

Osteoporosis in Chronic Kidney Disease

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OUR UNDERSTANDING of the pathogenesis of bone disorders has progressed considerably over the past 20 years. In individuals with normal kidney function, the focus has predominantly been on osteoporosis, whereas in individuals with impaired kidney function, the focus has been on the condition referred to as renal osteodystrophy. This pathologic understanding has led to significant advances in the therapy of bone disease as it affects these patient populations. Although these advances have tended to occur in parallel, there has been relatively little integration between the two.

The work group on Osteoporosis in Chronic Kidney Disease attempted to deal with the interface between osteoporosis and renal osteodystrophy. We recognized a major problematic issue of defining osteoporosis in relationship to the bone disease observed in the chronic kidney disease (CKD) patient. The National Institutes of Health (NIH) consensus statement on osteoporosis contains minimal reference to CKD as a cause of secondary osteoporosis. This lack of integration is important for several reasons. First, both fields likely can learn from advances made in the other; and second, assessment and management strategies may exhibit exploitable areas of overlap. In the clinical arena in particular, the increasing availability of dual x-ray absorptiometry (DEXA) and quantitative computed tomography (qCT) facilities for the measurement of bone mineral density (BMD) in both the CKD and non-CKD populations leads to the frequent identification of

patients with low BMD. In the case of the CKD patient with coexisting low BMD, the resulting referral path may be confusing, leading either to a nephrologist whose focus may not be on BMD measurements and the management of osteoporosis, or conversely to an "osteoporosis" physician (rheumatologist, endocrinologist, gynecologist, or geriatrician) whose focus may not be on renal osteodystrophy and its management.

The likelihood of the patient entering an appropriate pathway is further undermined by some of the terminology used. Thus, a measured BMD that satisfies the World Health Organization (WHO) definition of osteopenia or osteoporosis has a tendency to lead to the immediate application of that diagnostic label, even in circumstances in which the underlying pathogenesis may be one of the specific forms of renal osteodystrophy. This, in turn, creates a tendency for the management of such patients to focus on the osteoporosis/osteopenia rather than on the true underlying disease. Hyperparathyroidism or adynamic bone disease may, therefore, go unrecognized with the potential for exacerbation of underlying disease by inappropriate management and treatment.

SUMMARY OF GROUP DISCUSSION

Definitions and Terminology

Definitions of osteoporosis vary considerably in their applicability to the CKD patient. The most widely used definition is that of the WHO, which defines osteoporosis on the basis of BMD measurements applied to the lumbar spine or to the femoral neck. According to the WHO, a T score of -1.0 to -2.5 defines osteopenia, and a T score below -2.5 defines osteoporosis. This classification schema helps stratify appropriate patients according to fracture risk (Table 1). Strictly speaking, however, these definitions are applicable only to Caucasian women, and their applicability to men, children, and other ethnic groups and all cases of secondary osteoporosis remains uncertain. The definition of osteoporosis

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Table 1. WHO and Bone Density Classification

Classification	Definition	Risk
Normal	Bone density is no more than 1 SD below the young adult normal value.	• Risk of fracture is very low.
Osteopenia (low bone mass)	Bone density is 1 SD to 2.5 SDs below the young adult normal value (−1 SD to −2.5 SDs).	• There is a 4× risk of fracture compared to a normal BMD.
Osteoporosis	Bone density >2.5 SD below the young adult normal value (−2.5 SD).	• There is an 8× risk of fracture compared to a normal BMD.
Severe osteoporosis	Bone density >2.5 SD below the young adult normal value and there has been 1 or more fragility fractures (−2.5 SD).	• There is a 20× risk of fracture compared to a normal BMD.

developed by the NIH in its consensus statement was considered by the group to have more relevance to the CKD patient. Here, osteoporosis is defined as “a skeletal disorder characterized by compromised bone strength predisposing to an increased risk of fracture. Bone strength reflects the integration of two main features—bone density and bone quality.” The implication of this definition is that bone density is only one of the determinants of bone strength and fracture risk and that other quality issues such as architecture, turnover, damage accumulation and repair, and mineralization are all relevant. Unfortunately, the latter are often exceedingly difficult to measure, particularly in the routine clinical setting. This difficulty is likely to be one of the reasons for inappropriate emphasis being placed on the relatively straightforward measurement of bone density per se.

Therefore, the term osteoporosis probably has very limited diagnostic meaning in the context of CKD. Furthermore, the WHO groupings are extremely unlikely to be applicable in patients with CKD, based as they are on different patient populations. The work group recognized that there are no independent data based upon BMD that demonstrate clinical outcomes in the CKD population. Thus, the group considered that the classification of bone disease should be based on integration of bone quantity, which may be estimated from BMD, and bone quality, which is a function, in part, of bone turnover. Because “osteoporosis” may be a misleading term, implying that BMD measurements are the only important predictor of fractures, the work group considered it more appropriate to describe this constellation of bone disorders in CKD as “renal osteodystrophy.” This takes account of the notion that the

compromised bone strength in CKD patients is a function of bone turnover (assessed by bone biopsy), bone density (assessed by DEXA or qCT), and bone architecture (for which there are no current *in vivo* measurement technologies). Furthermore, we proposed that the categorization of bone density be simplified by classifying patients into 2 groups, namely those with “low bone density” and those with “normal/high bone density.” Thus, a patient may have high-turnover bone disease with low or normal/high bone density, or low-turnover bone disease with low or normal/high bone density. Furthermore, we proposed the standardization of BMD measurements be based on Z-score (bone mass adjusted for race, age, and sex) as opposed to T-score (adjusted to peak mass of a young adult adjusted for sex and race). A low bone density would be defined as a Z-score of −1 or less. These latter recommendations were controversial and did not meet with universal approval.

Specific Issues in Relation to CKD

The understanding of the pathology of renal osteodystrophy in patients with CKD has advanced greatly over the past 10 years. In parallel, there has been somewhat less spectacular advance in our understanding of the associated pathophysiology, partly because of the enormous heterogeneity of bone and mineral disorders that develop in patients with CKD.¹ In sharp contrast to the non-CKD patient with osteopenia/osteoporosis, in the renal osteodystrophy patient there is the potential for low bone mineral density to coexist with an enormous range of functional abnormalities, from the very high-turnover bone lesions seen in patients with uncontrolled hyperparathyroidism to the profound reduction of bone

remodelling activity seen in patients with adynamic bone disease. That the optimal management of low BMD is the same at these 2 extremes of bone turnover is exceedingly unlikely.

We considered available evidence in a range of patient groups, namely CKD stages 2, 3, 4, and 5 (although it is questionable whether predialysis and dialysis patients should be considered together), renal replacement therapy by hemodialysis, renal replacement therapy by peritoneal dialysis, and finally renal transplantation. Discussion also extended to the pediatric CKD population. These diverse treatment modalities for end-stage kidney disease likely have profoundly differing effects on the evolution of metabolic bone disease. The hemodialysis population is probably the best studied, with posttransplant bone disease also receiving considerable attention over the past 5 to 10 years. Patients with CKD Stages 2, 3, and 4 remain relatively underinvestigated, particularly in regard to the skeletal manifestations of their disordered mineral metabolism.

Imaging and bone measurements are currently dominated by DEXA technology. Currently, this method is generally applied to spine and hip, but the spine clearly presents problems in CKD, with misleading elevation of measured BMD in the AP projection due to the aortic calcifications frequently observed in CKD patients. Measurement of BMD at the hip and radius may give better precision with fewer artifacts. Agreement is needed on the optimum sites of DEXA measurement in the CKD population. qCT has definite advantages, particularly for spine measurement in CKD patients, as this technique can define uncontaminated regions of interest (cortical versus trabecular), which will provide meaningful measurements of bone density. The distinction between cortical and trabecular bone is clearly advantageous. The increased remodeling rate in high-turnover disease results in thickened, sclerotic trabeculae, while low-turnover disease results in abnormally thin trabeculae. Traditionally, assessment of renal osteodystrophy has focused on trabecular morphology, to the exclusion of cortical bone—illogical in that hyperparathyroidism, for example, may cause increased subperiosteal, endocortical, and intracortical resorption resulting in cortical bone loss on multiple surfaces.²

We considered at length the implications of low BMD in a patient with CKD. Correlations of BMD with bone histology are poor. BMD measurement per se has no role in the assessment of bone turnover. Although fracture risks are greatly increased in CKD patients, fracture risk does not correlate well with DEXA measurements of trabecular BMD in patients with kidney disease.²⁻⁸ Hemodialysis patients with vertebral fractures and fragility fractures have comparable lumbar spine BMD, compared to those without fractures.^{9,10} Certainly a BMD measurement alone does not constitute a diagnosis, but rather forms part of the overall data set required in a patient with CKD and bone disease. In particular, BMD should be viewed in the context of the clinical scenario, laboratory variables, and bone histology, if available.¹¹ The group also considered the application of well-established biochemical markers and agreed that there were limitations, undoubtedly due to the mixed nature of the bone biology as well as effect of renal clearance.¹² Assessment of calcium, phosphorus, parathyroid hormone (PTH), and bone alkaline phosphatase may have limited utility.

Special Clinical Groups

Pediatrics. The pediatric CKD population raises particular issues and challenges. Growth in children with kidney disease is poor and, although effectively treated with growth hormone, the use of this therapy is sporadic. The relationship between bone turnover and growth in children is unclear. There is a major problem with slowing of bone growth, in particular cortical thickness, at puberty, and after puberty, “catch up” growth is likely to be incomplete. This decrement has an inordinately large effect on bone strength, because bone strength is related to the 4th power of the periosteal radius. Further complicating factors include hypogonadism and metabolic acidosis, both of which alter growth dynamics.

Diabetes. In patients with CKD, there is little understanding of the distinction between type 1 and type 2 diabetes. Diabetic patients exhibit a tendency for low-turnover bone lesions, but this is not invariable. There is also a tendency towards relatively low PTH, but again, this is not invariable. Fracture risk is increased in posttransplantation diabetic patients relative to nondia-

Table 2. Use of Traditional Osteoporosis Therapeutic Agents in CKD

Estrogen
Potential use in hypogonadism
Safety data lacking
Increased drug half-life
Efficacy unknown—especially long-term use
Selective estrogen receptor modulators (SERMs)
Safety data lacking
Efficacy unknown
Bisphosphonates
Efficacy unknown—especially long-term use
Safety data lacking
Theoretically dangerous in adynamic bone disease
Should have a bone biopsy
Calcitonin
Efficacy unknown
Probably safe

betic graft recipients.¹³ Relative fracture risk of diabetic versus nondiabetic patients in CKD stages 3 to 5 is unclear. Appropriate strategies for the management of established adynamic bone disease in diabetic patients have not been defined.

Therapies. The use of standard therapies for osteoporosis used in the general population in patients with CKD is highly controversial (Table 2). Agents considered included the bisphosphonates (oral and intravenous), estrogen, selective estrogen receptor modulators (SERMs), calcitonin, and androgens/anabolic steroids. The impact of these agents on BMD in CKD is uncertain, as is the effect of these treatments on bone turnover, bone quality, and fracture risk. Safety issues are of concern with estrogen, SERMs, and bisphosphonates. Calcitonin is probably safe in this setting, but this therapy has to be considered in the light of uncertain efficacy. None of these agents has licensed indications within the field of renal osteodystrophy in the United States or in most European countries. At present it is safest and likely most efficacious to focus initially on correcting bone turnover abnormalities in CKD patients.

Newer Approaches

PTH/calcimimetics/calcilytics. There has been a resurgence of interest in the use of PTH as a bone anabolic agent in patients with osteoporosis. Recent studies have added further support to earlier work pointing to the efficacy of intermit-

tent parenteral PTH on improving BMD.¹⁴ However, the scenario in renal osteodystrophy is entirely different. PTH is already substantially elevated in many patients and is thought to exert a net catabolic effect on the skeleton. The role of otherwise normal PTH pulsatility is unclear in the CKD environment. Nevertheless, the possibility exists for creating pulsatile PTH secretion in these patients by a number of different means. Thus, low calcium dialysate, possibly alternating with high calcium dialysate, is clearly capable of effecting abrupt changes to PTH concentration. The effects on bone are unknown. Calcimimetic agents, used cyclically, are likely to be capable of achieving brisk and transient reduction of PTH. The use of calcilytic agents alone or in combination with calcimimetics might achieve greater amplitude of PTH pulsatility, but again this approach is currently speculative. Therefore, the use of exogenously administered PTH as a therapy for renal osteodystrophy is not recommended.

Kidney transplantation. The postrenal transplant environment is deleterious to the skeleton in a number of ways and is usually applied to the skeleton on a background of pre-existing renal osteodystrophy associated with CKD. The pattern of bone loss following kidney transplantation is brisk in the early phase, with a tendency to stabilize after 1 year. Evidence from a number of studies indicates that fracture rates are even higher in transplanted patients than in comparable dialysis patients, and this increase is greatest in diabetic recipients of kidney/pancreas transplants.^{13,15-18} Compared with normal subjects, women aged 25 to 44 experience an 18-fold increase in fracture rate following renal transplantation, and in the age range of 45 to 64 years the increase is 34-fold.¹⁸ Histological studies have been conducted in the posttransplant subgroup and a variety of lesions have been identified, including high turnover and low turnover lesions. Neither of these lesions is well predicted by PTH concentration.^{19,20}

In the phase of rapid bone loss, histological studies suggest that bone resorption rates are increased and, in relative terms at least, bone formation is decreased. Bone turnover after 1 year is variable and there is marked heterogeneity between and within patient groups.²⁰ Choice of therapy is difficult, therefore, and suggests

Table 3. Therapeutic Approaches After Renal Transplant

Minimize glucocorticoid use
Calcineurin inhibitor
Role controversial
Probably minimize use
Calcium
Probably benign
May be helpful
Effectiveness unproven
Vitamin D or Calcitriol
May be helpful
Effectiveness unproven
Risk of hypercalcemia
Bisphosphonates
Protect BMD early on
Theoretically reasonable for high turnover only
Fracture outcomes/long-term safety both unknown
Calcitonin
Few data
Gonadal hormones
Few data

that strategies will need to be individualized if the variation in underlying bone pathology is to be matched with appropriate therapies. Of course, this presupposes that the underlying pathology can be characterized adequately.

Therapies assessed in this patient group include bisphosphonates, vitamin D, calcitonin, and estrogen (Table 3). The strongest data exist for bisphosphonate therapy. Pamidronate, ibandronate, or zoledronate given at the time of transplantation effectively retard and largely prevent bone loss in the early posttransplant period.²¹⁻²³ Whether this approach also decreases fracture risk is unclear, nor is it clear whether potentially deleterious ultrastructural effects on bone are generated. Bisphosphonate use in the renal transplant recipient has become quite commonplace in a number of countries, despite the relatively weak evidence base. Safety issues remain a concern, and in most countries, the use of bisphosphonates in renal transplant recipients is unlicensed. Data for calcitriol, calcitonin, and gonadal hormone use in posttransplant patients are relatively sparse and no clear recommendations have emerged.

Areas Requiring Further Investigation

The consensus of the work group was that there is an urgent need for more studies, especially those with bone biopsy data. There is a

critical yet unknown linkage between BMD and clinical end points. Thus, studies are also urgently required to investigate the relationship between BMD and fracture, BMD and bone turnover, BMD and growth, and, finally, BMD and vascular calcification. Clinical outcome studies in CKD and transplantation are relatively few, and future studies should be powered to examine the impact of therapies on fracture rate and the diagnostic utility of noninvasive assessments of bone metabolism such as biochemical markers. The role of recurrent CKD in the failing transplant setting is unknown; it is likely that these patients often receive inadequate treatment for their recurring renal osteodystrophy. Hypogonadism is highly prevalent in both transplanted and dialyzed patients and is underinvestigated and undertreated. Opportunity and need exist for studies to evaluate the role of sex steroid intervention on preventing bone loss in CKD patients.

There is a great opportunity to advance the database in the posttransplant patient group because many new immunosuppressive protocols are being evaluated, in most cases sponsored by the pharmaceutical industry. Transplanted patients are extremely vulnerable to skeletal morbidity, and these studies should, wherever possible, include measures to assess skeletal health. This approach would rapidly increase the size of the overall database and also draw out specific advantages and drawbacks of the new regimens.

CONCLUSION

The management of reduced BMD in the CKD and posttransplant populations provides a good example of clinical practice tending to run ahead of our understanding of mechanisms and of the clinical evidence base. The potential for doing harm is considerable and there is an urgent need to strengthen the underpinning of the sometimes empirical management of these patients. It is critical to understand that BMD is only a single assessment tool for the understanding of bone mass in renal osteodystrophy and the extrapolation of diagnostic categories of BMD abnormalities (eg, osteoporosis and osteopenia) in the general population to the CKD population is problematic. More data exist on the diagnosis and treatment of abnormalities of bone turnover in CKD patients. Clinicians are encouraged to

focus first on correction of this component of renal osteodystrophy.

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