CALCITRIOL ALTERS THE PATHOLOGICAL PHENOTYPE OF LEFT VENTRICULAR HYPERTROPY IN AN EXPERIMENTAL MODEL OF CKD

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Introduction

At all stages of CKD, patients are more likely to die of CVD before ever requiring renal-replacement therapy[1]. Left ventricular hypertrophy is prevalent in CKD and a strong independent risk factor for heart failure and cardiovascular disease-related mortality[2].

Calcitriol, the active form of vitamin D_3 (1,25-OH D_3), is prescribed to control hyperparathyroidism in CKD and has been shown to improve all-cause and CVD-related mortality[3]. Calcitriol deficiency and selective vitamin D receptor KO in cardiomyocytes are linked to LVH generation[4].

LVH generation has been linked to hormonal and haemodynamic consequences of CKD that are exacerbated by calcitriol.

- Calcitriol upregulates fibroblast growth factor 23 (FGF23), which has been causally-linked to left ventricular hypertrophy generation[5].
- Both vascular calcification and increased pulse wave velocity have been associated with LVH generation[6].
- Pharmacological doses of calcitriol has been shown *in vivo* to increase vascular calcification.
- Aortic calcification increases vascular stiffness, which increases pulse wave velocity.
- This pathology can increase resistance and left ventricle afterload causing left ventricle hypertrophy[6].

Objectives

In a rat model of CKD, the study aimed to:

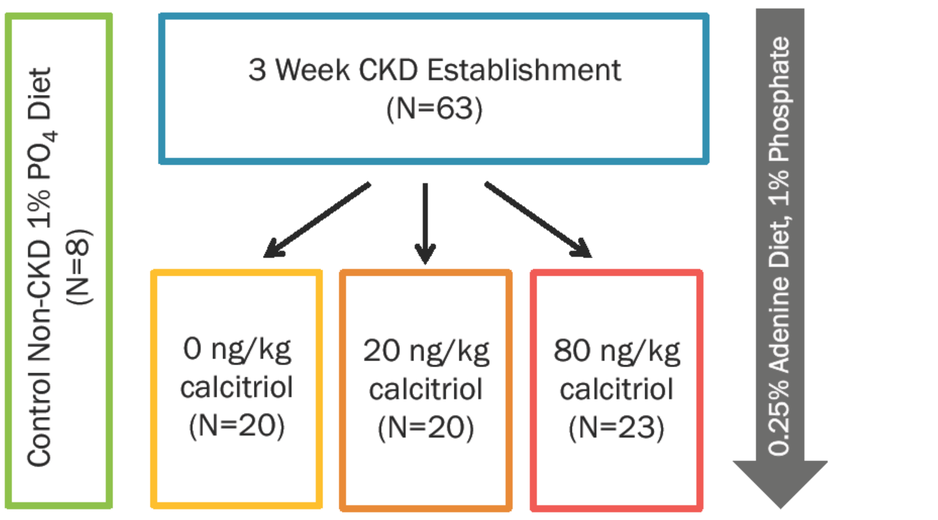
#1: Establish the impact of active calcitriol dosage on markers of phosphate homeostasis and risk factors of LVH

#2: Establish the impact of calcitriol dose on LVH

#3: In control CKD rats (0 ng/kg) and calcitriol treated(20 and 80 ng/kg) CKD rats, characterize the pathological phenotype of LVH

Methods

A longitudinal model of CKD was established over 7 weeks using dietary adenine.



**All diets contain nutritional 2mg/kg calcitirol pre-cursor (Cholecalciferol)*

End-point measures:

Indices of LVH:

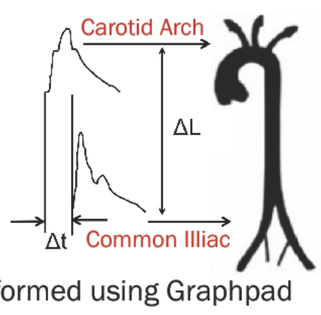
Left Ventricular Mass Index = $\frac{\text{Left Ventricle Mass (g)}}{\text{Bodyweight (kg)}}$

Blood Measures of Mineral Homeostasis:

PTH (ELISA Immunotopics™, intact)
FGF23 (ELISA Immunotopics™, C-terminal)
Minerals (Ca/PO4) – Colorimetric Assay
Creatinine (Quantikine™) – Enzyme Kinetic

Haemodynamic Measures:

(1) Aortic calcium content –homogenization + colorimetic assay
(2) Pulse Wave Velocity of aorta:
Using fluid filled catheters, measure time taken for pulse to travel from heart to the iliac bifurcation
- indicator of vascular stiffness *(Lab Chart 7)*



Analysis:

Data presented as mean +/- SD. Statistics performed using Graphpad Prism V6.

Summary & Conclusion:

- In CKD rats not treated with calcitrol, greater aortic calcification, pulse wave velocity and increased serum FGF-23 are linked to LVH
- In contrast, in CKD rats treated with calcitriol, despite the exacerbation of risk factors (↑FGF-23, ↑VC and ↑PWV) a further increase in LVH did NOT occur.
- Thus, it appears that calcitriol uncouples the relationship between some of the key CKD-associated risk factors and LVH generation in CKD.

Results

#1: Calcitriol treatment dose-dependently increases risk factors for LVH: FGF-23, aortic calcification and PVW.

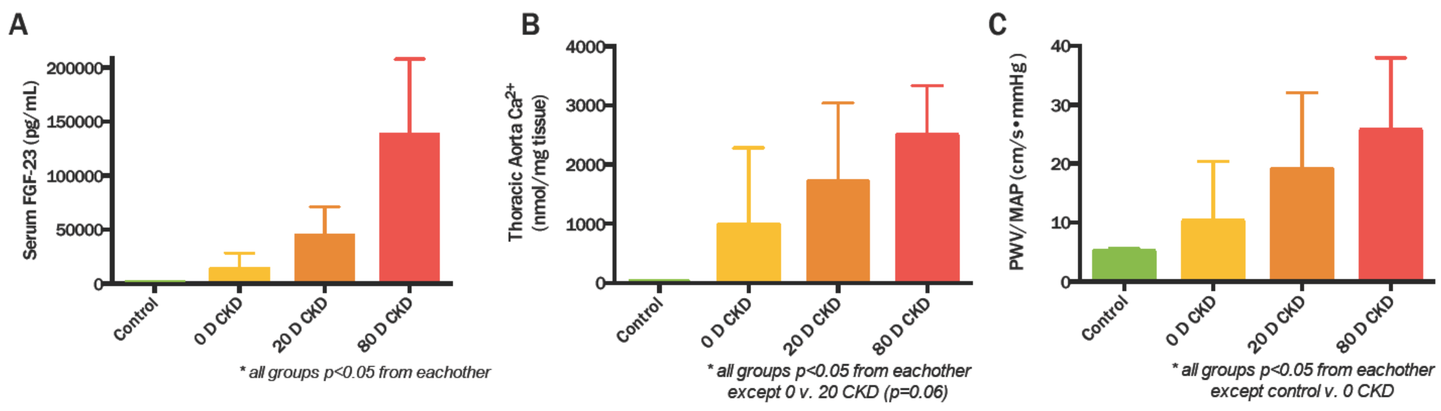


Figure 1: Risk factors for LVH by treatment group. **A-B** Non-parametric Kruskal-Wallis test with Dunn's multiple comparison. **C** One-way ANOVA, post-hoc T-test with Tukey correction.

#2: No significant impact of calcitriol dose on LVH.

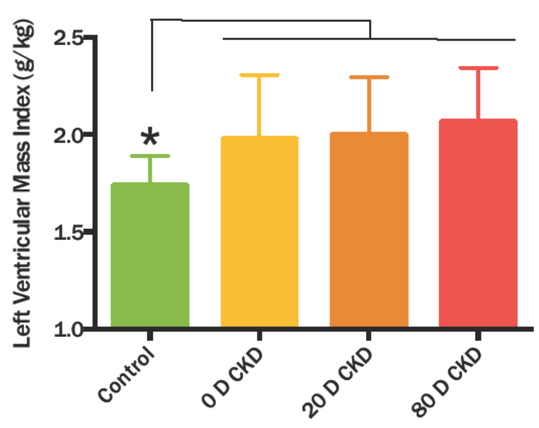


Figure 2: Left ventricular mass index by treatment group. CKD rats had significantly higher LVMI than control rats ($p<0.05$). One-way ANOVA, post-hoc T-test with Tukey correction.

Table 1: Cohort characteristics by treatment group

	Control	0 ng/kg	20 ng/kg	80 ng/kg
Bodyweight (g)	555±58*	501±48	482±36	497±47
Serum Creatinine (mM)	19.4±11****	214±81	211±62	201±44
Serum Calcium (mM)	2.4±0.4^	2.4±0.3^	2.7±0.3%	2.9±0.3
Serum Phosphate (mM)	2.1±0.5****	4.9±1.0	5.0±1.0	4.8±1.1
Serum PTH (pg/mL) #	532±150	5541±2929*	2615±1797*	1156±682

**** $p<0.001$ comparison for each treatment group, ^ $p<0.05$ comparison against 80ng/kg, % $p<0.05$ comparison against 20 ng/kg # All groups $p<0.05$ comparison against each other except control v. 80 ng/kg

#3: Calcitriol-treated groups do not show trends linking LVH with conventional risk factors.

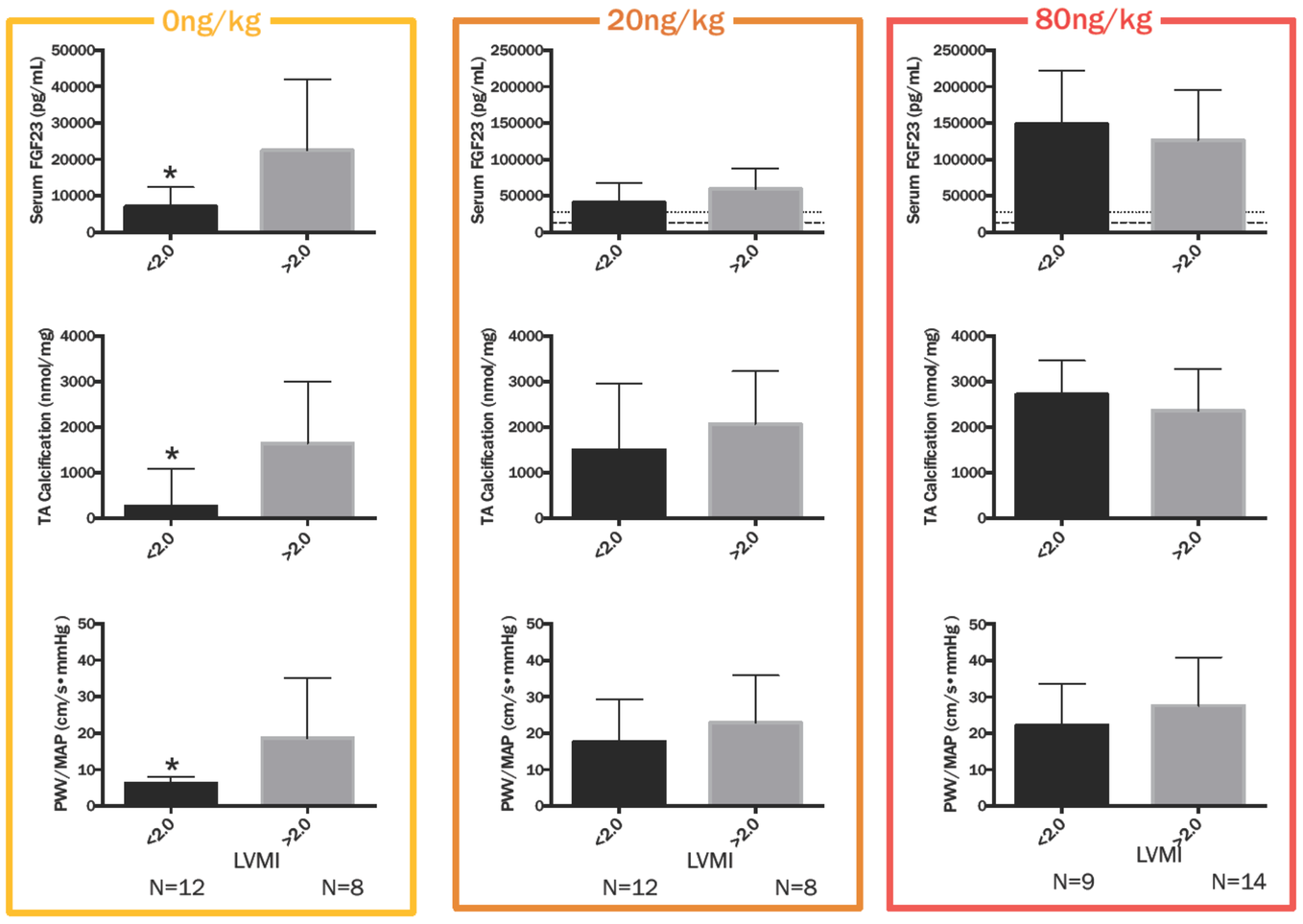


Figure 3: Comparison of RF for LVH within treatment group between rats with and without LVH as measured by LVMI >2.0 g/kg and <2.0g/kg respectively. 2.0 g/kg is 2 SD higher than control group. Comparison using Man-Whitney U-test for FGF23 and TA Ca, T-test for PVW. *P<0.05

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