Definition, evaluation, and classification of renal osteodystrophy: A position statement from Kidney Disease: Improving Global Outcomes (KDIGO)

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Disturbances in mineral and bone metabolism are prevalent in chronic kidney disease (CKD) and are an important cause of morbidity, decreased quality of life, and extraskeletal calcification that have been associated with increased cardiovascular mortality. These disturbances have traditionally been termed *renal osteodystrophy* and classified based on bone biopsy. Kidney Disease: Improving Global Outcomes (KDIGO) sponsored a Controversies Conference on Renal Osteodystrophy to (1) develop a clear, clinically relevant, and internationally acceptable definition and classification system, (2) develop a consensus for bone biopsy evaluation and classification, and (3) evaluate laboratory and imaging markers for the clinical assessment of patients with CKD. It is recommended that (1) the term *renal osteodystrophy* be used exclusively to define alterations in bone morphology associated with CKD, which can be further assessed by histomorphometry, and the results reported based on a unified classification system that includes parameters of turnover, mineralization, and volume, and (2) the term CKD-Mineral and Bone Disorder (CKD-MBD) be used to describe a broader clinical syndrome that develops as a systemic disorder of mineral and bone metabolism due to CKD, which is manifested by abnormalities in bone and mineral metabolism and/or extra-skeletal calcification. The international adoption of these recommendations will greatly enhance communication, facilitate clinical decision-making, and promote the evolution of evidence-based clinical practice guidelines worldwide.

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Chronic kidney disease (CKD) is a worldwide public health problem, with increasing prevalence and adverse outcomes, including progressive loss of kidney function, cardiovascular disease, and premature death.[1] Disturbances in mineral metabolism and bone disease are common complications of CKD and an important cause of morbidity and decreased quality of life. Importantly, there is increasing evidence suggesting that these disorders in mineral and bone metabolism are associated with increased risk for cardiovascular calcification, morbidity, and mortality.[2] The underlying mechanisms for this linkage are not completely understood, but are probably related to an effect on vascular calcification (VC) leading to changes in cardiovascular structure and function.[3,4] Evaluation of extraskeletal calcification therefore becomes an essential component in the work up and classification of the mineral and bone disorders in patients with CKD.

Renal osteodystrophy is the term that has been used traditionally to describe the abnormalities in bone morphology that develop in CKD.[5–8] In clinical practice, bone biopsy is used infrequently because it is an invasive and often expensive procedure and the samples obtained require specialized processing that is not widely available. The most common forms of renal osteodystrophy are attributable largely to variations in the plasma levels of parathyroid hormone (PTH). As such, circulating PTH levels have been used as a surrogate indicator of bone turnover, which are used together with measurements of serum calcium, phosphorus, and alkaline phosphatase levels to evaluate, diagnose, and guide the treatment of renal osteodystrophy. However, the specificity of PTH as an indicator of bone turnover has been questioned.[9,10] Several other circulating biochemical markers of bone formation and resorption have been investigated as clinical indicators of bone turnover,[11,12] but their clinical applicability remains to be established.

In addition to bone histology and serum biomarkers, imaging has been an important component of evaluating bone disease in the past, and remains the main tool in assessing extraskeletal calcification in CKD patients.[13] Ongoing developments in non-invasive imaging techniques almost certainly will lead to their improved and more widespread use in clinical diagnosis and decision-making in the near future.[14] In principle, the definition, evaluation, and classification of the mineral abnormalities and bone disease in CKD should include all three clinical components: serum biomarkers, non-invasive imaging, and bone abnormalities. Unfortunately, to date, there is no clear definition of renal osteodystrophy that incorporates all these components of disorders in mineral and bone metabolism encountered in CKD.

At the 2003 National Kidney Foundation Controversies Conference on Mineral Metabolism and Bone Disease in CKD, the following definition for renal osteodystrophy was proposed: *A constellation of bone disorders present or exacerbated by chronic kidney disease that lead to bone fragility and fractures, abnormal mineral metabolism, and extraskeletal manifestations*.[15] This definition, which incorporates the relevant elements of mineral and bone abnormalities and soft tissue calcification, has failed to gain worldwide acceptance. The historical absence of a generally accepted definition and diagnosis of renal osteodystrophy indicates the need for an international consensus, which the Board of Directors of Kidney Disease: Improving Global Outcomes (KDIGO) selected as a priority issue to address.

KDIGO was established in 2003 as an independently incorporated non-profit foundation governed by an international board of directors with the stated mission to 'improve the care and outcomes of kidney disease patients worldwide through promoting coordination, collaboration and integration of initiatives to develop and implement clinical practice guidelines'. One of the initiatives adopted by the KDIGO Board of Directors is a series of international Controversies Conferences to examine what is known, what can be done with what is known, and what needs to be known on controversial topics of clinical relevance. The first KDIGO Controversies Conference on 'Definition and Classification of Chronic Kidney Disease' was held in 2004.[16]

The second KDIGO Controversies Conference on 'Definition, Evaluation, and Classification of Renal Osteodystrophy' was held on September 15–17, 2005 in Madrid, Spain. The specific objectives for this conference were to

1. develop a clinically relevant, easily applicable definition and classification system for the constellation of disorders heretofore known as renal osteodystrophy;
2. examine current histologic categories of renal osteodystrophy and develop consensus on a unified evaluation and classification of bone histology; and
3. evaluate and assess the clinical utility of serum markers and imaging procedures that can allow the non-invasive diagnosis and classification of mineral and bone disorders specifically associated with CKD with reasonable accuracy.

The adoption of a clear definition and improved classification scheme based on readily available clinical parameters would greatly enhance the direction of future research and the development and implementation of evidence-based clinical practice guidelines for the management of mineral and bone abnormalities in CKD.

CONFERENCE PROCEEDINGS

KDIGO co-chairs (G Eknoyan and N Lameire) identified the conference co-chairs (T Drüeke and S Moe) and worked together to develop the agenda and participants list. Meeting participants were chosen based on their demonstrated expertise in mineral and bone metabolism and interest in global issues in guideline development and implementation. The conference was attended by more than 70 physicians, representing six continents and 21 countries (see Appendix A1). Prior to the conference, each of the participants was invited to submit an abstract of their work and concerns to facilitate the meeting discussions. Those abstracts and the conference agenda can be found at www.kdigo.org.

The meeting started with a plenary session during which a series of presentations were made, designed to provide both a historical perspective and an overview of recent developments in the areas of bone biopsy and histomorphometry, serum markers of bone metabolism, and assessment of bone health with imaging techniques. The plenary session was followed by breakout sessions of three separate work groups to address the following topics: bone biopsy and histomorphometry, biomarkers, and imaging techniques. Each of the work groups was asked to make recommendations on a name, definition, and classification system for the disorder. They were also challenged to critically examine the diagnostic parameters specific to their topic area and make recommendations on their utility and validity in the evaluation of the disease, and to make recommendations to guide clinical research studies aimed at evaluating the adequacy of their proposals. Owing to the complexity of the meeting objectives for the bone biopsy work group, members of this group were invited to begin their deliberations a day earlier than those of the other two work groups.

On the final day, work group leaders presented a summary of their group's deliberations and recommendations to the entire conference assembly. After discussion and refinement of the recommendations, the conference participants prioritized and voted on the recommendations. This paper contains the specific recommendations made at the meeting. It has been reviewed by the participants and approved as a position statement by the KDIGO Board of Directors.

FRAMING THE ISSUES

There was general agreement among the conference attendees on the following issues:

1. The traditional definition of renal osteodystrophy does not completely depict the underlying bone pathology or reflect the full spectrum of symptoms associated with mineral and bone disorders in CKD.
2. Bone biopsy remains a powerful and informative diagnostic tool for the determination of bone abnormalities. However, owing to its limited use, a biopsy-based definition and classification system does not provide an adequate means in clinical practice to clearly identify and classify CKD patients with mineral and bone disorders.
3. Although the mechanisms involved are still poorly understood, there is a clear association in CKD patients between mineral and bone abnormalities and the incidence and severity of VC and cardiovascular morbidity and mortality. The presence of abnormal values of circulating markers such as plasma phosphorus, as well as the presence and extent of VC, is associated with increased cardiovascular and all-cause morbidity and mortality in CKD stage 5 patients on hemodialysis.[17] Minimizing abnormalities in biochemical markers, such as hyperphosphatemia and hypercalcemia, and slowing or halting the progression of extraskeletal calcification is considered a critical component of the management of CKD patients for the prevention of bone disease and other related morbidities and mortality.[18–20]

RECOMMENDATIONS FOR DEFINITION, EVALUATION, AND CLASSIFICATION OF RENAL OSTEODYSTROPHY

The principal conclusion from the conference was that the current descriptive nomenclature for this pathophysiologic process should be reconsidered. It is recommended that the term *renal osteodystrophy* be used exclusively to define the bone pathology associated with CKD. The many clinical, biochemical, and imaging abnormalities that have heretofore been identified as correlates of renal osteodystrophy should be defined more broadly as a clinical entity or syndrome to be called *chronic kidney disease-mineral and bone disorder* (CKD-MBD). Conference participants examined these two issues separately and made recommendations for the definition, evaluation, and classification of each.

Renal osteodystrophy

Definition of renal osteodystrophy. The meeting participants agreed on a definition of renal osteodystrophy that is specific to bone pathology found in patients with CKD (Table 1). Renal osteodystrophy is one component of the mineral and bone disorders that occur as a complication of CKD.

Evaluation of renal osteodystrophy. The evaluation and definitive diagnosis of renal osteodystrophy requires a bone biopsy. Histomorphometry is not essential for clinical diagnosis, but should be performed in research studies. There was unanimous agreement that histomorphometric results are to be reported using standard nomenclature as recommended by the American Society for Bone and Mineral Research,[21] and that investigators would supply primary measurements used to report any derived parameters.

Classification of renal osteodystrophy. In order to clarify the interpretation of bone biopsy results in the evaluation of renal osteodystrophy, it was agreed to use three key histologic descriptors – bone turnover, mineralization, and volume (TMV system) – with any combination of each of the descriptors possible in a given specimen (Table 2). The TMV classification scheme provides a clinically relevant description of the underlying bone pathology as assessed by histomorphometry, which in turn helps define the pathophysiology, and thereby guide therapy.

Chronic kidney disease-mineral and bone disorder

Definition of CKD-MBD. The meeting participants agreed on a definition of CKD-MBD (Table 3) that incorporates elements of abnormal mineral metabolism, altered bone structure and composition, and extraskeletal calcification with the following caveats:

- Bone disease and VC are discreet entities that are not exclusive to the CKD population.
- Bone disease and VC are multifactorial processes, and disturbances in mineral metabolism due to CKD may not be their primary underlying etiology.
- The evidence for a link between mineral disturbances and VC in CKD is not yet fully established.

Evaluation of CKD-MBD. The initial evaluation of CKD-MBD should include PTH, calcium (either ionized or total corrected for albumin), phosphorus, alkaline phosphatases (total or bone-specific), bicarbonate, and imaging for soft tissue calcification.

- If there are inconsistencies in the biochemical markers (e.g. high PTH but low alkaline phosphatases), unexplained bone pain, or unexplained fractures, a bone biopsy would be indicated.

Table 1 | Definition of renal osteodystrophy

Renal osteodystrophy is an alteration of bone morphology in patients with CKD
It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy.

CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder.

Table 2 | TMV classification system for renal osteodystrophy

Turnover	Mineralization	Volume
Low	Normal	Low
Normal	Abnormal	Normal
High		High

TMV, bone turnover, mineralization, and volume.

Table 3 | Definition of CKD-MBD

A systemic disorder of mineral and bone metabolism due to CKD manifested by either one or a combination of the following:
Abnormalities of calcium, phosphorus, PTH, or vitamin D metabolism
Abnormalities in bone turnover, mineralization, volume, linear growth, or strength
Vascular or other soft tissue calcification

CKD, chronic kidney disease; CKD-MBD, chronic kidney disease-mineral and bone disorder; PTH, parathyroid hormone.

- Additional tests to assess linear growth rate are needed in children with CKD.

A proposed framework for classification of CKD-MBD. Disease classification systems can be simple or complex and may be based on severity, prognosis, outcomes, symptoms, or treatment modalities. General considerations in the adoption of a classification system include (1) availability of supporting data, (2) ease of clinical use, and (3) appropriateness in guiding clinical therapy.

An ideal classification system for CKD-MBD would allow categorization of patients based on readily available clinical diagnostic tools and would help guide treatment. The lack of adequate data and the nonlinearity of the disease process do not allow for the development of a classification based on severity or treatment at this time. The proposed framework for classifying CKD-MBD (Table 4) divides patients into four types based on the presence or absence of abnormalities in the three primary components used in the definition of the disorder: laboratory abnormalities (L), bone disease (B), and calcification of extraskeletal tissue (C). This framework is meant to be descriptive rather than predictive, as an initial attempt to improve communication and stimulate research. It is a working model that may have to be modified and improved in the future depending on further analysis of new data that become available. This simple framework lends itself to subsequent critical evaluation and refinement based on analysis of patient databases or the prospective evaluation of CKD patients.

Coexistence of CKD-MBD with other causes of bone and vascular disease. The use of CKD-MBD should be as specific as possible and limited to disturbances caused by significantly reduced kidney function. In general, adult patients with a glomerular filtration rate of >60 ml/min/1.73 m^2 should be excluded, as this is the level of glomerular filtration rate below which abnormalities in calcium, phosphorus, PTH, and vitamin D metabolism are detectable. In pediatric patients, the level of glomerular filtration rate at which CKD-MBD abnormalities are detectable is higher (glomerular filtration rate <89 ml/min/1.73 m^2). On the other hand, increased bone fragility observed with aging (senile or postmenopausal osteoporosis) and atherosclerotic disease with calcification that develops independent of CKD can be present in patients with CKD who have normal or only slightly reduced kidney function, and can coexist with CKD-MBD after its onset. This is an important consideration, as CKD may alter the diagnosis, treatment, and prognosis of osteoporosis and atherosclerosis. Bone, in particular, is likely to be more severely affected by CKD than might be expected from normal aging, either because of the extremes of turnover or remodeling that occur in CKD in adults and children, or because of abnormalities of modeling that occur in growing children. This in turn might have a major impact on bone strength, perhaps even more so than that of altered bone mass or volume. Because of this, the term osteoporosis should not be used in describing altered bone fragility in CKD patients.[22] By the same token, several studies have demonstrated that for any age group the atherosclerotic lesions are more calcified in CKD patients than in the general population.[23] The presence of increased calcification in these cases may affect the response to common therapies such as angioplasty. Thus, although CKD-MBD should refer to conditions that are caused by CKD, the precise contribution of CKD-related changes to disease states commonly found in the general population will require increased understanding of the underlying pathophysiology, more sensitive diagnostic tools, and a different therapeutic approach.

Table 4 | A framework for classification of CKD-MBD

Type[a]	Laboratory abnormalities	Bone disease	Calcification of vascular or other soft tissue
L	+	−	−
LB	+	+	−
LC	+	−	+
LBC	+	+	+

[a]L, laboratory abnormalities (of calcium, phosphate, PTH, alkaline phosphatases, or vitamin D metabolism); B, bone disease (abnormalities in bone turnover, mineralization, volume, linear growth, or strength); C, calcification of vascular or other soft tissue.
CKD-MBD, chronic kidney disease-mineral and bone disorder; PTH, parathyroid hormone.

WORK GROUP-SPECIFIC RECOMMENDATIONS

Assessment of bone by histomorphometry (co-chairs W Goodman and S Ott)

1. *Indications for bone biopsy*: Bone biopsy is not recommended as part of the routine evaluation for CKD-MBD, but remains a valuable diagnostic tool in the clinical evaluation and differential diagnosis of bone disease in selected patients with CKD. The clinical indications for bone biopsy include, but are not limited to the following:

- inconsistencies among biochemical parameters that preclude a definitive interpretation,
- unexplained skeletal fracture or bone pain,
- severe progressive VC,
- unexplained hypercalcemia,
- suspicion of overload or toxicity from aluminum, and possibly other metals,
- before parathyroidectomy if there has been significant exposure to aluminum in the past or if the results of biochemical determinations are not consistent with advanced secondary or tertiary hyperparathyroidism, and

- to be considered before beginning treatment with bisphosphonates.

2. *Histologic classification based upon TMV (turnover/mineralization/volume)*: A standardized nomenclature for reporting the results of bone histomorphometry, both for clinical and for research purposes, has been provided by the American Society for Bone and Mineral Research (ASBMR).[21] It is recommended that the same nomenclature be utilized for the assessment of renal osteodystrophy to promote a more widespread and consistent understanding of bone histomorphometry and the information that it provides. Such an approach would also facilitate valid comparisons among results from various research reports. If calculated parameters are used, it is expected that the primary measurements used to derive them are made available, using appendices or internet databases as necessary.

The components used to classify renal osteodystrophy include turnover, mineralization, and bone volume using the TMV classification system (Table 2). This new classification is consistent with the current commonly used one,[24] but provides more information on parameters other than turnover (Figure 1).

1. Turnover reflects the rate of skeletal remodeling, which is normally the coupled process of bone resorption and bone formation. It is assessed with histomorphometry by dynamic measurements of osteoblast function using the technique of double-tetracycline labeling. Bone formation rates and activation frequency represent acceptable parameters for assessing bone turnover. When bone formation rate is reported, the referent (bone surface, area, volume or tissue volume) should be specified. If expressed as a categorical variable (low, normal, or high), the cutoff values should be included. Bone turnover is affected mainly by hormones, cytokines, mechanical stimuli, and growth factors that influence the recruitment, differentiation, and activity of osteoclasts and osteoblasts.
   It is important to clarify that although bone formation rate is frequently similar to bone resorption rate, which cannot be measured directly, this is not always true. Imbalance in these processes can affect bone volume. For example, excess resorption over formation will lead to negative bone balance and decreased bone volume.
2. Mineralization reflects how well bone collagen becomes calcified during the formation phase of skeletal remodeling. It is assessed with histomorphometry by static measurements of osteoid volume and osteoid thickness and by dynamic, tetracycline-based measurements of mineralization lag time and osteoid maturation time. Causes of impaired mineralization include inadequate vitamin D nutrition, mineral deficiency, acidosis, or bone aluminum toxicity.
3. Volume indicates the amount of bone per unit volume of tissue. It is assessed with histomorphometry by static measurements of bone volume in cancellous bone. Sometimes, measurements of cortical bone volume and thickness may provide additional useful information. Determinants of bone volume in the general population and CKD patients include age, gender, race, genetic factors, nutrition, endocrine disorders, mechanical stimuli, toxicities, neurological function, vascular supply, growth factors, and cytokines.

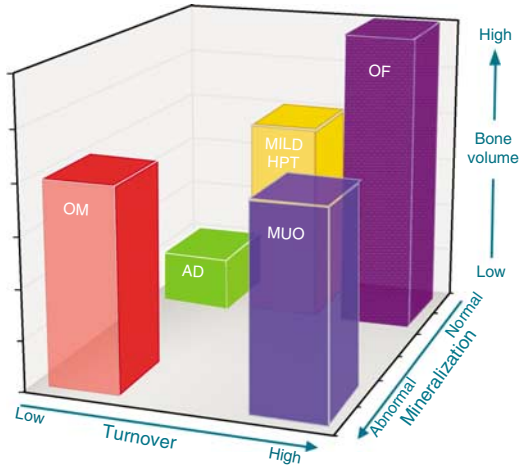

Figure 1 | TMV classification system for bone histomorphometry. The figure is a graphical example of how the TMV system provides more information than the present, commonly used classification scheme. Each axis represents one of the descriptors in the TMV classification: turnover (from low to high), mineralization (from normal to abnormal), and bone volume (from low to high). Individual patient parameters could be plotted on the graph, or means and ranges of grouped data could be shown. For example, many patients with renal osteodystrophy cluster in areas shown by the bars. The red bar (OM, osteomalacia) is currently described as low-turnover bone with abnormal mineralization. The bone volume may be low to medium, depending on the severity and duration of the process and other factors that affect bone. The green bar (AD, adynamic bone disease) is currently described as low-turnover bone with normal mineralization, and the bone volume in this example is at the lower end of the spectrum, but other patients with normal mineralization and low turnover will have normal bone volume. The yellow bar (mild HPT, mild hyperparathyroid-related bone disease) and purple bar (OF, osteitis fibrosa or advanced hyperparathyroid-related bone disease) are currently used distinct categories, but in actuality represent a range of abnormalities along a continuum of medium to high turnover, and any bone volume depending on the duration of the disease process. Finally, the blue bar (MUO, mixed uremic osteodystrophy) is variably defined internationally. In the present graph, it is depicted as high-turnover, normal bone volume, with abnormal mineralization. In summary, the TMV classification system more precisely describes the range of pathologic abnormalities that can occur in patients with CKD.

3. *Reporting of results*: It is recommended that publications that report histomorphometric measurements should include the following details in the methods section: biopsy technique, specimen size, tetracycline protocol, assessment of sample adequacy (e.g. exclusions due to crush artifacts), tissue area that was measured, magnification, minimal osteoid width measured, and normative data source when

appropriate. Each reporting laboratory should perform assessment studies of their methodology precision.

4. *Quality assurance*: There is a clear need to establish a cooperative international initiative to facilitate the development of a global quality assurance program and a data collection mechanism for bone histomorphometry results in CKD. Objectives include the following:

- Develop a quality control and assurance protocol with ongoing inter-laboratory exchange of bone biopsy material to determine the variability of histomorphometric results among laboratories and to promote standardization for the reporting of results.
- Develop a mechanism to collect all currently available normative data for bone biopsies, including an international effort to prospectively obtain bone biopsy samples from healthy volunteers. This should include evaluation of age, gender, and race variations in different geographic regions.

Research questions and considerations related to bone histomorphometry.

1. What changes in bone histomorphometry parameters occur as CKD progresses from stage 2 to 5?
2. What is the relationship of bone histomorphometric abnormalities to vascular and other soft tissue calcifications?
3. What is the relationship of bone histomorphometric abnormalities to the diminished linear growth in children?
4. What are the functional properties of bone in the maintenance of systemic calcium homeostasis?
5. What is the relationship between bone histomorphometric abnormalities and clinical outcomes?
6. How can bone biopsy be utilized best in clinical practice?
7. How do non-invasive techniques relate to histomorphometric findings?
8. How can more clinicians be trained to do bone biopsies and how can the number of centers doing bone histomorphometry be increased?

Assessment of biomarkers (co-chairs K Martin and K Olgaard)

This work group evaluated the clinical utility of biomarkers used in the assessment of mineral and bone abnormalities in CKD shown in Table 5.

Table 5 | Serum biomarkers examined by the biomarkers work group

PTH ('Intact')	Osteocalcin
1-84 PTH	Osteoprotegerin
1-84 PTH/7-84 PTH ratio	TRAP-5b
Phosphorus	Pyridinoline and deoxypyridinoline
Calcium	Procollagen type 1 amino-terminal
Calcium × phosphorus product	extension peptides
Bicarbonate	CTX
Alkaline phosphatases	25(OH)-vitamin D
Total	FGF23
Bone-specific	Fetuin-A

CTX, C-terminal crosslinks; FGF 23, fibroblast growth factor 23; PTH, parathyroid hormone; TRAP-5b, tartrate-resistant acid phosphatase. isoform 5b.

1. *Bone activity markers*: Although several serum or urine markers of bone activity have been investigated, there was general agreement that serum PTH levels remain the best clinical indicator of bone turnover at this time. Nearly all the currently available information on the correlation of PTH with bone histomorphometry and outcomes has been obtained with 'intact' PTH assays. Whereas the current published studies supporting a clinical advantage in measuring 1-84 PTH over the traditional 'intact' PTH assays are controversial, it is anticipated that commercial assays that measure only the 1-84 PTH peptide will gain increasing acceptance owing to their superior reproducibility across sites. Additional investigation is needed to determine the effect of 7-84 PTH and other large fragments of PTH on bone and the possible clinical value of the 7-84 PTH to 1-84 PTH ratio.
2. *Serum Calcium:* Measurement of ionized calcium is the preferred method for evaluating serum calcium. However, the sample processing and cost involved with routine ionized calcium measurement may preclude its clinical use. If total serum calcium concentration is used, it should be 'corrected' for albumin if its serum level is low, although there is currently a lack of standardization of the formulas used to determine 'corrected calcium' (National Kidney Foundation,[25] Guideline 6).
3. *Alkaline phosphatases*: Serum total alkaline phosphatases, in conjunction with PTH, can be helpful in predicting bone turnover.[26] Bone-specific alkaline phosphatase has marginal advantages, but it probably does not warrant the additional cost of measurement.
4. *Serum biomarkers*: The biomarkers, osteocalcin, osteoprotegerin, TRAP-5b, pyridinoline, deoxypyridinoline, procollagen type 1 amino-terminal extension peptides, and C-terminal crosslinks, have not been adequately studied in patients with CKD stage 3–5. A problem with several of these biomarkers is their kidney-dependent elimination that affects their measured levels depending on the degree of kidney dysfunction.

Research questions and considerations related to biomarkers.

1. Do the current formulas used to 'correct' serum total calcium based on serum albumin level provide a more accurate representation of calcium status than uncorrected serum total calcium?
2. What is the correlation of mineral and bone biomarker values to (1) morbidity and mortality, (2) bone fracture risk and occurrence, (3) bone histomorphometry data, (4) soft tissue calcifications, and (5) growth rate in children?

3. What is the precise role of C-terminal PTH fragments and the 7-84 PTH to 1-84 PTH ratio in the assessment of CKD-MBD and how can PTH assays be standardized internationally?
4. What is the preferred inter-dialytic interval for assessing serum phosphorus (e.g. after 2 or 3 days off dialysis)?
5. What is the role of Fetuin-A and FGF23[27,28] levels in the evaluation of CKD-MBD?
6. What is the role of other markers of bone metabolism in the evaluation of CKD-MBD?
7. What is the role of measuring 25(OH)-vitamin D levels in the assessment of CKD-MBD, and which assay is preferable in CKD?
8. How often must biomarkers be measured in stable clinical condition vs evolving high or low bone turnover disease to assess CKD-MBD?

Table 6 | Evaluation techniques examined by imaging work group

Bone mineral density – DXA (measures area per cm^2):	*Bone architecture:*
Lumbar spine	Micro-MRI/CT
Hip	Radioisotope imaging
Radius	*Extraskeletal calcification:*
Bone mineral density – qCT (measures volume per cm^3)	EBCT/MSCT
Bone structure:	Abdominal radiograph
Hand radiograph	CT scan
Hip radiograph	*Vascular stiffness:*
Skull radiograph	Pulse wave velocity
Clavicle radiograph	Pulse pressure
Ultrasound	

DXA, dual-energy X-ray absorptiometry; EBCT, electron beam computed tomography; micro-MRI/CT, micro-magentic resonance imaging/computed tomography; MSCT, multislice computed tomography; qCT, quantitative computed tomography.

Assessment of imaging techniques (co-chairs J Cunningham and S Sprague)

The radiologic imaging techniques used in the evaluation of the skeletal system and extraskeletal calcification that were considered are shown in Table 6.

1. *Bone mineral density measurement:*

- The value of bone density measurement (BMD) in the evaluation of CKD-MBD is not well established. Findings on the correlation of BMD values to fracture risk in the CKD population are inconsistent. However, several studies have shown that when BMD is measured at the distal radius site, it is predictive of fracture risk[29] and correlates well with PTH levels[30] in hemodialysis patients. Distal radius is therefore the preferred site of measurement in CKD patients. This is consistent with the recommendations of International Society of Clinical Densitometry in their 2005 Official Position Statement (http://www.iscd.org/Visitors/positions).
- There is concern that hip or spine BMD results, without full consideration of the underlying bone pathology, may be misleading and result in the inappropriate administration of anti-osteoporotic therapy to CKD patients.
- Serial BMD measurements are valuable in the evaluation of bone disease in kidney transplant recipients in adults (National Kidney Foundation,[25] Guideline 16), but not in children (National Kidney Foundation,[31] Guideline 2). Their role in CKD-MBD in adults and children remains to be determined.
- BMD measurement by quantitative computed tomography is valuable in differentiating cortical from trabecular bone. This is particularly advantageous in CKD-MBD, where hyperparathyroidism can lead to sclerotic thickening of trabecular bone with increased BMD but stimulates resorption in cortical bone with significant reductions in BMD. In contrast, low-turnover bone disorders frequently result in reductions in trabecular BMD.[32]

2. *Bone strength and quality:* The contribution of bone mass to bone strength is of uncertain value in patients with CKD who actually exhibit a wide spectrum of bone quality. Unfortunately, technologies that assess bone quality and strength are currently not available for clinical use. Plain X-ray films provide minimal information in the evaluation of CKD-MBD in the majority of CKD patients. Exceptions are advanced forms of bone disease such as severe osteitis fibrosa (subperiosteal resorption) or severe osteomalacia (Looser zones). However, radiographs remain an important part of the ongoing evaluation of CKD-MBD in children with CKD.[31]

3. *Assessment of VC*: Lateral abdominal radiography is a simple, low-cost screening tool for the detection of VC in adults.[33] The presence of visible aortic calcification on lateral abdominal radiographs indicates a positive VC finding, which can be submitted to semiquantitative evaluation. Although computed tomography scans may be more precise and/or sensitive for the quantitative assessment of VC than radiography, their use is not justified as a screening tool owing to limited availability in some areas and substantial additional cost.

Research questions and considerations related to imaging.

1. Does BMD measurement – hip or radial – predict hip fracture risk and occurrence in CKD patients?
2. Is there a relationship between changes in BMD and VC?
3. Is there an association between BMD values with biochemical marker values?
4. Can BMD be used in conjunction with biochemical marker values to define bone CKD-MBD or guide therapy?
5. What impact does delayed onset of puberty, postmenopausal status, corticosteroids, or senile osteoporosis have on CKD-MBD? Can BMD help in assessing this?
6. Can assessment of bone microarchitecture by radiologic techniques aid in the evaluation of CKD-MBD?

7. What is the validity (sensitivity and specificity) of plain abdominal radiography in the assessment of VC?
8. What is the relationship between the radiologic VC assessments and measurements of vascular stiffness such as pulse wave velocity and pul se pressure?
9. Is the presence and extent of coronary artery calcification predictive of mortality in CKD?

CONCLUSION

Mineral and bone disorders are complex abnormalities that cause morbidity and decreased quality of life in patients with CKD. In order to enhance communication and facilitate research, a more precise terminology of these abnormalities is needed. It is recommended that (1) the term *CKD-MBD* should be used to describe the syndrome of biochemical, bone, and extra-skeletal calcification abnormalities that occur in patients with CKD; and (2) the term *renal osteodystrophy* should be used exclusively to define alterations in bone morphology associated with CKD. The latter can be further assessed by histomorphometry with results reported based on a classification system that includes parameters of turnover, mineralization, and volume. It is expected that the international adoption of the proposed uniform terminology, definition, and classification to describe these two disorders due to CKD will greatly enhance communication, facilitate clinical decision-making, and promote the evolution of evidence-based clinical practice guidelines worldwide. Additional evidence-based evaluation is required to determine the (1) correlation of outcomes with the various biochemical parameters, (2) sensitivity and specificity of the available measures of both bone strength and VC, and (3) assessment of the effects of available treatment modalities on the outcomes in CKD-MBD.

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Appendix A1

Controversies Conference participants include the following: Dennis Andress, MD, USA, Rashad Barsoum, MD, Egypt, Ezequiel Bellorin-Font, MD, Venezuela, William Bennett,

MD, USA, Geoffrey Block, MD, USA, Brendan Boyce, MB, ChB, FRCPath, USA, Diego Brancaccio, MD, Italy, David Bushinsky, MD, USA, Jorge Cannata-Andia, MD, Spain, Glen Chertow, MD, USA, Russell Chesney, MD, USA, Giorgio Coen, MD, Italy, Michael Cassidy, MD, UK, Juliet Compston, MD, UK, John Cunningham, DM, FRCP, UK, Mark DeBroe, MD, PhD, FRCP, Belgium, Guenther Delling, MD, PhD, FRCP, Germany, Patrick C D'Haese, PhD, Belgium, Tilman Drüeke, MD, FRCP, France, Kai-Uwe Eckardt, MD, Germany, Garabed Eknoyan, MD, USA, Marie Claude Faugere, MD, USA, Arnold Felsenfeld, MD, USA, Manuel Anibal Ferreira, MD, Portugal, Denis Fouque, MD, PhD, France, Joao Frazao, MD, Portugal, Masafumi Fukagawa, MD, PhD, FASN, Japan, David Goldsmith, MD, UK, Esther Gonzales, MD, USA, William Goodman, MD, USA, Carmel Hawley, MD, Australia, Pascal Houillier, MD, France, Vivekanand Jha, MD, India, Vanda Jorgetti, MD, PhD, Brazil, Junichiro Kazama, MD, PhD, Japan, Markus Ketteler, MD, Germany, Helene Lafage-Proust, MD, France, Norbert Lameire, MD, Belgium, Craig Langman, MD, USA, Mary Leonard, MD, USA, Adeera Levin, MD, FRCP, Canada, Nathan Levin, MD, FRCP, USA, Francesco Locatelli, MD, Italy, Gerard London, MD, France, Victor Lorenzo, MD, Spain, Alison MacLeod, MD, Scotland, Hartmut Malluche, MD, USA, Kevin Martin, MB, BCh, FACP, USA, Sandro Mazzaferro, MD, Italy, James McCarthy, MD, USA, Otto Mehls, MD, Germany, Sharon Moe, MD, FACP, USA, Klaus Olgaard, MD, Denmark, Susan Ott, MD, USA, Mariano Rodriguez, MD, PhD, Spain, Isidro Salusky, MD, USA, Heinrich Schmidt-Gayk, MD, Germany, Donald Sherrard, MD, USA, Justin Silver, MD, Israel, Stuart Sprague, DO, USA, Steven Teitelbaum, MD, USA, Yusuke Tsukamoto, MD, Japan, Rowan Walker, MBBS, FRCP, MD, Australia, Angela Yee-Moon Wang, MD, FRCP, FASN, Hong Kong, Haiyan Wang, MD, China, Mei Wang, MD, China, Robert Weinstein, MD, USA, Jose R Weisinger, MD, FACP, Venezuela, David Wheeler, MD, FRCP, UK.