The role of FGF23 beyond CKD-MBD: Is it important?

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*(See DOI at www.era-edta.org)*
Role FGF23 in CKD-MBD

Phosphaturia

PTH

Calcium
Phosphate

Hyperphosphatemia or phosphate loading

Vitamin D metabolites

Calcium Phosphate
Classical FGF23 signaling

Renal effects
- CYP27B1
- Pi transport
- PTH

Parathyroid effects

Vervloet, Larsson Kidney Int Suppl 2011
FGF23 actions outside MBD

- Heart
- Infection
- Inflammation
- Volume control
- Vessels: vasodilation
Not about: non classical regulation

- Iron
- Inflammation
- Calcium
FGF23 and the heart
Causality for FGF23?

KDIGO
Framingham cohort

Cardiovascular mortality

All cause mortality

Haring et al. J Am Heart Ass 2016
FGF23 as effect modifier for ACE inhibition

Cardiovascular death or heart failure (%)

Placebo, elevated FGF23
Trandalopril, elevated FGF23
Trandalopril, low FGF23
Placebo, low FGF23

Udell, J Am Coll Card 2014
The role of FGF23

Faul, J Clin Invest 2011
**Figure A**

- **LV mass (mg)**
- **Heart weight/body weight (mg/g)**

**Figure B**

- **Sham**
- **5/6 Nephrectomy**
- **5/6 Nephrectomy + FGFR blocker**

**Figure C**

- **LV anterior wall thickness (mm)**
- **Relative wall thickness**

**Key Data**

- **MC**
- **WGA**
- **M-mode**

**Legend**

- Sham
- 5/6 Nx
- 5/6 Nx + FGFR blocker

**Faul 2011 JCI**

**KDIGO**
Klotho independency of FGF23: Heart

Faul et al. J Clin Invest 2011
FGF23 receptor in the heart

- Specific FGFR4 function

Grabner, Cell Metab 2015
Cardiac surgery

FGF23 measurements

Immediate post-CPB

Leaf et al. Kidney Int2016
CPB induces FGF23?
Experimental myocardial infarction increases FGF23
Heart failure increases FGF23

Human data

Acute decompensated HF versus Control

Andersen et al. Nephrol Dial Transplant 2016
HIF1α activation in bone cells

Primary osteocyte cell culture

Osteoblastic cell line

Hum et al. Bone Rep 2017
Hypoxia induces FGF23!
FGF23 actions outside MBD

- Heart
- Infection
- Inflammation
- Volume control
- Vessels: vasodilation
Infections

De Jager, Vervloet, Dekker Nat Rev Nephrol 2014
FGF23 and Infections

- Cardiovascular Health Study
- N=3141, age 78 ± 5 years (!)
- eGFR 71 ± 17 (ml/min/1.73 m²)
FGF23 and Infections

- Incidence Rate
- Infection-related Hosp
- Per 100 person-years

Nowak, J Am Soc Nephrol 2017
Klotho independent effect FGF23: neutrophils

FGF23 and inflammation

- Cross-sectional analysis (CRIC, n=3879)
- Age 58 ± 11 yrs
- eGFR 43
- CRP
- IL-6
Hepatocytes express FGFR4

Singh et al. Kidney Int 2016
FGF23 and inflammation
FGF23 actions outside MBD

- Heart
- Infection
- Inflammation
- **Volume control**
- **Vessels: vasoreactivity**
Rec. FGF23 in mouse model

Andrukhova et al. EMBO Mol Med 2014
FGF23 and vasodilation

- Clinical observational cohort (n=180)
- FGF23 and FMD, corrected for classical risk factors
- Excluded:
  - Previous CVD
  - Smokers
  - Diabetes
  - Users of ACE inhibitors, ARB, vit D or statins

Yilmaz et al. Kidney Int 2010
Effect modification analysis

FGF23

ADMA

FGF23

NO

Clinical endpoint

NO

Clinical endpoint

NO

KDIGO
Epidemiology is:
FGF23 may interfere with NO production

Risk for renal event by ADMA

- ADMA increases risk for renal event
- ADMA interferes with NO production and renal vasodilation
- High FGF23 overrides this effect

Examine vascular function on exogenous FGF23

gracilis artery of a mouse

Verkaik, Vervloet, under review
FGF23 impairs vasodilation in the absence of vascular klotho

Verkaik, Vervloet, under review
Mechanism of NO decline

Verkaik, Vervloet, under review
Conclusions

FGF23 has several effects beyond CKD-MBD

- Direct induction of LVH
- Heart failure in turn seems to amplify FGF23
- FGF23 increases risk for (bacterial) infection
- FGF23 directly induces inflammation
- FGF23 may induce sodium retention (unconfirmed)
- FGF23 limits vasodilation, probably via ADMA and/or NO
Thank you