





What is KDIGO?

KIDNEY DISEASE: IMPROVING GLOBAL OUTCOMES

Independently incorporated non-profit foundation governed by an international board 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

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KDIGO

Controversies Conference:

***Definition, Evaluation, and
Classification of Renal
Osteodystrophy***



Why Renal Osteodystrophy?



New Issues Confronting the Nephrologist

- New phosphate binders
- New vitamin D analogues
- New treatment options - calcimimetics
- New imaging techniques
- New PTH and other assays
- New emphasis on importance of extra-skeletal manifestations of mineral metabolism
- New emphasis on evidence based medicine by renal networks, insurance providers



The Paradigm Shift in ROD

courtesy of Sharon Moe

PREVIOUS	NOW
Push PTH as low as possible!	Well, not that low (and change assays <u>again</u>)
Give as much Vitamin D as possible!	Well, not that much (and change Vitamin D type)
Give lots of calcium, push that calcium UP!	Oh NO- don't give too much calcium!
A phosphorus of 7 and Ca X P product of 70 is ok	But that can cause petrified vessels and death!
25(OH)D is not important	Deficiency is common

Framing the Issues

- **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.**
- **Bone biopsy remains a powerful and informative diagnostic tool for the determination of bone abnormalities. However, due to limited use, a biopsy-based definition and classification system does not provide an adequate means in clinical practice to clearly identify, classify or treat CKD patients with mineral and bone disorders.**

Framing the Issues

- **While 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 vascular calcification and cardiovascular morbidity and mortality.**

Conference Purpose

- The absence of a general agreement on the definition and diagnosis of ROD shows that there is a need for international consensus to facilitate a better framework for ongoing investigation and clinical decision-making.
- Meeting focus:
 - review and confirm what we do know about the definition of ROD
 - establish a consensus on how we can most effectively use what we know to aid clinicians taking care of patients
 - identify what we don't know in preparation for future evidenced based guidelines
 - prioritize and make recommendations on how our knowledge can best be expanded

Conference Objectives

- Develop a clinically relevant, easily applicable definition and classification system for the constellation of disorders heretofore known as renal osteodystrophy.
- Examine current histologic categories of renal osteodystrophy and develop consensus on a unified evaluation and classification of bone histology.
- 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 in CKD

Conference Forum

- Three-day meeting in Madrid in Sept. 2005
- Attended by more than 70 physicians with expertise in bone and mineral metabolism, representing 6 continents and 21 countries
- Three workgroups on:
 - Bone biopsy and histomorphometry
 - Imaging techniques
 - Biomarkers



Recommendations from

KDIGO Controversies on Definition, Evaluation, and Classification of Renal Osteodystrophy

Naming the Disorder

- The term **renal osteodystrophy (ROD)** be used exclusively to define the bone pathology associated with CKD.
- The clinical, biochemical, and imaging abnormalities heretofore identified as correlates of renal osteodystrophy should be defined more broadly as a clinical entity or syndrome called **Chronic Kidney Disease-Mineral and Bone Disorder (CKD-MBD)**.

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

Evaluation of CKD-MBD

- The initial evaluation of CKD-MBD should include: PTH, calcium (either ionized or total corrected for albumin), phosphorus, alkaline phosphatase (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.
 - Additional tests to assess linear growth rate are needed in children with CKD.

Classification of CKD-MBD

- An ideal classification system would allow categorization of patients based on readily available clinical diagnostic tools and would help guide treatment.
- The lack of adequate data and the non-linearity of the disease process do not allow for the development of a definitive classification based on severity or treatment at this time.



Framework for Classification of CKD-MBD

- The classification framework proposed is a working model that can be modified and improved in the future depending on further analysis of new data that become available.
- It is meant to be descriptive rather than predictive, as an initial attempt to improve communication and stimulate research.

Framework for Classification of CKD-MBD

Type*	Laboratory Abnormalities	Bone Disease	Calcification of Vascular or Other Soft Tissue
L	+	-	-
LB	+	+	-
LC	+	-	+
LBC	+	+	+

* **L** = laboratory abnormalities (of calcium, phosphate, PTH, alkaline phosphatase 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.

Definition of ROD

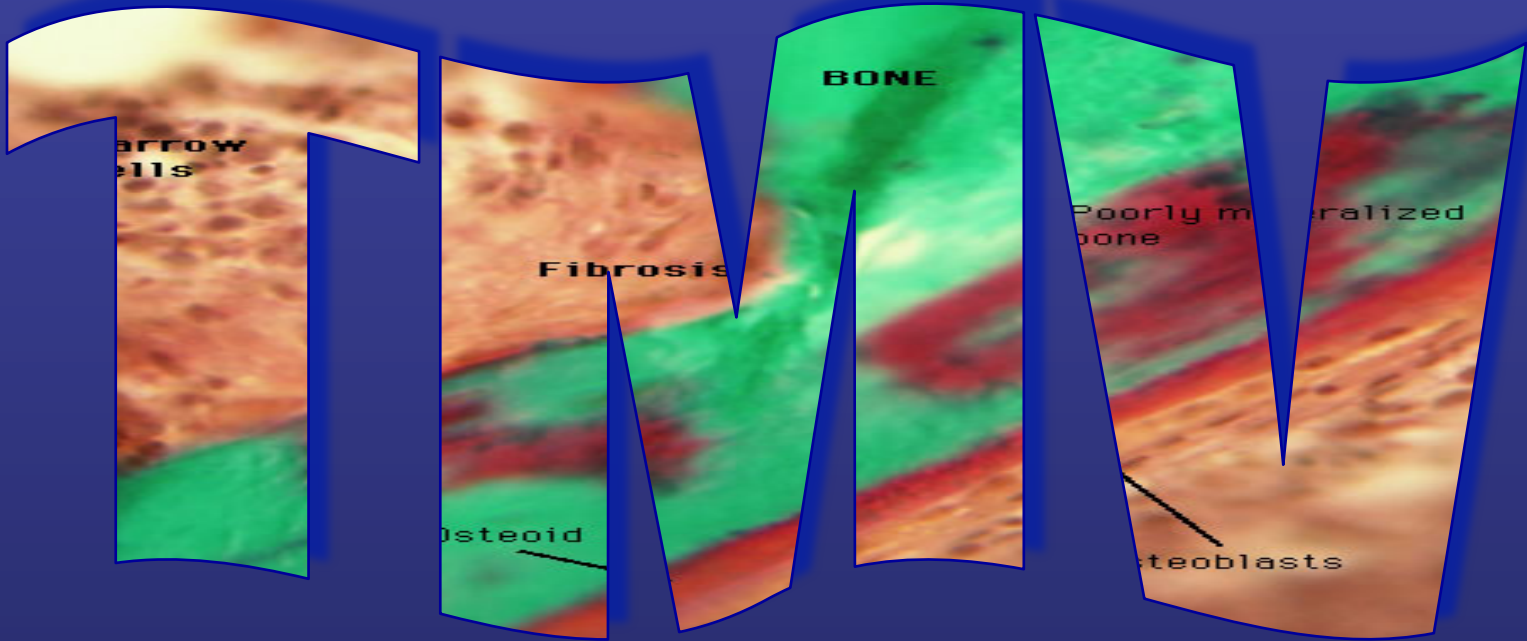
- Renal osteodystrophy is an alteration of bone morphology in patients with CKD.
- It is one measure of the skeletal component of the systemic disorder of CKD-MBD that is quantifiable by histomorphometry of bone biopsy.

Evaluation of ROD

- 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.
- Histomorphometric results are to be reported using standard nomenclature as recommended by the ASBMR.
- Investigators should supply primary measurements used to report any derived parameters.

Classification of ROD

Slide courtesy of Susan Ott



Turnover

- High
- Normal
- Low

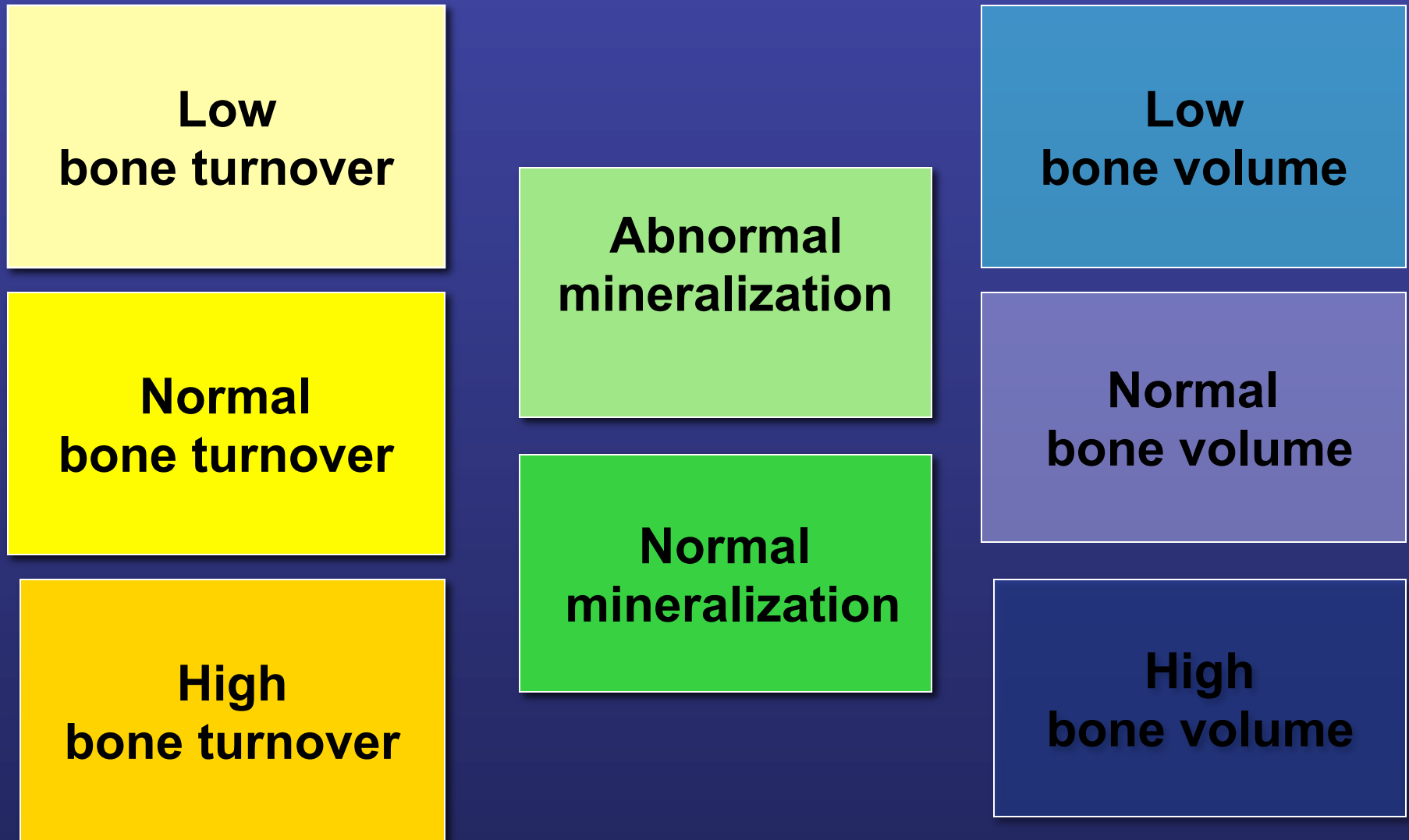
Mineralization

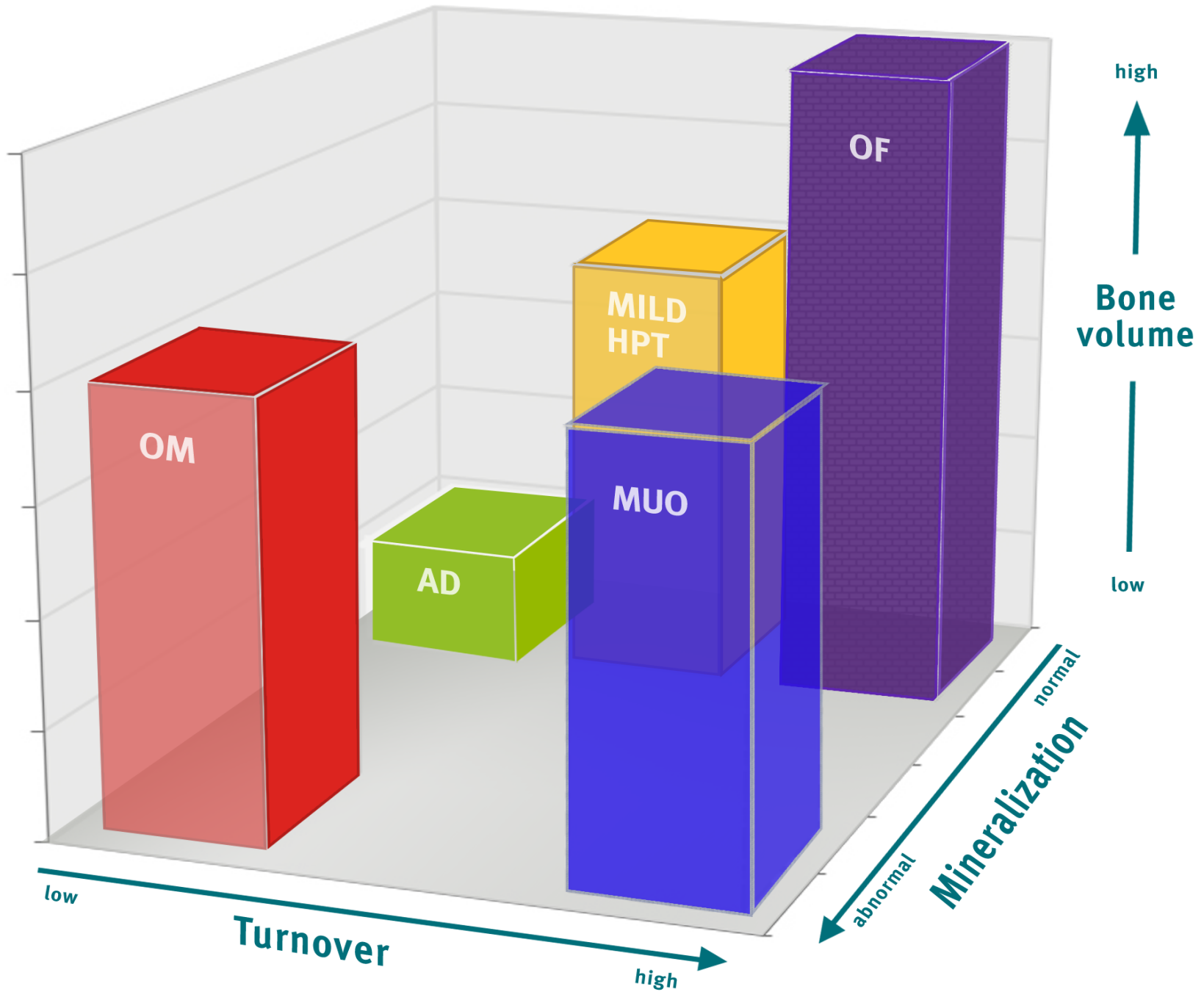
- Normal
- Abnormal

Volume

- High
- Normal
- Low

Classification of ROD





Recommendations on Bone Biopsy

- **Indications for Bone Biopsy**
 - Valuable diagnostic tool in selected patients
 - Not part of routine evaluation of CKD-MBD
- **Reporting of Results**
 - Standardized nomenclature-ASBMR
 - Provide primary measurements for calculated parameters
 - Research reporting
- **Quality Assurance Initiative**
 - Inter-laboratory exchange
 - Collecting normative data

Research Questions- Bone Biopsy

- What changes in bone histomorphometry parameters occur as CKD progresses from Stage 2-5?
- What is the relationship of bone histomorphometric abnormalities to vascular and other soft tissue calcifications?
- What is the relationship of bone histomorphometric abnormalities to the diminished linear growth in children?
- What are the functional properties of bone in the maintenance of systemic calcium homeostasis?

Research Questions- Bone Biopsy

- What is the relationship between bone histomorphometric abnormalities and clinical outcomes?
- How can bone biopsy best be utilized in clinical practice?
- How do non-invasive techniques relate to histomorphometric findings?
- How can more clinicians be trained to do bone biopsies and how can the number of centers doing bone histomorphometry be increased?



Recommendations on Biochemical Markers

- **Parathyroid Hormone**
 - Best clinical indicator of bone turnover
 - 1-84 PTH or “intact” assay
- **Serum Calcium**
 - Ionized or “corrected”
- **Alkaline Phosphatase**
 - Total or bone-specific
- **Other Biomarkers**

Research Questions-Biomarkers

- What is the preferred interdialytic interval for assessing serum phosphorus (e.g. after 2 or 3 days off dialysis)?
- What is the role of Fetuin-A and FGF23 data in the evaluation of CKD-MBD?
- What is the role of other markers of bone metabolism in the evaluation of CKD-MBD?
- What is the role of measuring 25(OH)-vitamin D levels in the assessment of CKD-MBD, and which assay is preferable in CKD?
- How often must biomarkers be measured in stable clinical condition versus evolving high or low bone turnover disease to assess CKD-MBD?

Research Questions- Biomarkers

- 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?
- 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?
- 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?

Recommendations on Imaging

- **Bone Mineral Density Measurement**
 - In CKD
 - As an indicator for therapy
 - In transplant recipients
 - qCT
- **Plain Radiographs**
 - Limited value except in severe bone disease
 - Important in children
- **Assessment of vascular calcification**
 - Abdominal radiograph vs CT scan in screening

Research Questions-Imaging

- Does BMD measurement—hip or radial—predict hip fracture risk and occurrence in CKD patients?
- Is there a relationship between changes in BMD and vascular calcification?
- Is there an association between BMD values with biochemical marker values?
- Can BMD be used in conjunction with biochemical marker values to define bone CKD-MBD or guide therapy?
- What impact does delayed onset of puberty, post menopausal status, corticosteroids, or senile osteoporosis have on CKD-MBD? Can BMD help in assessing this?

Research Questions-Imaging

- Can assessment of bone microarchitecture by radiologic techniques aid in the evaluation of CKD-MBD?
- What is the validity (sensitivity and specificity) of plain abdominal radiography in the assessment of vascular calcification?
- What is the relationship between the radiologic VC assessments and measurements of vascular stiffness such as pulse wave velocity and pulse pressure?
- Is the presence and extent of coronary artery calcification predictive of mortality in CKD?

Summary

- 1. CKD-Mineral and Bone Disorder (CKD-MBD):** used to describe the systemic disorder of mineral and bone metabolism in CKD, which is manifested by any 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; and vascular or other soft tissue calcification.
- 2. Renal Osteodystrophy:** 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 classification system that includes parameters of turnover, mineralization and volume.

Summary

3. International adoption of the proposed uniform terminology, definition, and classification of bone and mineral disorders will enhance communication, facilitate clinical decision-making, and promote the evolution of evidence-based clinical practice guidelines worldwide.
4. 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 vascular calcification, and (3) assessment of available treatment modalities on the outcomes in CKD-MBD.