INTRODUCTION

- FGF23 is a hormone released primarily from osteoblasts and osteocytes in response to elevated serum phosphorus which acts to decrease phosphate reabsorption and promote phosphate excretion.
- FGF23 serum levels rise with the progression of chronic kidney disease (CKD) and is associated with cardiovascular disease and mortality and can induce hypophosphatemia (Faul et al., 2011, Touchberry et al. 2013, Grabner et al. 2015).
- Our lab has previously shown that FGF23 exposure also induced an increase in cardiomyocyte intracellular Ca²⁺ levels and increased cardiac contractility (Touchberry et al. 2013).
- Recently, expression of FGF23 has been shown in cardiac tissue and cardiomyocytes from deceased adolescent CKD patients receiving renal replacement therapy in the form of dialysis or renal transplant (Leifheit-Nester et al. 2015). The aim of our study was to utilize adult mouse models of untreated CKD to further examine changes in cardiac expression of FGF23 during this disease.
- While bone response of FGF23 increases during CKD, it has not been fully elucidated if FGF23 expression in the heart can contribute to cardiac remodeling through paracrine mechanisms.
- We hypothesized that cardiac FGF23 expression would be elevated in two mouse models of CKD: Col4α3 null (Alport syndrome) and adenine-fed (chronic tubulointerstitial nephritis). We further hypothesized that exercise would reduce FGF23 levels in adenine-fed mice compared to sedentary adenine-fed mice.

METHODS

- Male Col4α3 null and wild-type (WT) mice were sacrificed at 10 weeks.
- For the adenine-diet model, male CD1 mice were fed 0.2% adenine daily for 12 weeks and a subset of these mice were exercised on a treadmill with a regimen of 60 minutes, 4 days/week, at 65% VO₂ max.
- Whole hearts were removed and real time RT-PCR was used to measure expression of FGF23 using 8-actin as the housekeeping gene. Analysis was performed using the 2⁻ΔΔCt method.
- Statistical significance for data were performed using one-way ANOVA with post-hoc Tukey’s analysis for multiple comparisons (Fig. 2-4), an unpaired t-test for one comparison (Fig. 6), or 2-sided t-tests between individual groups at each time point (Fig. 5).

RESULTS

Figure 2. Changes in fitness in exercised adenine-fed mice. Run time (A), run speed (B) and run distance (C) were measured in control (CON) mice (n=6) compared to controls (n=15) (P<0.05). Mice were exercised in exercised adenine-fed (AD+EX) mice (n=6) compared to AD alone (n=15) (P<0.05). These data indicate that the adenine-fed mice were less fit than control mice and that the 12-week exercise regimen induced significant fitness adaptation even with the progression of CKD caused by the adenine diet.

Figure 3. Induction of CKD in adenine-fed mice. Serum BUN (A), creatinine (B), phosphate (C) and calcium (D) were increased at week 12 in both AD (n=6) and ADX (n=6) mice compared to control (n=15, P<0.05). There were no statistical differences between serum values measured in AD mice compared to AD+EX mice. Serum values were obtained using a Technicon chemistry analyzer.

Figure 4. Cardiac FGF23 expression in control, adenine-fed and adenine-fed + exercise mice. FGF23 expression was elevated in adenine-fed (n=6) and adenine-fed + exercise mice (n=6) compared to control mice (P<0.05). FGF23 expression was not significantly different between adenine-fed and adenine-fed, exercised mice (P>0.05).

CONCLUSION

- Basal cardiac FGF23 expression was relatively low in control diet and Col4α3 null mice, with an average delta CT of 17.3 and 15.9, respectively, in relation to β-actin expression.
- Cardiac FGF23 expression was increased 3.0 fold in adenine-fed mice and 3.2 fold in Col4α3 null mice compared to control or WT mice, respectively.
- FGF23 expression was increased in the hearts of CKD mice indicating that FGF23 may have paracrine effects on cardiac remodeling during CKD and could prove to be an important therapeutic target.
- Exercise did not improve kidney function in adenine-fed mice and did not abate the increased cardiac FGF23 expression. With these factors still elevated, this particular exercise regimen may not be beneficial for CKD outcomes even with the improved fitness adaptations.

CREDITS/DISCLOSURE/REFERENCES

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- References: