MANAGEMENT OF FRAGILITY FRACTURE IN CHRONIC KIDNEY DISEASE

I. Paşcanu¹*, R.M. Neagoe²

¹University of Medicine and Pharmacy, Dept. of Endocrinology, ²Emergency Mureş County Hospital, Second Department of Surgery, Târgu Mureş, Romania

Abstract

Fragility fractures are more common in patients with chronic kidney disease (CKD), a growing public health issue, than in general population. The key issue in management of fragility fracture in CKD patients is determining whether fractures have occurred as a result of qualitative abnormalities (consequences of renal osteodystrophy or CKD-mineral and bone disorder), a reduced bone mineral density (osteoporosis) or a combination of both.

In CKD patients bone histomorphometry is the gold standard for evaluating bone quality and strength, but the routine use of this method is not practical. Fracture risk can be assessed in this population by DEXA (Dual-Energy X-Ray Absorptiometry), but biochemical markers, like intact PTH and bone-specific alkaline phosphatase may be helpful. The new and emerging high resolution imaging tools need more studies for a correct evaluation of their utility in predicting fracture risk.

Pharmacological therapies for fragility fracture based on current understanding of the metabolic disturbances in CKD will be reviewed. Antiresorptive and anabolic agents used in the treatment of osteoporosis are discussed with special focus on CKD population.

Key words: CKD, fragility fracture, mineral bone disorder.

INTRODUCTION

The term chronic kidney disease-mineral and bone disorder (CKD-MBD) has been implemented to describe the broad clinical and paraclinical abnormalities of bone and mineral metabolism that occur in patients with kidney disease. These disturbances are systemic and may manifest themselves by either one or a combination of the following three conditions (1):

1. Laboratory abnormalities of calcium, inorganic phosphorus, PTH or vitamin D metabolism;
2. Abnormalities of bone turnover, mineralization, volume, linear growth or strength;
3. Calcification of the vasculature or other soft tissues.

Instead, renal osteodystrophy (ROD) defines alterations in bone morphology and metabolism associated with CKD and has consequences on parameters of bone turnover, mineralization and volume (Table 1). The final diagnosis of ROD should include a transiliac bone biopsy done prior double tetracycline labeling followed by standardized analysis of bone histomorphometry using a unified classification system (TMV classification) (2, 3). However, bone biopsy is not always available for all patients. It is worth mentioning that the subtypes described does not correlate with low, high or normal bone mineral density (BMD) and may be associated with fragility fractures (1). A schematic representation of the physiopathology of CKD-MBD is presented in Figure 1.

Compared to general population fractures’ risk is 2-14 times higher in patients with CKD (4). In this specific population the key issue in diagnosis and treatment of fragility fracture is determining whether fractures have occurred as a result of qualitative abnormalities, (consequences of ROD), a reduced BMD or a combination of both.

TOOLS TO PREDICT FRACTURE RISK IN CKD

Dual-Energy X-Ray Absorptiometry (DEXA)

A DEXA image offers a 2-dimensional assessment of a 3-dimensional bone structure and therefore it will not provide effective discrimination between cortical and trabecular bone. In CKD mineral abnormalities, for example the frequent elevation in PTH level, are likely to have different effects on bone compartments. Typically, PTH increases bone turnover, exerting an anabolic effect on trabecular bone but also a well-known and more prominent catabolic effect on cortical bone with increased cortical porosity and a gross result of a thickened irregular bone. In
these circumstances the ability of BMD, measured by DEXA, to predict fracture risk in CKD population was considered futile.

The T score at lumbar spine, femoral neck or radius, we used for diagnosis of osteoporosis, provides limited insight into the pathogenesis and subtype of ROD and must be interpreted with caution. Because of this and also because earlier cross-sectional studies (5) suggested that measurement of BMD by DEXA did not provide sufficient useful information to support therapeutic decisions in the management of CKD patients, the 2009 KDIGO Guidelines did not recommend routine BMD testing in patients with CKD stages 3-5D with evidence of CKD-MBD (evidence level 2B) (1). However, recent prospective trials in patients with pre-dialysis CKD (6) and on hemodialysis (7) and after kidney transplantation (8) indicate that low areal BMD measured by DEXA at the forearm and hip, have predictive value for future fracture. Moreover, a recent meta-analysis of 13 studies, with a total of 1785 subjects and 486 fractures showed that BMD as measured by DEXA at all sites was significantly lower

### Table 1. The principal subtypes of ROD and their characteristics

<table>
<thead>
<tr>
<th>Subtypes of Renal osteodystrophy</th>
<th>Turnover</th>
<th>Mineralisation</th>
<th>Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Osteitis fibrosa (OF)</td>
<td>↑</td>
<td>N</td>
<td>Normal trabecular V, Severe cortical porosity</td>
</tr>
<tr>
<td>Osteomalacia (OM)</td>
<td>N</td>
<td>↓</td>
<td>Variable</td>
</tr>
<tr>
<td>Low-turnover osteomalacia</td>
<td>↓</td>
<td>↓</td>
<td>↓ trabecular V</td>
</tr>
<tr>
<td>Adynamic bone disease (ABD)</td>
<td>↓</td>
<td>N</td>
<td>↓ trabecular V, thinner cortices</td>
</tr>
<tr>
<td>Mixed bone disease</td>
<td>↑</td>
<td>↓</td>
<td>Variable</td>
</tr>
</tbody>
</table>

![Figure 1. Physiopathology of CKD-MBD](image-url)
in CKD patients (men and women) was compared to those without fractures (9). Finally, another recent prospective study (10) showed that not only a low DEXA score, but also a greater annualized percent decrease in BMD are risk factors for subsequent fracture in men and women with predialysis CKD.

The considered limited utility of DEXA in CKD should be therefore re-evaluate. Clinicians can rely on DEXA imaging because the World Health Organization definition of osteoporosis (T-score ≤ -2.5) is clinically relevant even in CKD population.

**FRAX® and clinical fracture risk assessment**

The 10-year probability of fracture (hip or major osteoporotic fracture) can be estimated by FRAX®, a widely used risk assessment tool developed by the World Health Organization (WHO). The value of FRAX® in patients with CKD is not clear. It has been demonstrated that for patients in stages 1-3 CKD, FRAX® can be applied in a manner similar to the postmenopausal osteoporosis populations without known CKD (11, 12) although changes in molecules affecting bone metabolism (PTH, FGF-23, phosphorus) may be seen even in stage 2 CKD.

In a cross-sectional study of 353 pre-dialysis CKD patients (one third had prevalent fractures), FRAX® did not perform better at discriminating among those with or without fractures than femoral neck BMD alone (13). The rationale for this result is the lack of information on biochemical markers of bone turnover (such as bone alkaline phosphatase, PTH, vitamin D) or results of neuromuscular tests, both of them have been demonstrated to increase discrimination of prevalent fractures in CKD patients (14, 15).

Moreover, in hemodialysis patients FRAX® appears to have no predictive ability (7). Factors consistently associated with an increased risk of fracture for patients on dialysis include: older age, female gender, longer time on dialysis, diabetes, cerebrovascular disease, peripheral vascular disease, low BMI, psychoactive medications, Caucasian race, previous kidney transplant, history of any fracture/vertebral fracture, PTH (high or low), ALP (high or low), low albumin, hyperhomocysteinemia or hyponatremia (16-18).

Prospective studies with larger sample sizes are needed in order to determine the utility of FRAX® as a fracture risk assessment tool in individuals with reduced kidney function.

**High-resolution radiologic tools**

Quantitative computed tomography (QCT) provides a true volumetric measurement of BMD and gives information about the geometry of cortical and trabecular compartments. QCT with a resolution of 300 µm³ can be applied to peripheral sites (radius and tibia) as well as central sites (lumbar spine and proximal femur). This method showed the predominance of cortical abnormalities in CKD patients and moreover it was both discriminatory and predictive for fragility fracture in this population (19).

Ultra-high-resolution peripheral QCT (HR-pQCT), currently used for research, with higher nominal resolution of 82 µm³, can visualize the trabecular number, thickness and separation. Finite element analysis is a mathematical model applied to three-dimensional HR-pQCT datasets that can test the bone strength. Although advanced HR-pQCT processing methods detect abnormalities in bone quality that negatively impact bone strength and elucidate the underlying microstructural defects (20), an improvement in the discriminatory ability for fractures of these methods compared to DEXA does not exist yet (21). All these new methods measure the structure and not bone turnover or mineralization so treatment decision cannot be based on these data. Other impediments are related to their limited availability, higher radiation dose and lack of well-established population standards (22).

**PTH and bone turnover markers**

There are some biomarkers that can be considered surrogate markers for bone turnover (Table 2) and a formal division recognises two categories: formation and resorption markers, although they can

<table>
<thead>
<tr>
<th>Formation markers</th>
<th>Resorption markers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone isoform of alkaline phosphatase (BALP)*</td>
<td>CTX - Collagen type 1 cross-linked C-telopeptide</td>
</tr>
<tr>
<td>Osteocalcin</td>
<td>NTX - Collagen type 1 cross-linked N-telopeptide</td>
</tr>
<tr>
<td>Sclerostin</td>
<td>Cathepsin K</td>
</tr>
<tr>
<td>Procollagen type I propeptide C-terminal (PICP)</td>
<td>PTH*</td>
</tr>
<tr>
<td>Procollagen type I propeptide N-terminal (PINP)</td>
<td>Matrix metalloproteinases (MMPs)</td>
</tr>
<tr>
<td>• Total (monomer+trimer)</td>
<td>Osteoprotegerin</td>
</tr>
<tr>
<td>• PINP intact trimerial*</td>
<td>Tartrate-resistant acid phosphatase (TRACP) 5b*</td>
</tr>
</tbody>
</table>

Table 2. Biomarkers available for bone resorption and bone formation. Those that can be used in CKD patients are highlighted (*)
be used interchangeably because inherent coupling between osteoblasts/osteocytes and osteoclasts is described. Only some of them are not excreted by the kidney or not influenced by renal function and can be used in CKD (they are highlighted in Table 2).

By far, PTH was the most used, despite the fact that many inconveniences from biological point of view (PTH has low stability), from physiological point of view (indirect action on the bone) and also controverses whether whole molecule or intact PTH assay should be used. The Dialysis Morbidity and Mortality Study (DMMS) Waves 1 to 4 showed in 9,007 dialysis patients a weak but significant U-shaped association between PTH level (both low and high) and hip and vertebral fracture, with the lowest risk observed around a PTH concentration of 300 pg/mL (ng/L) (23).

Similarly, BALP, a homodimeric glycoprotein, anchored to the membrane of osteoblasts, has been proved to be useful in predicting incident hip fracture in a single-centre cohort study of 485 hemodialysed Japanese patients (7).

Regarding discrimination among different subtypes of ROD, both BALP and PTH appear to be tightly linked to histological bone parameters; BALP may be a slightly better predictor of low-turnover bone disease, and in some series, has improved the specificity of PTH concentration for high-turnover bone disease (7, 11, 17, 22). This issue is of high importance in the management of patients with stages 4-5 CKD and low BMD on DEXA or fragility fractures, because prior to use an antiresorptive agent for treatment, adynamic bone disease must be excluded. In this context, if a low PTH and BALP are present in a CKD patient, at least in theory, drugs that would lower bone turnover when bone turnover is already low should be avoided.

In the future, combining biomarkers with high resolution imaging as well as the new biomarkers such as sclerostin and fibroblast growth factor 23 (FGF 23) may be promising in predicting fracture risk (24, 25). Larger prospective studies are required to evaluate their utility in CKD patients.

### TREATMENT OPTIONS OF FRAGILITY FRACTURE IN CKD

The first issue to address in these patients will be the correction of metabolic disturbances like metabolic acidosis or SHPT, both are likely to improve ROD. When mild SHPT is present, calcium based-phosphate binders, calcitriol or a vitamin D metabolite/analogue may have benefits especially if dietary calcium is low, but they can also have a detrimental effect by contributing to the development of low bone turnover ROD, like adynamic bone disease and/or worsening vascular calcifications (26). Vitamin D analogues or metabolites have been shown to reduce PTH level and improve BMD in patients with CKD (27), but the reduction of fracture incidence in this population was not assessed. Paricalcitol, very used in our region, is a vitamin D analogue not requiring activation, specifically developed to suppress PTH in renal patients with a limited calcemic effect.

An allosteric modulator of the calcium-sensing receptor is the calcimimetic cinacalcet; it’s effects are a concomitant reduction of PTH secretion and of serum calcium and phosphate. In one study, a pooled analysis of safety data from 4 randomized control trials involving 1184 patients with CKD and uncontrolled SHPT (intact PTH ≥ 300 pg/mL), a 54% reduction in fracture risk has been demonstrated (28). However, no reduction in fracture risk using cinacalcet compared to placebo was described in the more recent placebo-controlled trial EVOLVE, where 3883 hemodialysis patients with secondary hyperparathyroidism were randomized to receive cinacalcet or placebo for ≤ 64 months (29).

Parathyroidectomy was also reported to reduce fracture risk in CKD patients with severe SHPT unresponsive to medical therapy (30). In hemodialysed patients parathyroidectomy may provide a 31% lower risk for any analysed fracture (hip, vertebral, radial) compared to matched control (31).

**Raloxifene (selective estrogen - receptor modulator)**

First of all, it should be mentioned a possible renoprotective effect of raloxifen evidenced in a post-hoc analysis of MORE (Multiple Outcomes of Raloxifene Evaluation), a placebo-controlled trial. Compared with those in the placebo group, participants on raloxifene had a significantly slower yearly rate of decrease in eGFR over 3 years of follow-up and it was associated with significantly fewer kidney-related adverse events compared with placebo (32). In a prospective, multicentre study, on postmenopausal women on hemodialysis, raloxifene significantly improved BMD in the lumbar spine and produced a slight reduction of BMD in the radius (33).

**Bisphosphonates**

Bisphosphonates (BPs), synthetic analogues of pyrophosphate, not metabolized by pyrophosphatases, diffuse into bone matrix where they bind only
to the hydroxyapatite crystal surface, due to the physiochemical attachment.

The kidney toxicity is the first issue to be addressed regarding BPs. Intravenous administration of zoledronic acid may acutely reduce GFR by a lesion that mimics acute tubular necrosis, that can be related to dose and rate of infusion (34). Slow administration of zolendronic acid (e.g., over 60 minutes) is safe in clinical experience. Some case reports showed collapsing focal segmental glomerulosclerosis and nephrotic syndrome, not always reversible with both oral (alendronate) and intravenous ( pamidronate) administration of BPs (35, 36).

Both oral and intravenous BPS are excreted by the kidney (by filtration and active proximal tubular secretion). For this reason and because of the lack of clinical trials in CKD population, BPs carry either a warning or a contraindication label for use in patients with a creatinine clearance < 30 mL/min (stages 4 and 5 CKD).

The benefits of BPs treatment in CKD 4 and 5 are very difficult to define because there are no data in these patients. For less severe CKD, the initial clinical trials used only serum creatinine concentration as an inclusion/exclusion criterion and not eGFR or GFR. In these circumstances, some patients with creatinine concentration in the normal laboratory reference range could present, if they have a low body mass index, a significant reduction in GFR. These patients were analysed in two post hoc analyses, one for alendronate from FIT (fracture intervention trial) (37) and the other, a pooled analysis of risendronate from 9 trials over an average period of 2.6 years (38). In patients with postmenopausal osteoporosis and an estimated creatinine clearance (calculated by the Cockcroft-Gault formula) of 15-30 mL/min, both alendronate and risendronate in their original registration formulations (5 mg/day of risendronate and 10 mg/day of alendronate) effectively increased BMD and significantly reduced the incidence of all clinical fractures, including morphometric vertebral fractures, compared to placebo, without any change in kidney function (37, 38). Of note, these subgroups had no laboratory features of CKD-MBD. In severe CKD, especially in hemodialyzed patients, the potential problem of bisphosphonate therapy is the diminished bone remodelling that could lead to reduced repair of microdamage and impairment of bone strength (17).

Finally, in the past period, retrospective cohort data have shown that bisphosphonates may be associated with a reduction in all-cause mortality, including cardiovascular mortality (39). The mechanism is not well understood, but the alteration of cellular pathways in vascular endothelial cells that influence vascular calcification by BPs can be implicated (40). In a study on older female patients with moderate to advanced CKD, (9,604 eligible female patients; 3,234 were treated with BPs therapy; median follow-up of 3.9 years), although no cardioprotective association was observed, bisphosphonate treatment was associated with a 22% lower mortality risk in models adjusted for factors influencing survival (41).

**Denosumab**

Denosumab is a fully human monoclonal antibody against the receptor activator of nuclear factor-κB ligand, with an inhibitory effect on osteoclastogenesis. Its effect of reducing bone turnover markers and BMD is completely reversible after 6 months and because it is not cleared by the kidney has no lower eGFR warning or contraindication. In a post hoc analysis of the FREEDOM study (Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months) denosumab increased BMD and decreased the risk of fractures compared with placebo in patients with GFRs as low as 15 mL/min. No interaction between treatment effect and eGFR was identified (42). Regarding safety consideration immune suppression is of concern especially in patients treated with other biologic products or those posttransplant. Hypocalcemia has been reported as a serious adverse effect after the administration of denosumab. In one study, univariate logistic regression analysis revealed that the patients who had lower creatinine clearance (the cut-off value was 50 mL/min) appeared to have a higher risk of hypocalcemia (43). Ensuring adequate 25-hydroxyvitamin D levels and calcium intake in patients receiving denosumab is, therefore, necessary.

Before prescribing any kind of antiresorptive agent, clinicians must first take into consideration the potential exacerbation of low turnover bone disease by this class of drugs in CKD patients!

**Strontium ranelate**

There are very limited data regarding the use of strontium ranelate in CKD. It has a double effect, both on resorption and bone formation, but the basic mechanisms by which strontium ranelate acts on bone are still unclear. The concern derived from animal studies regarding a possible strontium-induced osteomalacia was not confirmed in a study on hemodyalysed patients where no correlation between
different histomorphometric parameters and bone strontium/calcium ratio was found (44).

**Anabolic agents**

Teriparatide, a recombinant form of the first 34 amino acids of PTH, is the only true anabolic agent available at this moment. As for other antiosteoporotic agents the pivotal trial for teriparatide did not assign participants with known stages 4-5 CKD, but small subsets with eGFR 30-80 mL/min were included. A post-hoc analysis showed that the effect of teriparatide to reduce the incidence of vertebral and nonvertebral fragility fractures was statistically consistent in patients with normal and impaired renal function (45). PTH level in this trial was normal, a sustained, uncorrected high level of PTH, seen in more severe CKD stages, would
make its use inappropriate. Teriparatidum was also used, off label, in proven adynamic bone disease, based on the speculation that an anabolic agent can increase bone turnover and improves bone microarchitecture in a disease with no known treatment (46).

A pragmatic approach to managing fragility fractures in CKD is presented in Figure 2.

In conclusion, although the gold standard in diagnosis of CKD-MBD is invasive, advances in imaging methods combined with serum bone biomarkers permit an evaluation of structural aspects of bone disease that drive increased skeletal fragility. In stages 1-3 CKD without abnormalities of markers of mineral metabolism, the management of patients with fragility fracture should not differ from those with normal eGFR. In patients with more advanced CKD (4-5) treatment decision need collaboration with a nephrologist and if possible should be based on transiliac bone biopsy. The exclusion of renal adynamic bone disease is important if an antiresorptive drug is considered. None of the therapeutic agents used in osteoporosis had any proved effect on the risk of fractures in stage 4-5 CKD patients. There is a great need for randomised controlled trials of known anti-osteoporotic medication regarding the reduction of fracture risk in all stages of CKD. This will improve the ability of the clinician to take the right therapeutic decision and will lead to an increased quality of life for patients with fracture and CKD.

Conflict of interest
The authors declare that they have no conflict of interest concerning this article.

Abbreviation
ABD - adynamic bone disease.
BALP - Bone isoform of alkaline phosphatase.
BMD - bone mineral density.
BPs - bisphosphonates.
CKD - chronic kidney disease.
CKD-MBD - chronic kidney disease-mineral and bone disorder.
DEXA - Dual-Energy X-Ray Absorptiometry.
eGFR - estimated Glomerular Filtration Rate.
FGF-23 - Fibroblast growth factor 23.
KDIGO - Kidney Disease: Improving Global Outcomes.
PTH - parathyroid hormone.
ROD - renal osteodystrophy.
SHPT - secondary hyperparathyroidism.

References
Fragility fracture in CKD


Professor Hossein Gharib, endocrinologist, Mayo Clinic, Rochester, USA, received the title *Doctor Honoris Causa* of the University of Medicine and Pharmacy “Carol Davila”, Bucharest, Romania, awarded by the Rector Ioanel Sinescu on 29th September 2015.

The first personality who received this distinction from “Carol Davila” University was Adolf Butenandt, Max Planck Institute, Germany, in 1966.