Osteoporosis in mineral and bone disorders of chronic kidney disease

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ABSTRACT

Osteoporosis is one of the epidemics in modern aging societies. Epidemiological studies indicate that many patients with osteoporosis are also characterized by diminished glomerular filtration rate (GFR), which indicates various degrees of chronic kidney disease (CKD). On the other hand, the status of osteoporosis in the classification of mineral and bone disorders in CKD has not been well defined. In the present paper, we review the epidemiology of osteoporosis in the context of kidney failure, discuss tools used to diagnose osteoporosis in patients with CKD, present data on fracture risk in patients with kidney diseases, and describe the relationship between metabolic bone diseases and the development of vascular calcification. We also present current treatments in osteoporosis with special attention to the outcomes of these treatments in patients with low GFR.

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Introduction   In a recent review, Matuszkiewicz-Rowińska[1] discussed the guidelines regarding diagnosis and treatment of mineral and bone disorders of chronic kidney disease (CKD-MBD). Looking at the spectrum of bone diseases in CKD patients, one may be surprised by the lack of "classic" osteoporosis in the classification of CKD-MBD. This classification has traditionally included adynamic bone disease, high-turnover bone disease (osteitis fibrosa cystica), osteomalacia, and mixed uremic osteodystrophy, and has been based on bone biopsy studies performed in advanced CKD. This is even more surprising given the mean age of patients with CKD. More than 75% of all people with the estimated glomerular filtration rate (eGFR) of less than 60 ml/min./1.73 m^2 are older than 70 years, and patients older than 75 years are the most prevalent and the fastest growing group on dialysis. Among subjects randomized into large, placebo-controlled studies on osteoporosis, patients with the eGFR of less than 60 ml/min/1.73 m^2 (CKD stage III) represent a significant proportion (even one-third) of the study groups, with high prevalence of subjects with eGFR reduced to 35 to 45 ml/min/1.73 m^2.[1-6]

The above data may thus be confusing: most of the patients with CKD are in the "osteoporotic", age and most of the patients with osteoporosis have at least some degree of renal failure. Nonetheless, osteoporosis is not included in the CKD-MBD classification. In our opinion, the question of how much osteoporosis there is in CKD-MBD and the evaluation of the relationship between renal function and the prevalence of osteoporosis (or other causes of bone disorders) are of paramount importance because – as we will discuss at the end of this review – many traditional drugs used in the treatment of osteoporosis are not approved for use in patients with moderate-to-advanced CKD.

Risk of fractures and low bone mineral density in patients with chronic kidney disease   Epidemiological data demonstrated a significantly increased risk of fractures among patients with end-stage renal disease (ESRD). The reports of the United States Renal Data System indicated that men on dialysis have a 7.5-fold higher and women 13.6-fold higher risk of hip fracture compared with the general population.[7] An observational study performed in dialysis patients in 11 countries on 4 continents (including the United States, Asia, Australia and New Zealand, and Europe) revealed that the overall risk of a new hip fracture is on average 9-fold higher in patients on dialysis compared with the reference population. The factors independently increasing the risk for a new fracture were the history of hip fracture, age, female sex, history of renal transplantation, and low

plasma albumin levels. Dialysis- or uremia-related parameters, such as dialysis vintage, parathyroid hormone (PTH) level, history of parathyreoidectomy, or serum calcium and phosphate concentrations, were not associated with the risk of fractures.[8] This may suggest that routine measurement of the parameters of CKD-MBD in dialysis units does not help predict the risk of fractures.

In a study comprising only men (US Veteran Affairs database), the risk of hip fractures in stage 3 CKD (eGFR, 30–60 ml/min./1.73 m^2) was on average only 13% higher compared with the reference population, but, in the youngest age group (50–59 years), it increased by factor 3. CKD stage 4 was associated with a further increase in fracture risk.[9] In the NHANES III analysis of 6270 men and women aged above 50 years, the risk of hip fractures did not increase with the fall of eGFR from normal to 60 ml/min/1.73 m^2; however, eGFR below this threshold was associated with the odds ratio of fractures of 2.32 (vs. >60 ml/min/1.73 m^2).[10] In another study, which included 9704 patients, a multi-adjusted analysis demonstrated an association between decreasing GFR and risk of trochanteric fractures (more than 5-fold higher risk for GFR <45 vs. ≥60 ml/min/1.73 m^2), but not of those of the femoral neck.[11] In yet another study, the Z-scores of the lumbar spine and femoral neck and the one-third radius bone mineral density (BMD) in 659 postmenopausal women were inversely associated with GFR when measured using creatinine clearance, but not with eGFR calculated by the Modification of Diet Renal Disease (MDRD) formula (and were independent from PTH levels).[12] The latter analysis illustrates one of the key problems in the CKD research, namely, the questionable reliability of the different formulas used for GFR estimation.

Numerous recent studies criticized the most popular "anthropometric" formulas (i.e., MDRD and Cockcroft–Gault formulas). It seems that they significantly overestimate the prevalence of early stages of CKD. Anthropometric formulas confronted with the techniques that objectively measure a true GFR showed poor sensitivity and reproducibility in assessing GFR.[13] Attempts were also made to introduce and validate new formulas for the estimation of GFR.[14] This "methodological" issue is especially significant in the context of osteoporosis: variables used to estimate GFR include age, sex, and body weight, which are also the key determinants of osteoporosis and are incorporated into the FRAX score (a tool used to predict the risk of fractures).[15,16] This leads to an important question concerning the relationship between GFR and osteoporosis: is such a relationship a biologically relevant and pathophysiologically justified link or just a mathematical correlation? Unfortunately, there are no studies that would analyze the prevalence of osteoporosis or fractures using a reference assessment of GFR (e.g., based on iothalamate elimination or radioisotope techniques). In conclusion, the available data suggest a significantly higher risk of fractures among patients with CKD, although they do not allow to conclude what contributes more to low BMD or fracture risk: CKD-specific bone disorders or osteoporosis. In our opinion, CKD-MBD contributes to fractures mostly in stages 4 and 5 of CKD.

Use of dual energy X-ray absorptiometry and other diagnostic tools in detecting osteoporosis in chronic kidney disease

Dual energy X-ray absorptiometry (DEXA) remains the most important and widely available tool to measure BMD. However, several concerns may be raised against the usefulness and credibility of this method. Up to 50% of postmenopausal women with fractures do not fulfill the DEXA-based criteria of osteoporosis. Certain therapies decrease the risk of fractures more than it might be calculated from treatment-related increase in BMD, and vice versa – measures effective in BMD improvement have a relatively low effect on fracture risk.[17,18] There is virtually no correlation between DEXA-BMD and the type of bone lesions on histomorphometric assessment in patients with CKD: patients with low, normal, or high BMD may have adynamic bone disease, high-turnover bone disease (osteitis fibrosa cystica), osteomalacia, or mixed uremic osteodystrophy. Osteosclerosis of vertebral endplates in otherwise osteoporotic CKD patients as well as massive calcification of the abdominal aorta may falsely increase the BMD value in the lumbar spine.[18] BMD at different sites in patients with advanced CKD failed to predict the risk of fractures.[17] New techniques used in assessing bone structure and density, such as quantitative high-resolution computed tomography (peripheral skeleton – radius, tibia; central skeleton – lumbar spine, proximal femur) or micromagnetic resonance imaging appear to be promising tools; however, they need to be validated as predictors of fracture risk in CKD and are not widely available.[17,19] FRAX, World Health Organization Fracture Risk Assessment tool, which incorporates anthropometric and demographic data, previous fractures, exposure to steroids, history of rheumatoid disease, and other causes of secondary osteoporosis as well as BMD of the femoral neck, has not been validated as a predictor of fractures in patients with moderate-to-advanced CKD.[20]

The more mineral disappears from the bone, the more mineral goes to the vessels

The relationship between increased risk of cardiovascular complications, death, decreased BMD, and fractures has been described in the general population, especially among postmenopausal women. The mechanisms that may increase all-cause mortality after fracture are quite obvious because fractures affect elderly, frail patients who are immobilized following this complication, need hospitalization and surgery, are exposed to additional risk of infection, thromboembolic events, etc. Interestingly, fractures and low BMD seem to predict all-cause

mortality also after adjustment for age, years of menopause, presence of hypertension, smoking, and abnormalities in the lipid profile. Indices of osteoporosis predict also cardiovascular mortality.[21] Several studies suggested that along with the development of osteoporosis, minerals released from the bones are not simply eliminated with urine but, at least in some amount, also accumulate within the vessels. Decreasing BMD was shown to be associated with increased aortic calcification, measured using radiological methods (X-ray, computed tomography), and with pulse wave velocity (the measure of arterial stiffness, also increasing with calcium–phosphate accumulation).[22-24] In longitudinal observations, progressive loss of BMD was associated with increment in aortic calcification.[23] Taken together, these data suggest that osteoporosis may lead to increased calcification and vascular stiffness, thus translating into increased cardiovascular risk.

The relationship between bone disease and all-cause and cardiovascular mortality has also been described for patients with CKD. Although, as mentioned above, the role and usefulness of DEXA in assessing bone status is not well-defined, it has been demonstrated that patients with advanced CKD and low DEXA-BMD have a significantly shorter survival.[25] Moreover, the history of vertebral fracture has a significant negative effect on survival in this group of patients.[26] It has been long recognized that CKD-MBD (formerly referred to as renal osteodystrophy) has a significant impact on vascular calcification. London et al.[27] demonstrated that arterial pulse wave velocity and aortic calcification are increased in CKD patients with decreased bone turnover, namely, in those who do not easily incorporate minerals into the bone, but also do not release them from the skeleton (clinical entity known as adynamic bone disease, usually characterized by low or low-normal PTH levels).[27] The search for correlations between such parameters of mineral metabolism as alkaline phosphatase, bone-specific alkaline phosphatase, PTH, calcium and phosphate, BMD, and vascular calcification in CKD has provided no firm conclusions so far. It is generally acknowledged, however, that low PTH levels, low alkaline phosphatase activity, and low BMD (indices of low bone turnover) are associated with more extensive vascular calcification.[27-33]

Osteoporosis or other clinical conditions with increased calcium and phosphate mobilization from the skeleton result in hypercalciuria and phosphaturia in patients with healthy kidneys (and may eventually contribute to the formation of renal stones). In subjects with CKD, the kidneys are no longer a "safety valve" for increased amounts of calcium and phosphate. Elevated serum phosphate is a well-recognized factor that stimulates osteoblastic transformation of vascular smooth muscle cells. These cells, upon stimulation by phosphate and several other factors, present in excess in uremic serum (for example proinflammatory cytokines), change their

phenotype into "osteoblast-like", and start to form bone-like structures within the vessel walls (utilizing bone-derived calcium and phosphate as substrates).[31-35] Some preliminary studies demonstrated that bisphosphonates are effective in decreasing the intima–media thickness of the common carotid artery and degree of calcification in coronary arteries in patients with CKD.[36,37]

Treatment of osteoporosis in chronic kidney disease In this section, we will not focus on the treatment of CKD-MBD in patients with advanced kidney disease, which has been recently discussed in detail by Matuszkiewicz-Rowińska.[1] Rather, we would like to discuss the effect of drugs used in the treatment of osteoporosis with respect to kidney function in recent large, prospective, randomized trials.

Knowledge on the use of estrogens in CKD is limited and probably will not be extended due to decreasing therapeutic utility of these agents. The most cited paper in the field is the study published by Matuszkiewicz-Rowińska et al.[38] who applied estradiol combined with norethisterone in transdermal patches in premenopausal women on dialysis and noticed significant improvement in the lumbar Z-score after 1 year, as compared with controls; Z-scores in other locations also tended to improve at the end of the trial. Nowadays, estrogens have been replaced with a selective modulator of estrogen receptor, namely, raloxifen. In the Multiple Outcomes of Raloxifene Evaluation (MORE) trial that included 7705 postmenopausal women, raloxifen demonstrated its efficacy in preventing vertebral fractures after 3 years.[39] Secondary analyses showed that raloxifen effectively increased BMD in the femoral neck and lumbar spine in women with GFR of less than 45 and between 45 and 60 ml/min/1.73 m^2, and this effect tended to be better in patients with lower GFR (and did not depend on the technique of the GFR estimation, i.e., MDRD formula vs. creatinine clearance). The drug was also effective in preventing lumbar spine fractures (risk reduced by 50%) in patients with low GFR.[3]

Bisphosphonates seem to be equally effective in patients with normal renal function and with mild-to-moderate kidney failure. In the Fracture Intervention Trial, 6458 osteoporotic women with high risk of fractures (femoral neck Z-score <-2.5 or the history of fracture in the past) were randomized to alendronic acid or placebo. Use of alendronian was associated with a significant reduction of fracture risk in most of the locations.[39] Also in this trial, patients with moderately (45–59 ml/min; 37.3% of the subjects) or severely reduced GFR (below 45 ml/min; 9.9%) benefited from alendronian and experienced significant improvement in BMD as well as reduction of spine and hip fractures (both total hip and femoral neck fractures).[4] It is also worth to mention the results of a study that summarized 9 randomized and controlled trials with risendronian: 6 in the treatment of postmenopausal osteoporosis,

1 in the prevention of postmenopausal osteoporosis, 1 in the treatment of post-steroid osteoporosis, and 1 in the prevention of post-steroid osteoporosis. In the group of 9983 patients (half receiving the drug and the other half – placebo), only 9% had eGFR exceeding 80 ml/min; in 48% eGFR (estimated using the Cockcroft–Gault formula) was between 50 and 80 ml/min; 45% suffered from moderate CKD (eGFR between 30 and 50 ml/min); and in remaining 7%, eGFR was below 30 ml/min. In all groups, risendronian was equally effective in preventing lumbar spine fractures and led to an increase in the BMD of the lumbar spine. Interestingly, in all eGFR ranges, the spectrum of adverse events did not differ substantially between patients taking bisphosphonate versus those on placebo.[5] This observation is particularly interesting because according to the Food and Drug Administration labeling, bisphosphonates should not be used when GFR falls below 30 ml/min and they are not approved for use in patients with advanced renal failure. These precautions are based on the animal toxicity studies and reports of acute kidney injury following rapid intravenous injection of zolendronic acid. Hence, serum creatinine of more than 2.0 mg/dl (approximately 180 µmol/l) was an exclusion criterion in most of bisphosphonate trials.[40]

It seems that restrictions on the use of bisphosphonates in patients with kidney disease need to be revised. The clinical practice indicates that patients reaching the threshold of 30 ml/min discontinue bisphosphonates in the treatment of osteoporosis or when they are given to control metastases to the bone. On the other hand, multiple reports indicate safe use of these drugs in patients with multiple myeloma with severe bone resorption and kidney failure.[41,42] Ibadronate appears to be the safest bisphosphonate in patients with kidney failure, with the highest risk associated with zolendronic acid. Bisphosphonates, although potentially attractive in ESRD (may improve bone mineralization and reverse or decrease soft tissue calcification), should not be used in patients on dialysis because the nature of bone lesions cannot be predicted based on any lab test. Only bone biopsy can discriminate between high-turnover bone disease (in which bisphosphonates may potentially be effective) and low-turnover bone disease (in which bisphosphonates may worsen bone metabolism). Since bone biopsy is not performed routinely (due to high invasiveness and limited number of pathologists with good experience in bone histomorphometry), the recommendation to use bisphosphonates based on bone biopsy results remains hard to implement. Interestingly, participants of the Multi-Ethnic Study of Atherosclerosis experienced less calcification in the thoracic aorta, aortic valve, aortic valve ring, mitral valve, and coronary arteries when they were treated with bisphosphonates, although this effect was limited to women older than 65 years. On the contrary, women younger than 65 years treated with bisphosphonates experienced more calcification in all the above vascular sites, as compared with non-users.[43]

Another agent that has emerged recently in the treatment of osteoporosis is teriparatide, a PTH analogue (N-terminal iPTH 34-amino acid sequence). Dose-dependent efficacy of this drug in preventing fractures and BMD loss was demonstrated in the Fracture Prevention Trial, which included 1637 postmenopausal women.[44] As in the case of all previous therapies, teriparatide was also much more effective than placebo in preventing vertebral and nonvertebral fragility fractures as well as BMD loss in patients with GFR reduced to 30–49 or to 50–80 ml/min. Effectiveness of teriparatide in all GFR ranges was similar, with no substantial difference in the safety profile.[6]

Interacting with RANK–RANKL–osteoprotegerin axis: is it effective in chronic kidney disease?   Receptor activator of nuclear factor κ-B ligand (RANKL) is a cytokine that belongs to the tumor necrosis factor superfamily and is expressed by multiple cell types, including T cells, osteoblasts, osteoclasts, chondrocytes, and endothelial and mesenchymal cells. This cytokine activates osteoclasts, prolongs their survival, and stimulates their differentiation and adhesion to the bone surfaces. Thus, by interacting with respective receptor (RANK) on osteoclasts, it stimulates bone resorption.[45] Osteoprotegerin is a circulating receptor that binds and inactivates RANKL before it reaches receptor on osteoclasts (thus, RANKL was also called "osteoprotegerin ligand").[46] This molecule attracted attention of scientists as a potential target for treatment of osteoporosis. Human monoclonal antibody against RANKL has been developed, initially called AMG162 and now widely known as denosumab.[47]

In the Fracture Reduction Evaluation of Denosumab in Osteoporosis Every 6 Months (FREEDOM), 7868 women with postmenopausal osteoporosis and a T-score less than –2.5 in the lumbar spine or the femoral neck were randomized to denosumab or placebo. The use of drug significantly delayed the time to first vertebral fracture, hip fracture, and other nonvertebral fracture and led to an increase in the BMD of the lumbar spine and femur.[48] Almost half of the patients included in the FREEDOM trial were characterized by impaired renal function (GFR <60 ml/min; calculated using the Cockcroft–Gault formula). The results obtained in patients with CKD were essentially the same as in study subjects with GFR between 60 and 90 ml/min, and more or equal to 90 ml/min, both in term of fracture prevention and improvement in BMD. The safety profile of the drug did not differ in different GFR ranges. Of note, using denosumab was neutral in terms of the effect on renal function, namely, there were no signs of accelerated GFR loss in patients on active treatment vs. those on placebo.[49] Given the fact that denosumab is not excreted with urine, does not accumulate in the bone,

and may be used together with active vitamin D preparations (essential in CKD), it seems very promising in the treatment of abnormal bone metabolism in patients with reduced kidney function (although the use of denosumab in patients with ESRD cannot be recommended at this stage).

Summary and conclusion   The status of osteoporosis in CKD remains dubious. On one hand, the demographic characteristics of patients with CKD clearly indicate that many of them may suffer from osteoporosis. This assumption is largely confirmed by epidemiological studies indicating that substantial percentage of patients with osteoporosis have also some degree of kidney failure. Also in prospective randomized trials conducted in subjects with osteoporosis, even after exclusion of patients with elevated serum creatinine, still up to one-third of the subjects suffered from CKD stages 3 and 4. On the other hand, there is no place for osteoporosis in the contemporary classification of CKD-related bone disorders (which applies mostly to patients with ESRD). We believe that the classic form of osteoporosis is highly prevalent in patients with mild-to-moderate CKD. In patients with stage 4 of CKD and ESRD (i.e., those with GFR <30 ml/min and on dialysis), bone lesions that may be related to osteoporosis are heavily afftected by other forms of renal osteodystrophy. This explains why, according to some authors, using the term "osteoporosis" in patients with advanced CKD may be inappropriate and questionable. This issue is even more complicated in patients with CKD and the history of renal transplantation and those in whom CKD developed due to primary glomerulonephritis, systemic lupus, or immunovasculitis (i.e., those who were exposed to high-dose steroids). It seems that most of the drugs used for osteoporosis are equally effective and safe in patients with CKD, unless the GFR value falls below 30 ml/min. It should be kept in mind, however, that – to the best of our knowledge – no prospective study has addressed this issue so far. All the available data are the retrospective analyses of large trials. The therapeutic approach to bone lesions found in more advanced stages is uncertain and the role of classic drugs used in osteoporosis is unknown.

In summary, osteoporosis in the setting of CKD remains an "undiscovered land". Given the data from the general population, this disease should also be expected in a large proportion of older patients with CKD but may remain undetected due to an overlap with other forms of bone disease. In our opinion, osteoporosis is a predominant form of bone disorder in patients with CKD, except those with the most advanced stages of renal failure (i.e., GFR below 30 ml/min). We are convinced that all treatment options recommended in osteoporosis should also be applied in patients with CKD unless eGFR falls below the above threshold.

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Osteoporoza we współczesnej klasyfikacji zaburzeń mineralno-kostnych w przewlekłej chorobie nerek

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SŁOWA KLUCZOWE

bisfosfoniany,
denosumab,
menopauza,
osteoporoza,
zaburzenia
mineralno-kostne
w przewlekłej
chorobie nerek

STRESZCZENIE

Osteoporoza jest jedną z epidemii dotykających współczesne, starzejące się społeczeństwa. Badania epidemiologiczne wskazują, że u wielu pacjentów z osteoporozą występuje także obniżenie wskaźnika przesączania kłębuszkowego (*glomerular filtration rate* – GFR), a więc mają różny stopień zaawansowania przewlekłej choroby nerek (PChN). Z drugiej jednak strony, miejsce osteoporozy w klasyfikacji zaburzeń mineralno-kostnych PChN nie zostało jednoznacznie zdefiniowane. W niniejszej publikacji omówiono zagadnienia epidemiologiczne związane ze współistnieniem osteoporozy i upośledzonej czynności nerek, przedyskutowano przydatność narzędzi służących do rozpoznawania osteoporozy u chorych PChN, przedstawiono dane dotyczące ryzyka złamań u osób z chorobami nerek, opisano zależności między zaburzeniami metabolizmu kości oraz rozwojem zwapnień w układzie naczyniowym. Omówiono także współczesne metody leczenia osteoporozy, ze szczególnym uwzględnieniem wyników leczenia u chorych z obniżonym współczynnikiem GFR.