CKD-MBD: Is the Term Still Justified?

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Potential conflicts of interest

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assessments. 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.
CKD-Mineral and Bone Disorder (CKD-MBD) – Definition –

- CKD-MBD is 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
CHRONIC KIDNEY DISEASE—MINERAL AND BONE DISORDER

LABORATORY ABNORMALITIES

BONE ABNORMALITIES

CVD

FRACTURES

MORTALITY

VASCULAR CALCIFICATION

CKD-MBD
“Renal Osteodystrophy” – term to be reserved for abnormalities in bone structure

Moe S et al, KI 2006;69:1945-53
The term CKD-MBD still justified?
On which basis?

• Numerical criteria?
• Pathophysiology – new developments?
• Treatment & prevention – new data?
The term CKD-MBD still justified?
On which basis?

• **Numerical criteria**
  – usage in clinical/basic science publications
  – introduction into clinical practice
Published reports using the term ‘CKD-MBD’ since its creation in 2006 \textit{(PubMed)}

- 245 publications \textit{(as of 14 October 2013)}
  - 5 in 2006
  - 15 in 2007
  - 10 in 2008
  - 42 in 2009
  - 44 in 2010
  - 39 in 2011
  - 42 in 2012
  - 46 in 2013
Who were the first to use the term ‘CKD-MBD’ since its creation in 2006 (PubMed)?

- The first 5 all from Japan:
  - Honda H et al, Clin Calcium 2006
  - Fukagawa M & Kazama JJ, Pediatr Nephrol 2006
  - Hamada Y & Fukagawa M, Nihon Rinsho 2006
  - Fukagawa M et al, Clin Exp Nephrol. 2006
  - Fukagawa M et al, J Bone Miner Metab 2006
What happened to the term ‘Renal Osteodystrophy’ (PubMed)?

- 3878 publications (as of end 2012)
  - 1 in 1942
  - 7 in 1952
  - 11 in 1962
  - 61 in 1972
  - 97 in 1982
  - 75 in 1992
  - 89 in 2002
  - 74 in 2012
How about the utility of ‘CKD-MBD’ targets and the use of the term in the clinic?

- Evaluation of CKD-MBD targets and outcomes
- Use in day-to-day practice
Relationship between KDOQI biochemical targets achieved and risk for death (model 2)

Danese MD et al, CJASN 2008;3:1423-9
Percentage of patients within K/DOQI and KDIGO targets in hemodialysis patients in Europe (COSMOS)
How about the use of the term ‘CKD-MBD’ in clinical practice?

- Evaluation of CKD-MBD targets and outcomes
- Use in day-to-day practice
  - Translation into local languages
  - Example France: ‘TMO-MRC’ \textit{(troubles du métabolisme minéral et osseux liés à la maladie rénale chronique)}
The term ‘CKD-MBD’ still justified?
On which basis?

• Numerical criteria?
• Pathophysiology – new developments?
• Treatment & prevention – new data?
Pathogenesis of 2° Hyperparathyroidism

Calcitriol

Ca

Pi

Normal

ESRD

J. Cunningham 1999, modified
Importance of optimal control of mineral and bone disease (MBD) in patients with CKD

High-turnover bone disease

Hypo/hypercalcemia
Hyperphosphatemia

Low-turnover bone disease

Hypo/hypercalcemia
Hyperphosphatemia

PTH
Ca^{++}
Mg^{++}
PO_{4}^{--}

Soft Tissue Deposits

Vascular calcification – Mortality?
Pathogenesis of 2° Hyperparathyroidism

Ca

PTH

Pi

Calcitriol

FGF23 + Klotho

Normal

ESRD

FGF23 + Klotho

J. Cunningham 1999, modified
Pathogenesis of 2° Hyperparathyroidism

Calcium
- Calcitriol (VDR, c-myc, p21)
- Calcitriol (calcium-sensing receptor)
- FGF23 (FGF-R, Klotho)
- PTH synthesis/secretion/degradation
- Parathyroid hyperplasia
  - diffuse
  - nodular
- Apoptosis
- Mitogens
  - Enhancer genes?
  - Repressor genes?
- Phosphate
  - Receptor?
  - Calcitriol
  - PTHrp
  - PTH7-84

Calcium:
- (-)
- (+)

Phosphate:
- (-)
- (+)

Calcium-sensing receptor:
- (-)

FGF-R + Klotho:
- (-)

Parathyroid hyperplasia:
- diffuse
- nodular

Apoptosis:
- (-)
- (+)

Mitogens:
- (+)

Enhancer genes?

Repressor genes?
Pathogenesis of 2° Hyperparathyroidism

Calcium

Calcium-sensing receptor

VDR

Calcitriol

Calcium

Phosphate

Phosphate receptor?

FGF23

FGF-R + Klotho

Parathyroid hyperplasia

diffuse  
nodular

Apoptosis

Calcitriol

(c-myc, p21)

Calcium

(±) Ca

Phosphate

(TGFα)

PTH synthesis/
secretion/degradation

Mitogens

Enhancer genes?

Repressor genes?

PTH receptors?

PTHrp

PTH7-84

FGF23

KDIGO
Regulation of FGF23 synthesis/secretion by osteocytes

Christov & Jüppner, Kidney Int 2013;84:639-41
Effects of increased FGF23 secretion

Komaba and Fukagawa, Nat Rev Nephrol 2012;8:484-90
Independent association of high FGF23 with mortality in HD patients (FGF23 level quartiles)

Gutierrez OM et al, NEJM 2008; 359: 584-92
Cardiovascular effects of decreased Klotho levels

Moe SM, Circulation 2012; 74(3):265-7
Change the term ‘CKD-MBD’ based on new insight into pathophysiology?

- “CKD-MBVD”? (‘V’ for ‘vascular’)
- “CKD-MBCVD”? (‘CV’ for ‘cardiovascular’)
The term ‘CKD-MBD’ still justified? On which basis?

- Numerical criteria?
- Pathophysiology – new developments?
- Treatment & prevention – new data?
  - Phosphate binders
  - Vitamin D
  - Calcimimetics
Sevelamer improves all-cause mortality (1° endpoint) in CKD stage 3-4 (212 patients; pilot RCT)

Di Iorio B et al, CJASN 2012;7:581-7
Sevelamer improves cardiovascular survival in incident HD patients (*466 patients; open-label RCT*)

Di Iorio B et al, AJKD 2013;62:771-8
Vitamin D Therapy and Cardiac Structure and Function in Patients With Chronic Kidney Disease
The PRIMO Randomized Controlled Trial
Thadhani R et al, JAMA 2012;307:674-84

Main Outcome Measures  Change in left ventricular mass index over 48 weeks by cardiovascular magnetic resonance imaging. Secondary end points included echocardiographic changes in left ventricular diastolic function.

Results  Treatment with paricalcitol reduced parathyroid hormone levels within 4 weeks and maintained levels within the normal range throughout the study duration. At 48 weeks, the change in left ventricular mass index did not differ between treatment groups (paricalcitol group, 0.34 g/m².7 [95% CI, −0.14 to 0.83 g/m².7] vs placebo group, −0.07 g/m².7 [95% CI, −0.55 to 0.42 g/m².7]). Doppler measures of diastolic function including peak early diastolic lateral mitral annular tissue velocity (paricalcitol group, −0.01 cm/s [95% CI, −0.63 to 0.60 cm/s] vs placebo group, −0.30 cm/s [95% CI, −0.93 to 0.34 cm/s]) also did not differ. Episodes of hypercalcemia were more frequent in the paricalcitol group compared with the placebo group.
Effect of cinacalcet (+ low dose vitamin D) vs. flexible vit. D doses on coron. artery calcification (ADVANCE)

Raggi P et al, NDT 2011;26:1327-39
EVOLVE – Primary Composite Endpoint (ITT) not met:
Non-significant 7% Reduction in the Risk of Death or Cardiovascular Events

Kaplan-Meier plot of the time to the primary composite endpoint (death, myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event) in EVOLVE™.

Hazard ratio, 0.93 (95% CI, 0.85, 1.02)
Log-rank, $P = 0.11$

Subjects at risk:
- **Placebo**: 1935, 1804, 1693, 1579, 1476, 1384, 1312, 1224, 1160, 1109, 1053, 996, 940, 650, 404, 114
- **Cinacalcet**: 1948, 1842, 1739, 1638, 1556, 1472, 1384, 1303, 1230, 1177, 1115, 1051, 989, 679, 399, 113

Prespecified 6 Months Lag Censoring Analysis:
Nominally Significant 15% Reduction in Death and Cardiovascular Events

Kaplan-Meir plot of the time to the primary composite endpoint (death, myocardial infarction, hospitalization for unstable angina, heart failure, or peripheral vascular event) in EVOLVE™.

Hazard ratio, 0.85 (95% CI, 0.76, 0.95)
Log-rank, $P = 0.003$

Subjects at risk:
- Placebo: 1935, 1789, 1615, 1299, 1080, 875, 739, 625, 525, 474, 419, 353, 303, 180, 93, 26
- Cinacalcet: 1948, 1835, 1627, 1376, 1179, 1002, 847, 731, 632, 551, 491, 425, 362, 239, 130, 28

The term ‘CKD-MBD’ still justified?
On which basis?

- Numerical criteria?
- Pathophysiology – new developments?
- Treatment & prevention – new data?
  - no RCT aimed at reduction of fractures
Change the term ‘CKD-MBD’ based on new data from RCTs?

• Answer probably ‘NO’ *(to be discussed at present meeting)*
‘CKD-MBD’ – to change or not to change?

Advantage
- Well-accepted term

Disadvantage
- Does not contain link to CV disease
The Good and the Bad of a New Disease Term
– The consensus conference will decide –