

SPECIAL REPORT

Controversies in Bone and Mineral Metabolism in Chronic Kidney Disease

A Bridge to Improving Healthcare Outcomes and Quality of Life

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THE FIELD OF mineral metabolism and bone disease in patients with chronic kidney disease (CKD) has advanced significantly in the last 10 years. Many new and exciting basic research discoveries have been translated to new therapeutic approaches. We have seen the development of new phosphate binders, new vitamin D analogs, new imaging techniques, new assays for parathyroid hormone (PTH) and other biochemical markers, and, most importantly, a new understanding and appreciation of the extraskeletal manifestations of mineral metabolism.

These advances have resulted in a fundamental change in our approach to patients with CKD (Table 1). In addition, advances in the basic sciences of bone and vascular biology have led to improved understanding of vascular pathology and calcification, as well as new diagnostic techniques and therapies for the management of osteoporosis in the general population.

Traditionally, the term “renal osteodystrophy” described abnormalities of bone turnover in patients with CKD. More recently, abnormalities in bone density (traditionally called osteoporosis) and abnormalities in extraskeletal calcification are increasingly recognized as interrelated with abnormalities of bone turnover. These interrelationships create yet another complex area of potential controversy. The difficulties confronting the nephrologist are how to integrate these

advances and findings into clinical practice. Due to a lack of current consensus on therapeutic approaches, the clinical management of mineral metabolism disorders in CKD patients is fragmented and inconsistent among practitioners.

CURRENT GUIDELINES

As a result of these advances in knowledge and ongoing controversies in patient management, several sets of clinical practice guidelines on the management of bone metabolism in CKD have been developed. The first was the European Algorithms on Renal Osteodystrophy (*Nephrol Dial Transplant* 2000; 15 [Suppl 5]), developed cooperatively by clinical and scientific experts and the Division of Medicine of Fresenius Medical Care International. The intent of these algorithms dealing with cardiovascular risk factors and osteodystrophy was to “improve prevention and treatment of disease in our patients.” The guidelines were reviewed by the European Scientific Council and the Medical Directors of the Fresenius Medical Care Centers. The second guidelines document, The Australian CARI (Caring for Australians with Renal Impairment) Guidelines of March 2000, also recommended target goals for the management of renal osteodystrophy.

Most recently, the National Kidney Foundation (NKF), as part of its Kidney Disease Outcomes Quality Initiative (K/DOQI), formed a bone metabolism and disease work group that published a comprehensive set of 16 clinical practice guidelines for the management of bone metabolism disorders in CKD patients (*Am J Kidney Dis* 42:S1-S202, 2003 [suppl 3]). This guideline work group was led by Drs Shaul Massry and Jack Coburn. These guidelines were based on an evidence report generated by an external team of experts who screened over 4,700 articles, of which approximately 500 were subjected to detailed analysis and included in the final report.

As shown in Table 2, the target laboratory

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Table 1. The Paradigm Shift in Renal Osteodystrophy

Previous	Now
Aggressive suppression of PTH.	Caution against over-suppression. Uncertainty regarding use of newer PTH assays.
Liberal use of vitamin D.	More selective use of vitamin D, possibly using new vitamin D analogs.
Aggressive use of calcium as phosphate binder.	Avoidance of excessive calcium-containing phosphate binders.
Acceptance of Ca × P product of 70 as desirable endpoint.	Lower target Ca × P product values to reduce risk of extraskeletal calcification.
Little concern for 25-(OH) vitamin D status.	Recognition that 25-(OH) vitamin D deficiency is common.

values proposed by these 3 groups closely parallel each other, supporting an international consensus for intensive regulation of *bone-related* mineral abnormalities in CKD patients. However, the therapeutic approaches necessary to achieve these targets were detailed only in the K/DOQI Guidelines.

As an initial step in the implementation of the K/DOQI Guidelines, the NKF held a conference on March 14-16, 2003, entitled “Controversies in Mineral Metabolism and Bone Disease in CKD.” One purpose of this conference was to identify consensus and controversies that exist among experts in this area, and to identify therapeutic approaches to achieving the target goals outlined in Table 2.

Furthermore, the recent increased emphasis on extraskeletal manifestations of bone and mineral metabolism indicates that research is needed to address certain key questions that create integrated pathways for the management of mineral metabolism, balancing both the skeletal and extraskeletal manifestations of the disease. Therefore, the conference sought to examine the field

of mineral metabolism by re-evaluating traditional views of renal osteodystrophy and to examine the interrelationship between bone turnover, osteoporosis, and vascular calcification.

Another goal of the conference was to identify recommendations to help guide physicians in this difficult and sometimes confusing area of care. A final objective of the conference was to identify key questions in bone and mineral metabolism in CKD where controversy remained despite available data and guidelines. These questions could then be used to generate hypotheses to be tested, to discuss methods for testing these hypotheses, and to prioritize research initiatives. Identification of these controversies would also facilitate their ongoing and continuous examination in light of future clinical and scientific observations.

NKF CONFERENCE PROCEEDINGS

The meeting, led by Drs Sharon Moe and Tilman Drüeke, was structured around a theme of “what we know, what we can do with what we know, and what we need to know.” Day 1 fo-

Table 2. Comparison of European, Australian, and NKF-K/DOQI Guidelines for Management of Bone Metabolism in CKD

	Target Calcium (mg/dL)		Target Phosphorus (mg/dL)		Target Intact PTH (pg/mL)	
	Stage 3-4 CKD	Stage 5 CKD	Stage 3-4 CKD	Stage 5 CKD	Stage 3-4 CKD	Stage 5 CKD
Europe (2000)	8.8-11.0	8.8-11.0	2.5-4.6	4.6-5.6	85-170	85-170
Australia (2000)	No recommendation	8.8-10.4	No recommendation	<6.8, preferably <5.6	No recommendation	2-3 times upper limit of normal
K/DOQI (2003)	“Normal”	8.8-9.5*	3.0-4.6	3.5-5.5	35-110	150-300

NOTE. To convert calcium in mg/dL to mmol/L, multiply by 0.2495; to convert phosphorus in mg/dL to mmol/L, multiply by 0.3229; to convert PTH in pg/mL to ng/L, multiply by 1.

*Hypercalcemia defined as ≥10.2 mg/dL.

cused on reviewing key topics in the fields of bone, mineral, and vascular disease. It began with a discussion of the K/DOQI and European Guidelines, and an outline of the evolution in bone and mineral metabolism over the past 20 years. Selected individuals presented basic and clinical science advances in the fields of bone biology, vascular pathology, parathyroid, vitamin D, and gonadal hormones, as well as the capabilities of current diagnostic endpoints of radiographic imaging and bone biopsy.

Day 2 focused on a discussion of several key questions by each of 3 distinct work groups. Group I, Bone Turnover, was led by Drs Klaus Olgaard and Kevin Martin; Group II, Osteoporosis in CKD, was led by Drs John Cunningham and Stuart Sprague; and Group III, Vascular Calcification, was led by Drs William Goodman and Gerard London. On day 3, the groups presented results of their deliberations, and further discussion confirmed the presentations of the three work groups. The conference concluded by prioritizing education and research initiatives. An in-depth review of the discussions of each work group appears in the articles that follow in this issue, but a brief summary is provided below. A list of the conference participants is provided at the end of this introduction and in the manuscripts reporting on each of the work groups.

The discussion in **Group I (Bone Turnover)** focused on the epidemiology, diagnosis, and assessment of renal osteodystrophy, with particular focus on bone turnover. The group concluded that bone biopsy remains the standard against which all serum biochemistry and noninvasive assessments of bone metabolism must be compared. However, a clear need exists for new cross-sectional studies of bone biopsy in CKD Stages 3 to 5, in order to update our knowledge of the current epidemiology of renal osteodystrophy. (See Table 3 for staging system for CKD.) Furthermore, standardized techniques are needed for performing and reading bone biopsies. The impact of age, sex, race, and geographic location of individuals with CKD needs to be considered and appropriately matched to healthy control subjects.

The group also concurred that at the present time, intact PTH and bone-specific alkaline phosphatase are the most useful parameters for noninvasive assessment of bone histology. The group

Table 3. The 5-Stage Classification System for CKD as Outlined in the NKF K/DOQI Clinical Practice Guidelines for CKD: Evaluation, Classification, and Stratification (2002)

Stage	GFR (mL/min/1.73 m ²)	Description
1	≥90	Kidney damage with normal or ↑ GFR
2	60-89	Kidney damage with mild ↓ GFR
3	30-59	Moderate ↓ GFR
4	15-29	Severe ↓ GFR
5	<15 or dialysis	Kidney failure

felt that the new 1-84 PTH assays offer potential for improved worldwide standardization, but that further validation and standardization of these assays must be done prior to their widespread adoption. New therapies, including vitamin D analogs, new phosphate binders such as sevelamer and lanthanum, and calcimimetics offer improved therapeutic options, but their efficacy must be assessed using bone histology. The group recommended expansion of the current models of uremic rats and mice to answer many questions on the toxicity and effectiveness of these therapies. In addition, improved skeletal imaging and noninvasive methods to assess bone turnover are needed.

Group II (Osteoporosis) felt that use of the term “osteoporosis” should be discontinued in patients with CKD, as it has fracture and therapeutic implications that may not be applicable to the CKD population. The group favored the National Institute of Health definition of osteoporosis: “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.” (See http://consensus.nih.gov/cons/111/111_statement.htm#1 for the NIH Consensus Statement on Osteoporosis.)

The term “renal osteodystrophy,” considered by the group to be the more appropriate term, is a function of bone turnover (assessed by bone biopsy), bone density (assessed by dual x-ray absorptiometry [DEXA] or quantitative CT [qCT]), and bone architecture (for which there are currently no in vivo measurement technologies). Bone mineral density (BMD) alone should

not be used to make a diagnosis, but should be performed to help in the diagnosis of renal osteodystrophy and to assist in determining appropriate therapies. Despite these limitations, BMD should be evaluated for patients with Stage 5 CKD at entry to dialysis and every 2 years thereafter; and for transplant patients, at the time of transplant, 1 year posttransplant, and every 2 years thereafter. BMD measurement in Stage 3 and 4 CKD is optional as part of the evaluation of renal osteodystrophy, but is indicated in conditions applicable to the general population.

Treatment with traditional antiosteoporosis agents, including bisphosphonates and other antiresorptives, is not recommended without bone biopsy. These agents should be secondary to the optimization of bone turnover, as there is much more evidence on the long-term consequences and therapeutic approach to abnormalities of bone turnover. The pediatric population is particularly prone to bone abnormalities, and the use of growth hormone among practicing pediatric specialists is unacceptably low. Furthermore, the differentiation of cortical and trabecular bone changes may not be proportional, and differential growth of one compartment over the other may have a strong impact on outcomes. The advent of calcimimetics in the near future may improve the overall therapy of renal osteodystrophy.

Group III (Vascular Calcification) felt that physicians need to appreciate that there are 2 types of calcification—medial calcification and intimal (atherosclerotic) calcification. Both forms are common and are associated with significant cardiovascular endpoints. Current techniques do not allow imaging differentiation of the type of vascular calcification. Its prevalence in CKD patients is higher than in the general population, and the magnitude of calcification in Stage 5 CKD is severe. Calcification is a regulated process, and much remains to be learned about the causes and natural history of this disorder. The risk factors for intimal and medial calcification may vary, as detailed in subsequent papers. Clearly, there are certain genetic factors as well as proteins that may be naturally occurring inhibitors of calcification. Further work should be done to improve our understanding of these protective factors.

The group felt that individuals should undergo screening for vascular calcification, and that a

vascular calcification index should be developed and validated to better characterize the disease process in CKD patients. Animal models, while theoretically useful, currently fall short of extension to the clinical setting. Further work is required to develop and adapt them to solve clinically important questions and define new treatment strategies.

SUMMARY AND NEXT STEPS

“The Controversies in Mineral Metabolism and Bone Disease in CKD” conference served as a starting point for generating international acceptance within the nephrology community of a more uniform approach to achieving biochemical targets and structurally sound bone. Finally, the conference highlighted that abnormalities in bone and mineral metabolism were linked to extraskeletal manifestations and emphasizes the need to provide a systematic approach rather than a target organ approach to the control of mineral metabolism.

It is important that the nephrology community understand that the term **renal osteodystrophy** encompasses abnormalities of bone turnover and bone mineral density/content (DEXA or qCT), and that the ultimate goal is to decrease bone pain, fracture risk, and the extraskeletal manifestations of altered mineral metabolism that result from renal osteodystrophy. We hope that this conference will be the first of many in a number of clinical areas that will improve the health and quality of life of CKD patients worldwide. As we move forward from the K/DOQI and other guidelines with the **Global Bone and Mineral Initiative**, we hope to accomplish several educational and research initiatives to truly advance the care we provide our patients.

EDUCATIONAL INITIATIVES

The proposed educational initiatives included:

1. Wider dissemination and adoption of the target goals for calcium, phosphorus, and PTH as presented in the K/DOQI bone metabolism and disease guidelines.
2. Continued educational programs on the importance of controlling serum phosphorus. The approach to the patient with renal osteodystrophy is multifaceted. In the past, physicians have focused on PTH as the initial assay on which to base therapy;

however, the group felt that beginning with phosphorus, as suggested in the K/DOQI algorithms, is the logical approach. The relative place of calcium-based and calcium-free phosphate binders to achieve phosphorus control still needs to be defined. Further explanation of the new PTH assays is also needed. The consensus was that adoption of these assays is premature. In addition, work needs to be done in collaboration with clinical pathology associations to standardize PTH assays.

3. Programs to help nephrologists and other physicians appreciate the 2 processes of intimal and medial vascular calcification and the variable risk factors for each. Educational programs should stress that control of both processes is important in ensuring the health of CKD patients.
4. Training more nephrologists in the procedures of bone biopsy. Conference participants suggested that the NKF offer hands-on training sessions to train individuals in the indications, interpretation, and use of bone biopsies.
5. Standardizing the nomenclature for renal osteodystrophy and definitions of bone turnover by histomorphometry.
6. Education on the appropriate approach to a CKD patient with low BMD by DEXA, due to the lack of safety and efficacy of existing therapies in the CKD population.

RESEARCH INITIATIVES

Proposed research priorities included:

1. A bone biopsy study in Stage 3, 4, and 5 CKD. The bone biopsy study should include bone markers, stored serum for use in assays of future bone markers, DEXA of the wrist and hip, and a DNA sample stored for future analysis.
2. The development and standardization of a vascular calcification risk factor profile or index and correlation of this index with various cardiovascular end-points.
3. Standardization of PTH assays across clinical pathology reports.
4. Development of new noninvasive techniques or assays to quantify bone turnover.
5. Studies in patients with CKD and kidney

transplants evaluating osteoporosis therapies utilized in the general population.

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