CKD-MBD Update 2014

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Is chronic kidney disease—mineral and bone disorder (CKD-MBD) really a syndrome?
CV Disease Is the Greatest Contributor to Mortality on HD

"We suggest that the National Cholesterol Education Program and other groups include CKD in the highest-risk group for recommendations for prevention, detection, and treatment of CVD risk factors." — American Heart Association
Schulz E, Arfai K, Liu X et al.  
**Aortic calcification and the risk of osteoporosis and fractures.**  
*J Clin Endocrinol Metab* 2004; **89**: 4246–4253.

Naves M, Rodríguez-García M, Díaz-López JB et al.  
**Progression of vascular calcifications is associated with greater bone loss and increased bone fractures.**  
*Osteoporos Int* 2008; **19**: 1161–1166.

Higher rates of vascular calcification in the presence of low bone turnover in patients with kidney disease
Bone Fractures & Death

Mortality and hospitalization rates 2–9 times higher

Tentori F et al., Kidney Int 2013
Bone Fractures in HD patients

Fracture risk 1.5- to 8-fold

Tentori F et al., Kidney Int 2013
Bone Fractures & Hospitalization

Tentori F et al., Kidney Int 2013
sHPT: the old concept
sHPT: the new concept
Klotho protein is a co-receptor specific for FGF-23
Klotho^{-/-} & FGF23^{-/-} mice

Premature aging

Abnormal mineral metabolism
- Vascular calcification
- Hyperphosphatemia
- Hypercalemia
- Hypervitaminosis D

Skin and muscle atrophy

Hypoglycemia
The Klotho Centric View

High-affinity endocrine targets of Klotho

Phosphate

“Phosphatonin”

Kidney

Parathyroid

Klotho

FGF-23

1,25(OH)₂D
Increased FGF23 develops earlier than increased phosphate or PTH

*Isakova T et al., Kidney Int 2011*
Parathyroid hyperplasia with constitutively raised PTH is a risk of long-term CKD-MBD.

**PTH Levels/Disease Severity**

- **Secretion**
  - Normal
  - Adaptive

- **Synthesis**
  - Diffuse hyperplasia
  - Early nodularity
  - Nodular

- **Progression of hyperplasia**
  - Pathologic
  - Single nodule

**Minutes**

- PTH secretion

**Hours/Days**

- Adaptive Pathologic

**Weeks/Years**

- Normal Parathyroid hyperplasia with consituently raised PTH is a risk of long-term CKD-MBD.
GLOBAL reduction of Serum Phosphate by 25% during the last 15 years!
FGF23 and All-cause Mortality

Blocking FGF23 . . .

Improved sHPT: PTH normalized
Better bone increased Vit D

Increased phosphate
Aortic calcification

Shalhoub V et al., J Clin Invest 2012
FGF-23 and mortality in the community

Ärnlöv J et al., Kidney Int 2013
FGF-23 and CV events in CKD

Atherosclerotic

CHF

Scialla JJ et al., JASN 2014
FGF-23 and Mortality and Renal Tx

FGF-23 as INDEPENDENT risk factor

Leandro C et al., CJASN 2014
FGF-23: no CAC association

Chronic Renal Insufficiency Cohort

Scialla JJ et al., Kidney Int 2013
FGF-23 and Cardiovascular Events in CKD

Atherosclerotic

No association with LVH!
No association with CKD stages!
No association with traditional risk factors!

CHF

Scialla JJ et al., JASN 2014
Cardiovascular abnormalities in CKD

No hypertension
No vascular calcification

8 weeks

Maizel J et al. Kidney Int. 2013
8 weeks: FGF-23 unchanged
LVH unchanged
improved diastolic function
improved aortic stiffness

LVH STABLE
DD Regression

RR normal

Maizel J et al. Kidney Int. 2013
Hyperphosphatemia aggravates cardiac fibrosis in experimental uremia

Subtotal nephrectomy

**low phosphorus diet**

**high phosphorus diet**

*Amann et al. Kidney Int. 2003*
Phosphate restriction . . .

Effect on established calcification!

Finch JL et al. Kidney Int. 2013
Regression of LV fibrosis (& inflammation)
Dietary phosphorus is associated with a significant increase in left ventricular mass

Kalani T. Yamamoto, MD¹, Cassianne Robinson-Cohen, MS², Marcia C. de Oliveira, PhD³,

General Population
Phosphorus intake > 1g/d
Women (postmenopausal) > Men
CKD
No association: intake : P-serum
Dietary phosphate restriction suppresses phosphaturia but does not prevent FGF23 elevation.

FGF23 still a marker of phosphate burden?!
Effects of Dietary Phosphate Restriction and Phosphate Binders on FGF23 Levels in CKD

Independent of Urine and Serum Phosphate !!

Isakova T et al., CJASN 2013
FGF23

Gutierrez OM et al., JASN 2011
Association Phosphorus and Death/ESRD in CKD?

Kidney Early Evaluation Program (KEEP): > 10,000 pts (most CKD 3)

Serum Phosphorus is not an independent predictor of death in a lower risk CKD community

Mehrotra R et al. Kidney Int 2013
24-h Urine Phosphorus Excretion & Mortality and CV Events

880 pts, stable CVD, CKD 1-2
Serum P independent!
FGF-23 is NOT a Serum-P “HbA1c“

HD patients over 4 weeks: plasma FGF-23 higher intraindividual variation than plasma phosphate

Seiler S et al., CJASN 2013
Association P, Ca$^{2+}$, PTH & Death in CKD?

N = 327,644 patients

“In conclusion, the evidence for an association between serum levels of phosphorus, Ca$^{2+}$, or PTH as risk factors for outcomes in individuals with CKD (at any stage) is currently insufficient to inform clinical decision making, policy, or practice guidelines.”

Palmer S et al., JAMA 2011
What should a guideline panel do when evidence is inconclusive?

The case of treatments for CKD-mineral and bone disorder (CKD-MBD).
HR of serum phosphate

KDIGO targets . . .
3 years
8377 MHD patients

0.8 - 2.12 mM

Fouque D et al., Nephrol Dial Transplant 2013
HR of serum total calcium

2.13 - 2.41 mM

Fouque D et al., Nephrol Dial Transplant 2013
Phosphate Binder and Death in HD Pts?

COSMOS study a 3-year follow-up, observational prospective study: 6797 pts, 227 dialysis centers, 20 European countries

All-cause Mortality 41-29%
CV Mortality 25-22%
Prevalent pts: Survivorship bias
Open cohort design

Cannata-Andia JBR et al. Kidney Int 2013
Association Phosphorus and Death in HD Pts?
IDEAL
Randomized Trial

Tight < 1.6 mM

Liberal < 2.5 mM

Mortality
CV Events
Side effects
QoL
Serum phosphorus in people with chronic kidney disease: you are what you eat

Marcello Tonelli

This issue of *Kidney International* includes two important articles about serum phosphorus and its treatment. The article by Cannata-Andía and colleagues describes a rigorous observational study of the association between serum phosphorus level, phosphate binder use, and clinical outcomes including all-cause and cardiovascular mortality. The article by Mehrotra and colleagues addresses the association between serum phosphorus, socioeconomic status, and mortality among participants in the US-based KEEP program.

“Currently, there are no FDA requirements to list the phosphorus content of food products.”

Nephro Community:
Deemphasize P Targets ?!
Diet P Targeting ?
Oral calcium carbonate affects calcium but not phosphorus balance in CKD 3–4

Hill K et al. Kidney Int 2013
Calcium & Phosphate homeostasis in CKD . . .

FGF-23

Vit-D

Phosphate absorption impaired in CKD !
Cardiovascular effects of sevelamer in CKD 3
CRIB-PHOS study

Chue C et al., JASN 2013
No CV effects of sevelamer . . .

Hypothesis: Primary Prevention . . .

Chue C et al., JASN 2013