Does elevated FGF23 cause Left Ventricular Hypertrophy?

Investigations in a knockout mouse model

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The Problem

- Fibroblast Growth Factor 23 (FGF23) is a hormone that is secreted primarily by the bone and acts on the kidney to increase phosphate excretion. FGF23 also regulates 1,25 Vitamin D homeostasis.
- FGF23 levels are high in states of chronic kidney disease (CKD) and end stage renal disease (ESRD).
- Cardiovascular disease is a key cause of morbidity and mortality in CKD/ESRD of which cardiac dysfunction and left ventricular hypertrophy (LVH) are key components.
- Recent reports have shown conflicting results about the role of FGF23 in causing left ventricular hypertrophy (LVH).
- The *in vivo* mouse models of FGF23 excess used thus far suffer from disordered mineral metabolism and/or kidney function - these are not ideal to isolate the role of FGF23 in cardiac dysfunction or LVH.
- A new model was needed to test the effect of elevated FGF23 levels on the heart in the absence of those confounders.

The Model

- A novel kidney-conditional FGF receptor knockout mouse model was generated.
- FGF receptor genes (FGFR1, FGFR4) were deleted only from the kidney using a loxp-cre technology. The heart continued to express the FGF receptors.
- These "Kidney-Conditional Double Knockouts" (KDKO) are ideal because they have:
  - ✓ Endogenously elevated FGF23 levels.
  - ✓ Intact receptors on the myocardium to respond to the elevated levels.
  - ✓ Intact kidney function, and only modest elevations of serum phosphate.

Methods

- Two cohorts of mice were studied: Kidney-conditional Double Knockouts (KDKO) and Wild Type (WT) mice.
- Serum markers of mineral metabolism and kidney function were assessed at 2-4 months of age.
- LV mass and function were assessed using echocardiography at 6 months of age -
  - ✓ LV Mass by a cubed formula on M-mode parasternal short axis views.
  - ✓ Ejection fraction in %.
- Gross heart weight to body weight ratios were also measured at 6 months of age.
- 2-tailed unpaired T-test was used to compare the groups.

Fig 1. Mouse shaved and prepared for echocardiography under Isoflurane anesthesia

Results

	Wild Type Mice	Knockout Mice (KDKO)	P value
Serum FGF23 (pg/ml)	173.0 ± 13.9 (n=6)	**5158.0 ± 1024.6 (n=8)**	p<0.001
Serum Phosphate (mg/dl)	5.6 ± 0.3 (n=13)	7.4 ± 0.4 (n=6)	p<0.001
Serum Urea (mg/dl)	71.0 ± 3.4 (n=16)	65.4 ± 3.1 (n=18)	NS

Table 1. Serum chemistry at 2-4 months of age

Results

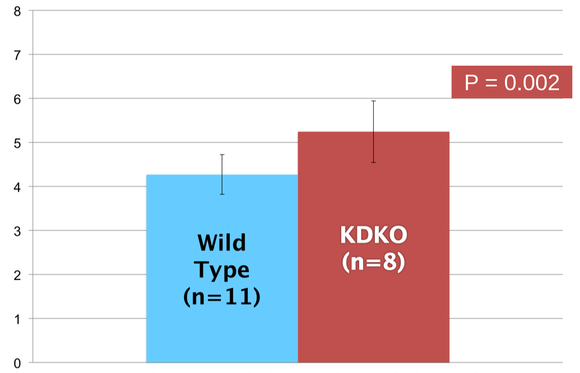

Fig 2. Gross heart weight/body weight ratio (mg/gm), Mean ± S.D.

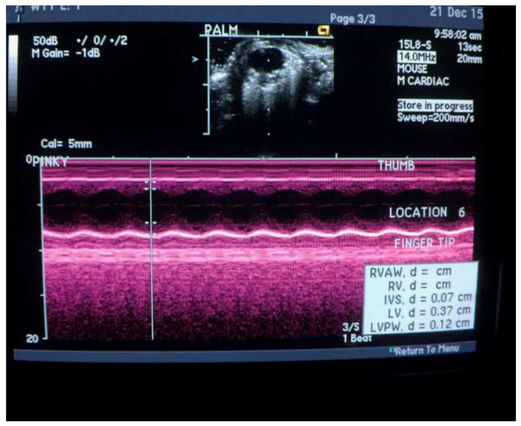

Fig 3. M-Mode echo image showing heart wall and chamber measurements

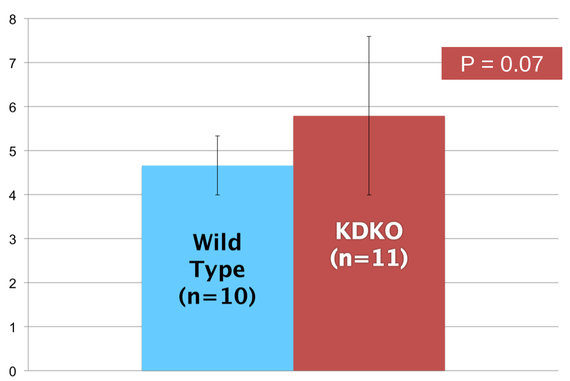

Fig 4. Heart weight/body weight ratio by Echo (mg/gm), Mean ± S.D.

Results

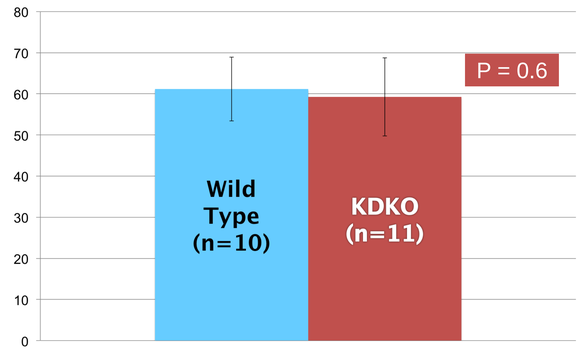

Fig 5. Ejection Fraction (%), Mean ± S.D.

- Our results suggest that FGF23, on prolonged exposure, may contribute to LVH even in the absence of CKD.
- The gross heart weight to body weight ratio was elevated in the test animals compared to controls (Fig. 2). The echocardiographic measures also showed the same trend but did not reach statistical significance (Fig. 4).
- At the 6-month mark, no effect was seen on cardiac function as measured by Ejection Fraction (Fig. 5).

Conclusion

- FGF23, a phosphaturic hormone whose levels are elevated in CKD/ESRD, may be an independent cause of left ventricular hypertrophy.

Future Directions

- Use larger sample sizes and longer exposure times (10-12 months).
- Identify the intracellular signaling pathway for FGF23 in the myocardium.
- Induce hyperphosphatemia and CKD in our test mice to study their additive effects on LVH.
- Perform cardiac MRI for a more accurate measurement of LV mass and function.