoc* analysis of a post-marketing study in Japan also showed promising results in female patients with CKD G4–G5D not yet on dialysis [159]. Pilot studies in dialysis patients focused on patients with hypoparathyroidism [160] or proven adynamic bone disease [123, 161]. In these patients, teriparatide increased (lumbar spine) BMD and biomarkers of bone formation. Taken together, teriparatide may be a valid option in patients with CKD G4–G5D in whom high bone turnover has been excluded. The optimal dosing regimen (dose, frequency) remains to be determined. Patients with irreversible adynamic bone disease (e.g. due to post-parathyroidectomy hypoparathyroidism) may be particularly suited for teriparatide therapy. Experimental and clinical evidence demonstrate the ability of abaloparatide to increase bone mass and formation with less risk of hypercalcaemia. Data in patients with CKD-MBD are lacking.

Safety. Transient hypotension has been reported in 36% of HD patients treated with once-weekly teriparatide [160]. Because of the long-term risk of osteosarcoma in preclinical models, the duration of therapy with PTH should not exceed 2 years.

Romozosumab. *Mode of action.* Romozosumab is a fully human monoclonal antibody against sclerostin. Sclerostin is a glycoprotein almost exclusively secreted by osteocytes. It inhibits Wnt signalling, which is a key negative regulator of bone formation over resorption, it could provide great utility in treating osteoporosis in patients with CKD G4–G5D, given the high prevalence of low bone turnover in this patient population. Of note, anti-sclerostin antibody treatment in animals with advanced CKD improves bone properties only when the PTH

levels are low [162]. These data raise the hypothesis that anti-sclerostin antibodies might not work in the presence of high PTH. However, this hypothesis conflicts with other experimental studies showing synergistic effects of PTH analogues and sclerostin antibodies [163].

Pharmacokinetics and pharmacodynamics. Data on the impact of CKD G4–G5D on the pharmacokinetics and pharmacodynamics of romozosumab are limited. Following a 210-mg dose of romozosumab in a clinical study of 16 patients with CKD G4–G5D, the mean maximum serum concentration and area under the curve were 29% and 44% higher, respectively, in patients with severe renal impairment compared with healthy subjects, Romozosumab exposure was similar between patients with end-stage renal disease requiring HD and healthy subjects (UCB data on file: 2.7.2 Romozosumab Summary of Clinical Pharmacology Studies; Section 3.3. Subjects with renal impairment; p. 83).

Population pharmacokinetic analysis indicated an increase in romozosumab exposure with increasing severity of renal impairment. However, as the exposure in severely impaired renal function is below that of tolerated clinical doses, this increase is not considered clinically meaningful and no dose adjustment is necessary in these patients.

Efficacy. In clinical trials, romozosumab resulted in an increase in BMD to a greater extent than alendronate and teriparatide and a decrease in the risk of vertebral and non-vertebral fractures in postmenopausal women [164–166]. Romozosumab also increased the spine and hip BMD compared with placebo in men with osteoporosis [114]. Furthermore, of great interest to patients with CKD, which is associated with cortical losses from the actions of PTH, Langdahl *et al.* [167] reported that cortical BMD increased in greater proportion to trabecular BMD >12 months in patients switched from a bisphosphonate to romozosumab. Moreover, the comparator group, in which subjects were switched to teriparatide, experienced a decrease in cortical BMD. It is interesting to note that the BTM data from these trials suggested an uncoupling of bone remodelling in favour of bone formation, which might be an advantageous pharmacologic property for patients with CKD. For example, bone formation markers increased within a week of administration of romozosumab and peaked at 14 days to 1 month before declining towards or below baseline levels, whereas bone resorption markers decreased from baseline within a week of administration and remained below baseline for at least 12 months [164–166]. Recent follow-up data indicate that the sequence of romozosumab followed by denosumab may be a promising regimen for the treatment of osteoporosis [168]. On 9 April 2019, the US Food and Drug Administration approved romozosumab for the treatment of postmenopausal women, with no eGFR cut-off. Data on the efficacy of romozosumab in CKD patients are lacking. Similar to denosumab, a bone turnover rebound and rapid bone loss have been observed after romozosumab. Hence patients who discontinue romozosumab should rapidly transition to an antiresorptive treatment.

Safety. Some of the large registration trials raised some concerns with regard to the cardiovascular safety of romozosumab. Saag *et al.* [165] showed an increase in serious cardiovascular

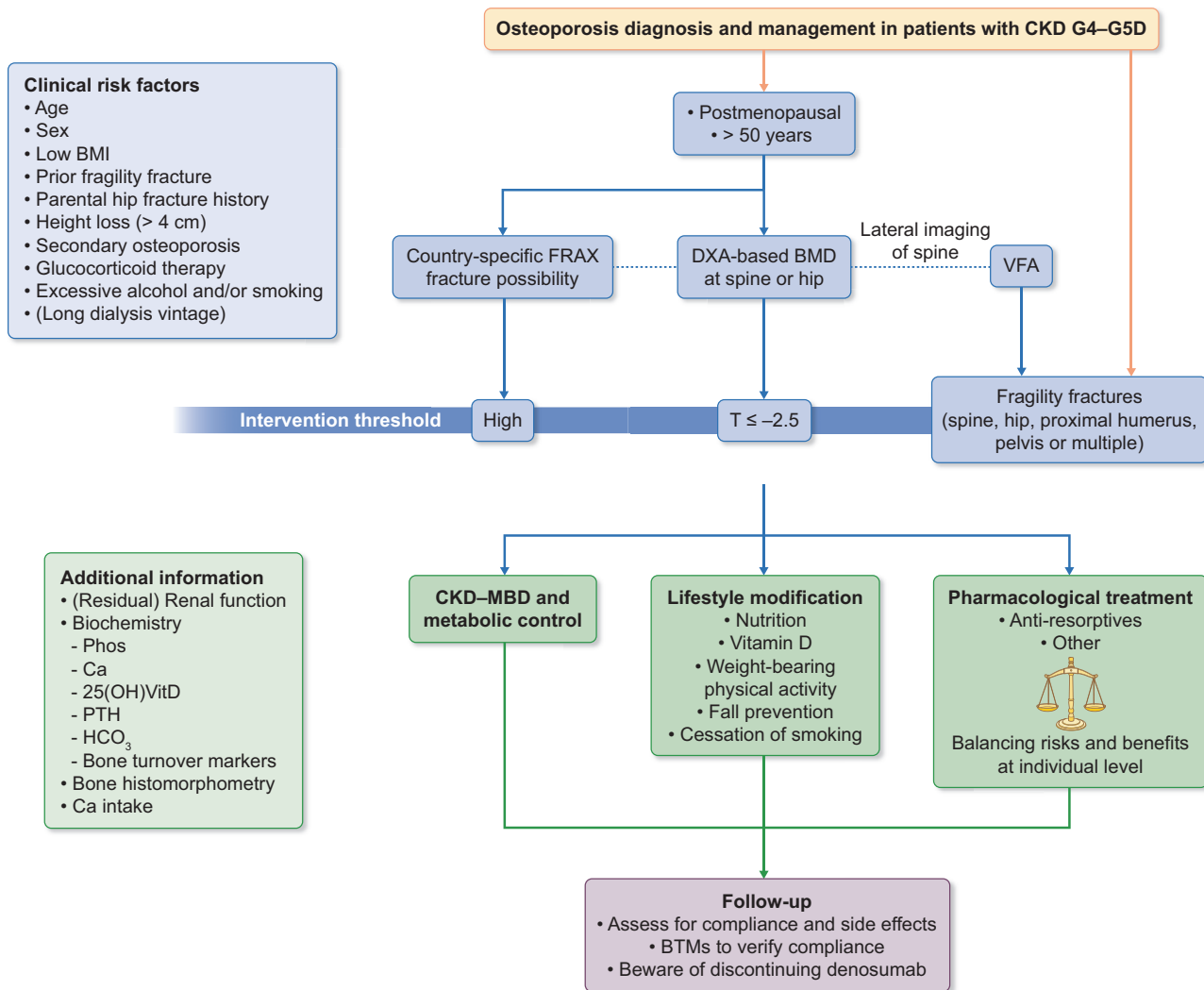


FIGURE 1: Pragmatic approach to patients with CKD G4–G5D and osteoporosis.

adverse events [odds ratio 1.31 (95% confidence interval 0.85–2.00)] in postmenopausal women with osteoporosis given 12 months of romosozumab followed by 12 months of alendronate versus 24 continuous months of alendronate [165]. It is important to note that cardiovascular events have not been reported in other studies [166, 167]. Whether these results indicate that romosozumab increases cardiac risk, or that alendronate is cardioprotective is not known. In a recent phase 3 randomized placebo-controlled double-blind study in men with osteoporosis, Liewicki *et al.* [168] also noted a high number of adjudicated cardiovascular serious adverse events in romosozumab-treated patients (4.9% versus placebo 2.5%). Sclerostin is constitutively expressed in the arterial vasculature and upregulated in foci of vascular calcification. Similar findings have been shown in experimental models with other Wnt inhibitors such as dickkopf-related protein 1 (DKK1) and secreted frizzled-related protein (Sfrp) [38]. Vascular sclerostin may provide a pathophysiological clue to the putative increased cardiovascular risk in romosozumab-treated individuals. Experimental and clinical data suggest that sclerostin may act as a paracrine calcification inhibitor, similar to OPG [169, 170].

Additional experimental and clinical studies are required to investigate the vascular role of sclerostin and to define whether systemic blocking of sclerostin confers cardiovascular risks, and if so, whether this is condition-dependent [171].

MONITORING

Adherence

Non-adherence to medical therapy is a widespread public health problem, and especially common in patients with CKD, including those on dialysis. Several patient-, disease- and treatment-related factors can contribute to non-adherence in CKD patients [172]. In general, overcoming non-adherence presents particular challenges in asymptomatic bone diseases and other chronic, asymptomatic conditions. One-year compliance is 50–70% for antihypertensives and 25–40% for statins. Similarly, compliance is poor with osteoporosis therapies, ranging from <25% to ~75% at 1 year, with mean persistence around 245 days [173]. In such settings, the level of perceived threat to health does not motivate the patient to adhere to therapy. In

Table 1. Clinical risk factors used for assessment of fracture probability

General risk factors
Older age
Gender (female)
Low BMI
Previous fragility fracture, particularly of the hip, wrist and spine, including morphometric vertebral fracture in adult life
Parental history of hip fracture
Glucocorticoid treatment (>5 mg prednisolone daily or equivalent for ≥ 3 months)
Current smoking
Alcohol intake ≥ 3 units daily
Causes of secondary osteoporosis
Rheumatoid arthritis
Untreated hypogonadism in men and women
Inflammatory bowel disease
Prolonged immobility
Organ transplantation
Type 1 and type 2 diabetes
Thyroid disorders, e.g. untreated hyperthyroidism, thyroid hormone suppressive therapy
Chronic obstructive pulmonary disease
HIV infection
CKD-related risk factor
Dialysis vintage

addition, risk of non-adherence with any therapy increases with increased duration of treatment. Poor adherence to medication is associated with adverse effects on outcomes. Patients' belief in a medication contributes to better adherence, emphasizing the important role of patient education and counselling.

Methods of monitoring of treatment

The different methods of monitoring response to anti-osteoporosis medication include patient-reported outcomes, clinician interview, patient questionnaire, BTMs, BMD and other imaging modalities.

BMD as assessed by DXA. Treatment periods ≥ 3 years are necessary to show a measurable and reproducible BMD response to oral bisphosphonate therapy in postmenopausal women [59]. Early monitoring of BMD thus has limited value in the prediction of treatment responses, at least with inhibitors of bone resorption, and as such is of little value to give biofeedback [23]. On the other hand, analyses of randomized placebo-controlled trials of approved agents to treat osteoporosis have generally shown that larger increases in BMD are associated with a greater reduction in fracture risk, at least in postmenopausal women. The paradigm of treat-to-target is aimed at enhancing and individualizing the care of patients with osteoporosis. Based on the best available data, the most promising target is a T-score > -2.5 . More data are needed to see whether this target is relevant in CKD.

BTMs. Treatment-induced changes in BTMs are more rapid and do inform on BMD changes, also in the setting of CKD [174]. The absence of suppression of BTMs 3–6 months or so after starting antiresorptive treatment should trigger a reassessment of adherence to the treatment and other potential issues with the drug (e.g. improper drug administration) [23, 175].

Given the high biological variability of BTMs, least significant changes (LSCs) should be considered when evaluating the treatment response. Biofeedback by BTMs only results in a beneficial response to treatment [173] in those demonstrating a positive response. The measurement of BTMs after withdrawal of osteoporosis therapy is potentially also useful to evaluate patients who are taking a pause from treatment. An increase in BTMs more than the LSCs reflects a loss of treatment effect and identifies patients who are likely to have a decrease in BMD. Such changes could provide an indication for reintroduction of treatment [151]. As previously mentioned, non-kidney-retained BTMs (BALP, trimeric PINP, TRAP5b) are preferentially used in the setting of CKD, especially in patients with non-stable kidney function [94]. Further, PINP and CTX are significantly and variably increased after a fragility fracture, limiting their use in the post-fracture setting [84].

FRACTURE LIAISON SERVICES

The risk of subsequent fracture is time-dependent, with much higher fracture risk in the first 2 years after an index fracture. This so-called imminent fracture risk requires rapid treatment initiation with agents with a short time to onset [176]. Since the majority of patients presenting with fragility fracture do not receive appropriate assessment and treatment, fracture liaison services (FLSs) address this need through a systematic approach to identify cases and assess the risk of further fractures (including falls risk) and the need for treatment [177]. A nephrologist should be part of the multidisciplinary team to guarantee optimal osteoporosis care to patients with CKD G4–5D. The benefits of FLSs to ensure appropriate management of patients without advanced CKD following a fracture are well established: improved adherence to osteoporosis drugs with an expected reduction of the incident fracture rate and decreased post-fracture mortality [23, 178].

RESEARCH QUESTIONS/PERSPECTIVES

- Determine whether arithmetic adjustments to conventional FRAX estimates have to be made with knowledge of CKD G4–G5D.
- Determine whether ROD subtypes associate with fracture risk.
- Define the efficacy and safety of anti-osteoporosis agents (bisphosphonates, denosumab, PTH analogues, raloxifene, romosozumab) in patients with CKD G4–G5D.
- Investigate the role of primary and secondary mineralization in ROD.
- Compare bone strength in iatrogenic (e.g. bisphosphonates) versus idiopathic (e.g. CKD related) low bone turnover.
- Define whether antiresorptive therapy in patients with adynamic bone disease (ABD) or low bone turnover confers harm. Otherwise stated, is the harm of giving antiresorptives to patients with ABD or low bone turnover real or just theoretical?

Table 2. Efficacy and safety of common osteoporosis drugs in the setting of CKD

Drugs	Renal retention	Efficacy Preclinical	<i>Post hoc</i> (postmenopausal women)	Clinical trial (advanced CKD)	Safety (postmenopausal women)	Comments
Nitrogen-containing bisphosphonates (alendronate, ibandronate, risedronate and zoledronic acid)	Yes [118, 119]	Yes [129, 157]	Fracture ↓ [120–122]	BMD (↑) [123–127]	Atypical fracture, ONJ, oesophagitis, (hypocalcemia, renal dysfunction) [131, 137–139]	Dose adjustments?
Denosumab	No [141]	Yes [145]	Fracture ↓ [142]	BMD ↑ [126, 143, 144, 147, 156]	Atypical fracture, ONJ, hypocalcaemia [138, 143]	Beware: offset of effect [150]
PTH analogues (teriparatide, abaloparatide)	No	Yes [157]	Fracture ↓ [158, 159]	BMD ↑, in patients with ABD or hypoparathyroidism [123, 160, 161]	Hypotension [160]	Dose adjustments? Therapy to be limited to a maximum of 2 years
Romosozumab	Unlikely	Yes, low PTH only [162]	No data	No data	Cardiovascular adverse events ↑ [165] (hypocalcaemia)	Beware: offset of effect

CONCLUSIONS

Less than 20% of all patients experiencing a fragility fracture receive therapy to reduce future fractures within the year following the fracture [179]. The main reason for this care gap is that osteoporosis and post-fracture management are still considered a low priority among clinicians. The fragility fracture and osteoporosis care gap are probably even higher in patients with CKD G4–G5D. In these patients, ROD is thought to play a dominant role and the benefit:cost ratio of available therapeutics is thought to be low. Adhering to Hippocrates oath ‘first, do no harm’, many clinicians follow a wait-and-see approach. Recent insights question the appropriateness of this approach and may foster a paradigm shift with regard to osteoporosis care in CKD. First, as CKD is a state of premature ageing, features of primary osteoporosis may be prominent in CKD patients. The contribution of ROD to bone fragility, conversely, may have been overemphasized in the past. Second, high-level evidence with regard to the efficacy of available osteoporosis drugs in patients with CKD G4–G5D is lacking. However, the absence of evidence does not equal evidence of absence of effect. *Post hoc* analyses of large registration trials and data from small and uncontrolled trials suggest a similar efficacy of common osteoporosis drugs in patients with CKD G4–G5D as in the general population. Third, there are no strong reasons to assume that the risk:benefit ratio of therapy with antiresorptive agents, which is excellent in the general population, is different in patients with CKD G4–G5D. In an era of personalized medicine, the risk:benefit ratio of osteoporosis drugs should be evaluated case by case and discussed with the patient prior to initiation of therapy.

The recent KDIGO CKD-MBD guidelines allow for a more liberal use of antiresorptive agents in patients with CKD G4–G5D [52] and several expert panels already presented algorithms for fracture risk screening and initiation of antifracture strategies in patients with CKD [15, 26, 180]. Although none of

these algorithms have been validated by outcome data, they may—together with this consensus paper—provide pragmatic guidance pending further evidence (Figure 1).

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