

# Fibroblast Growth Factor 23 and Iron in Chronic Kidney Disease



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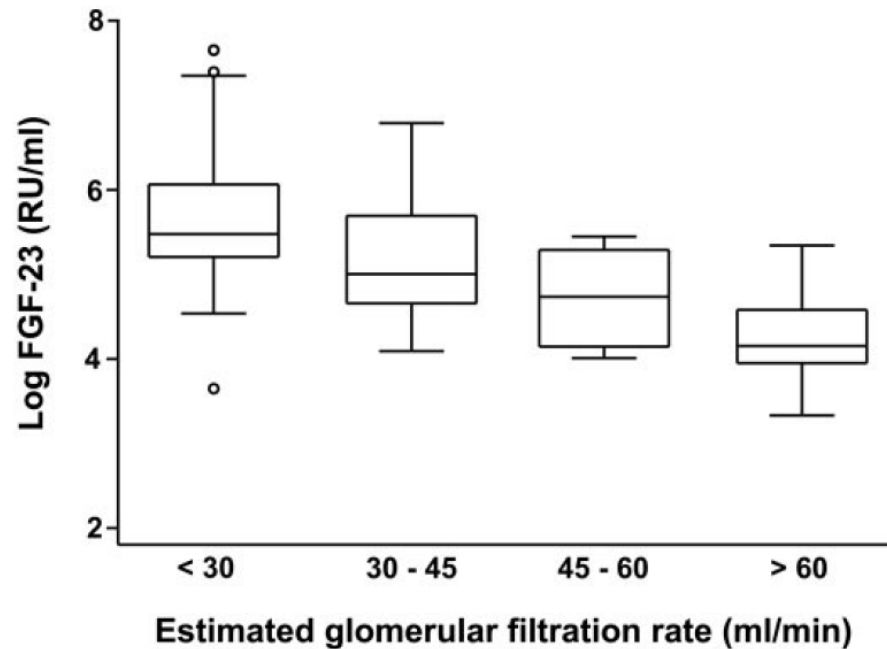




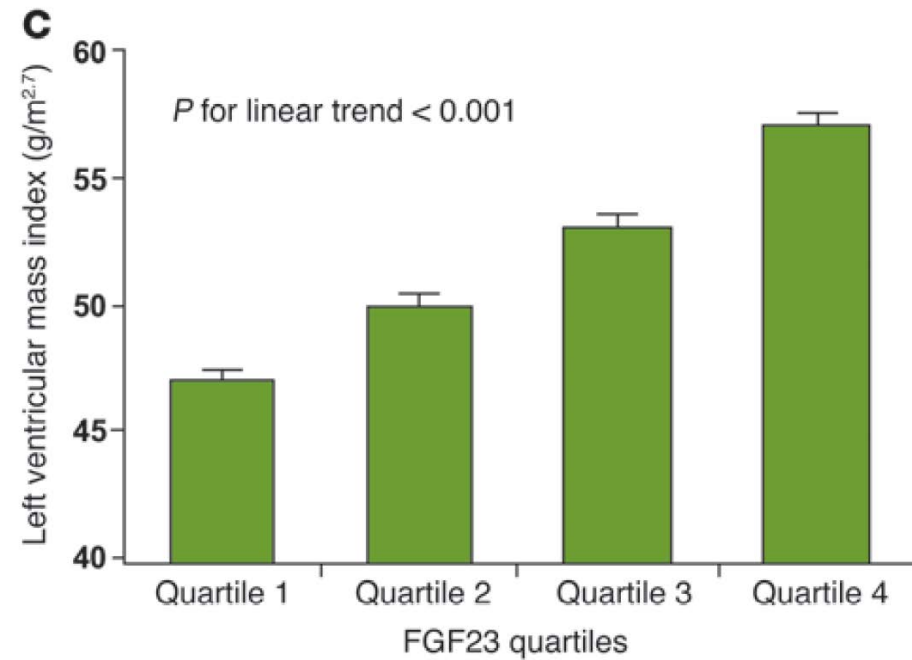
# Fibroblast Growth Factor 23

- FGF23 is a hormone secreted by osteocytes that functions as a phosphatonin.
- Increased phosphorus intake results in increased circulating FGF23 levels.
- FGF23 lowers serum phosphorus levels by inhibiting proximal tubular phosphorus reabsorption and by lowering active vitamin D levels.

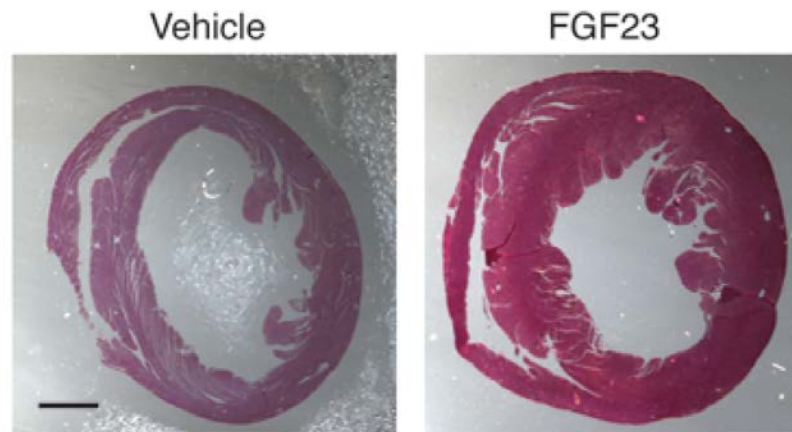
# FGF23 in Chronic Kidney Disease



Gutierrez et al, J Am Soc Nephrol 2005.

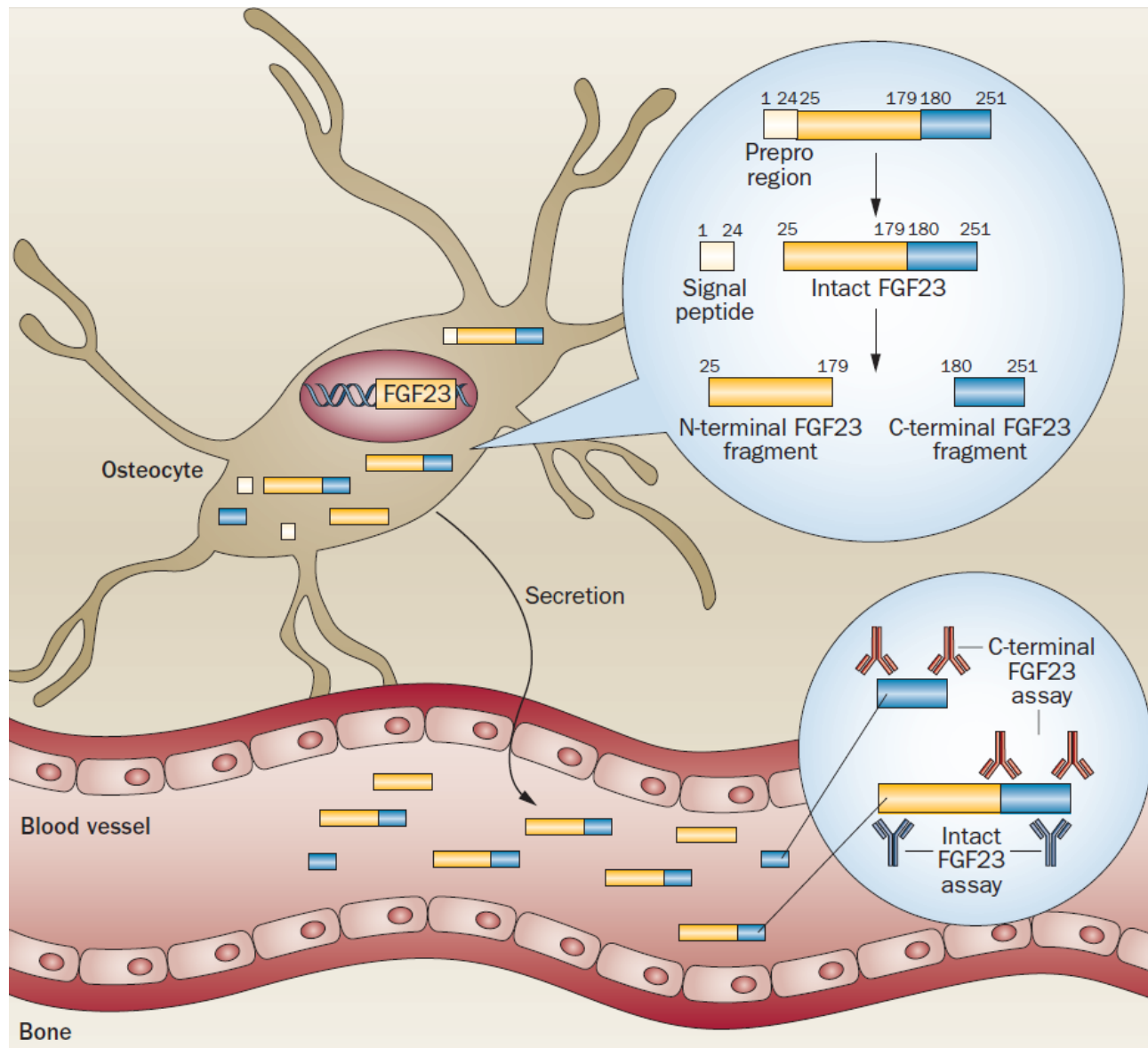


Faul et al, J Clin Invest 2011.

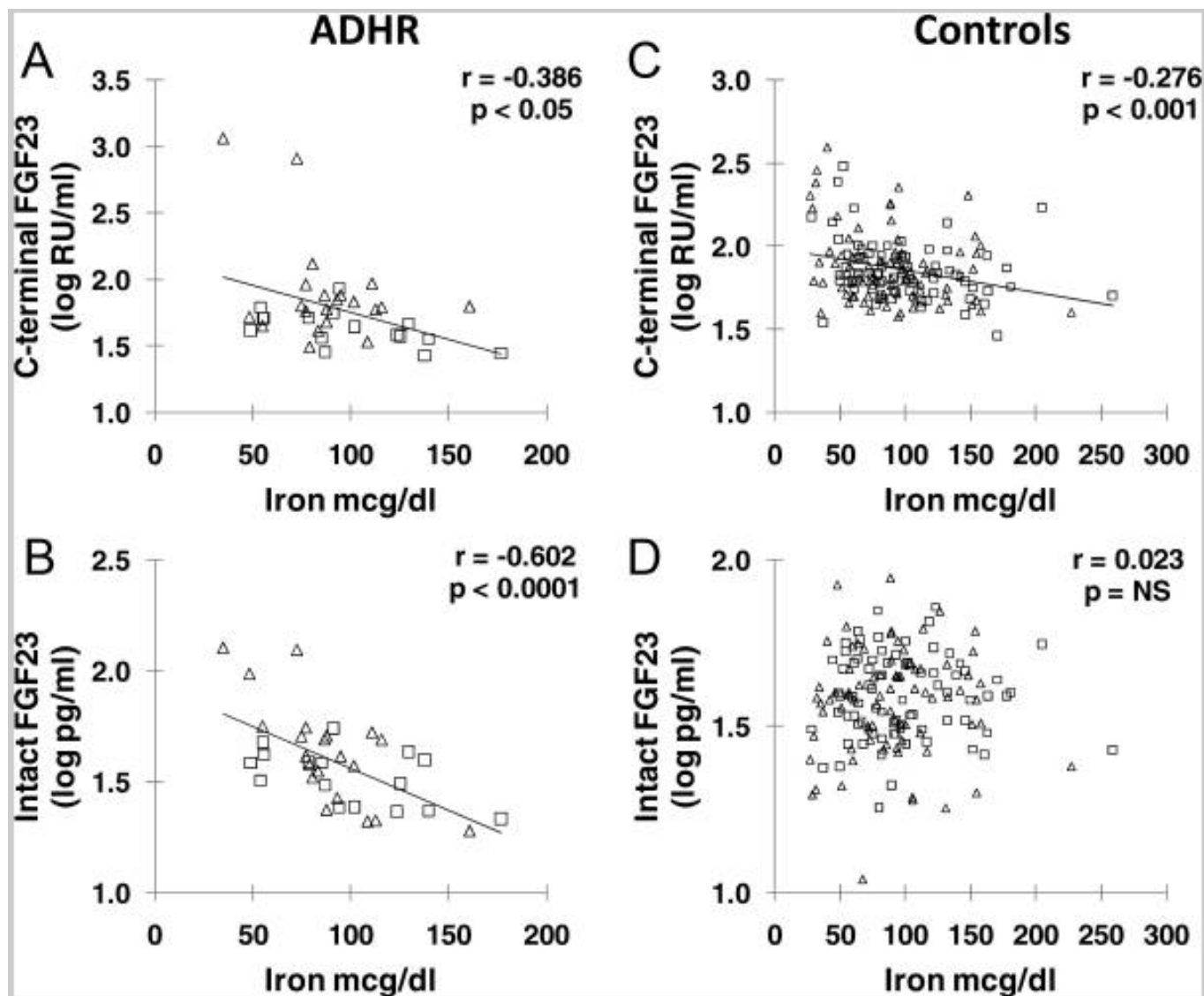


Faul et al, J Clin Invest 2011.

# FGF23 Processing



# FGF23 and Iron





# Objective

- To determine whether or not iron status affects FGF23 production and metabolism in the setting of CKD.



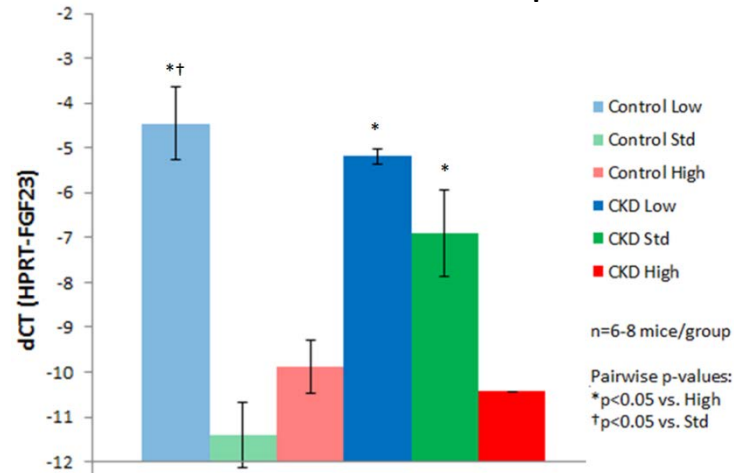
# C57BL/6 Mouse Groups and Diets

Genotype	Dietary Adenine	Dietary Iron	n
Wild type	No	Low (4 ppm)	12
Wild type	No	Standard (335 ppm)	12
Wild type	No	High (10,000 ppm)	8
Wild type	Yes	Low (4 ppm)	12
Wild type	Yes	Standard (335 ppm)	14
Wild type	Yes	High (10,000 ppm)	15

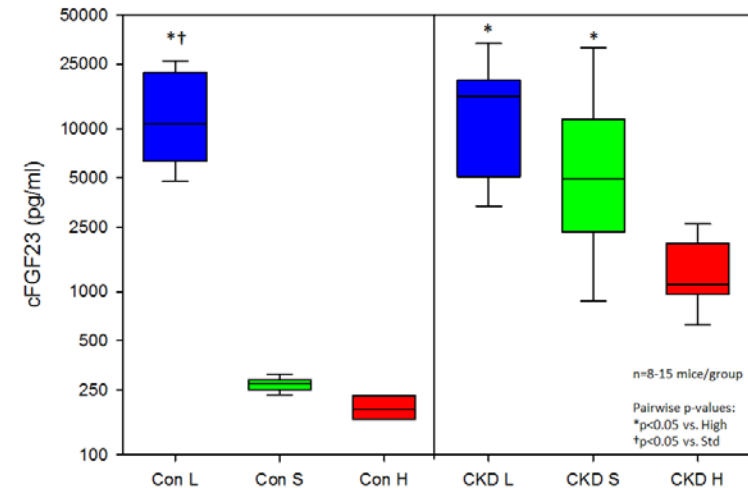
# FGF23 Parameters

**A**

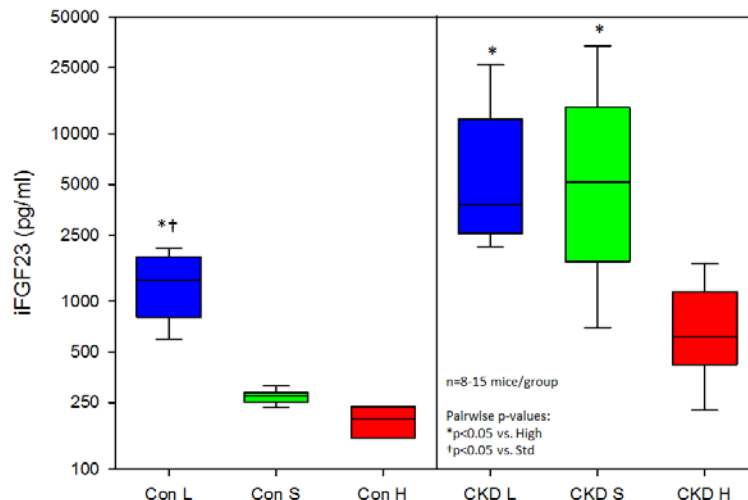
## Bone FGF23 mRNA Expression

**B**

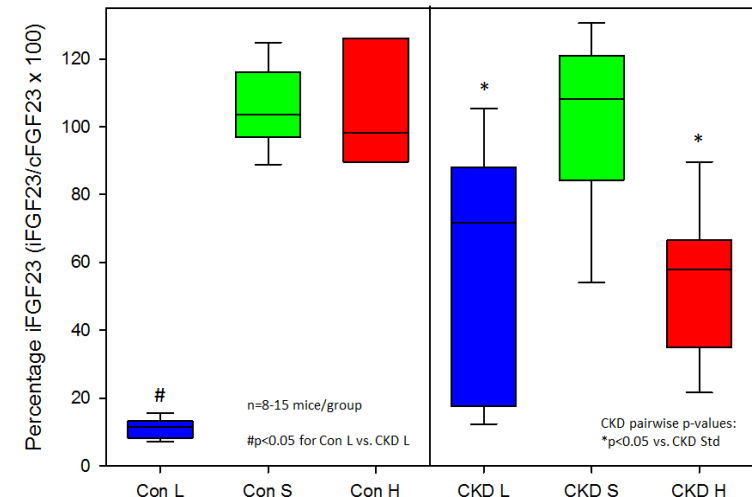
## Plasma C-terminal FGF23 Levels

**C**

## Plasma Intact FGF23 Levels

**D**

## Percentage Intact FGF23



**In CKD, the high iron diet was associated with less FGF23 production and a lower percentage circulating intact FGF23.**



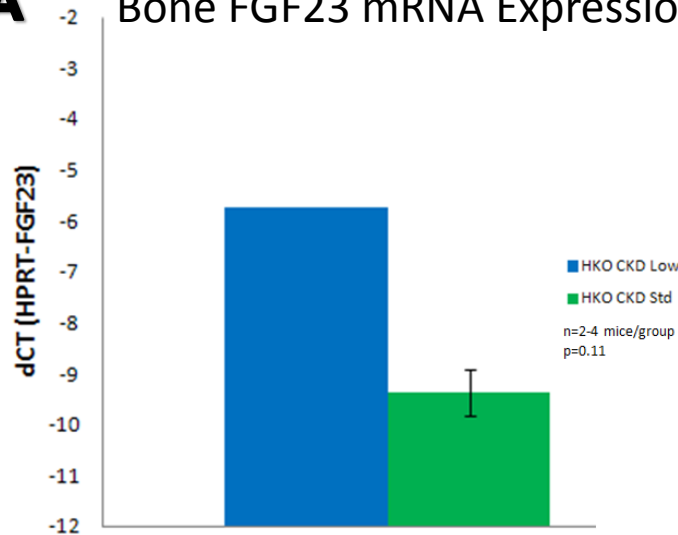


# C57BL/6 Mouse Groups and Diets

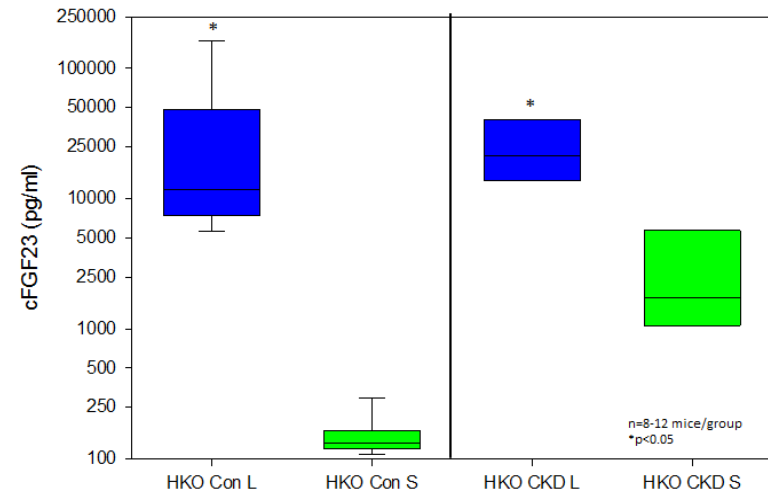
Genotype	Dietary Adenine	Dietary Iron	n
Hepcidin knockout	No	Low (4 ppm)	9
Hepcidin knockout	No	Standard (335 ppm)	12
Hepcidin knockout	Yes	Low (4 ppm)	8
Hepcidin knockout	Yes	Standard (335 ppm)	8

# FGF23 Parameters

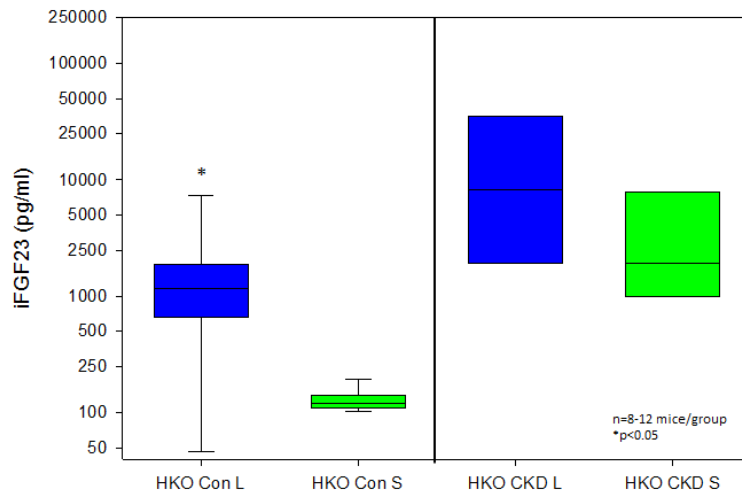
**A** Bone FGF23 mRNA Expression



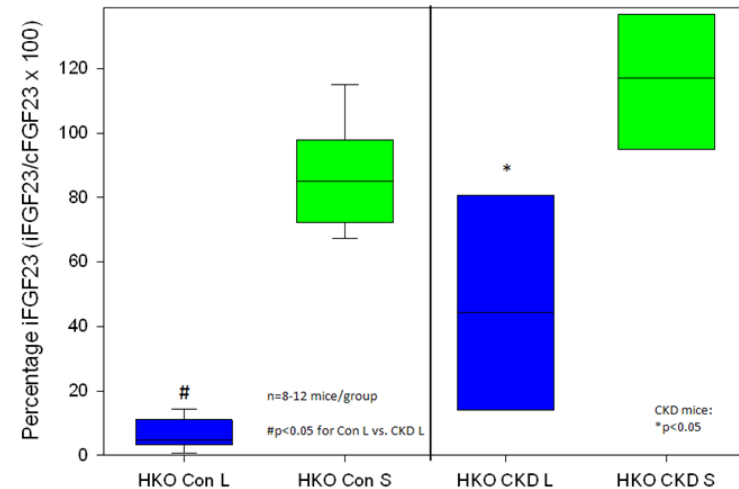
**B** Plasma C-terminal FGF23 Levels



**C** Plasma Intact FGF23 Levels



**D** Percentage Intact FGF23



The CKD iron deficient and iron loaded groups had similar phosphorus levels; however, the CKD iron loaded group had less FGF23 production.



# Multiple Linear Regression Modeling

Association of predictor variables with log cFGF23 in CKD mice:

Predictor Variable	Coefficient (95% CI)	p-value	Adjusted R <sup>2</sup>	n
Standardized Serum Phosphorus	0.23 (0.10, 0.36)	0.001	0.29	57
Standardized Liver Iron	-0.17 (-0.30, -0.04)	0.013		

Association of predictor variables with percentage intact FGF23 in CKD mice:

Predictor Variable	Coefficient (95% CI)	p-value	Adjusted R <sup>2</sup>	n
Standardized Serum Phosphorus	13.7 (3.9, 23.3)	0.008	0.13	57
Standardized Liver Iron	11.4 (1.7, 21.1)	0.025		

**In CKD, both iron and phosphorus were independently associated with C-terminal FGF23 levels and percentage intact FGF23.**



# Conclusions

- In mice with impaired kidney function, iron status affects FGF23 production and metabolism, independent of the effects of serum phosphorus.
- Iron may represent a potentially modifiable determinant of FGF23 levels in CKD patients.



# Future Directions

- Conduct *in vitro* and *in vivo* studies to assess how iron and phosphorus may affect expression and bioactivity of regulatory enzymes involved in FGF23 cleavage.



# Thank You

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