Doxycycline administration differentially affects vascular mineral accrual in CKD based on vessel anatomical location

Bruno Svajger[1], Jason G.E. Zelt[1], Kimberly Laverty[1], Rachel M. Holden[2], Michael A. Adams[1]
[1]Department of Biomedical and Molecular Sciences & [2]Department of Medicine, Queen's University, Kingston, ON, Canada

Introduction

Background: The leading cause of mortality in chronic kidney disease (CKD) is cardiovascular disease[1]. Abnormal calcium (Ca^{2+}) and phosphate (PO_4^{3-}) levels occur in CKD due to decreases in renal function; alterations to systemic mineral levels may result in pathologies.[2,3] In CKD, build-up of a Ca^{2+}-PO_4^{3-} product in vascular walls is common, leading to vascular calcification (VC).[4] Degradation of the vascular extracellular matrix (ECM) by the activity of matrix metalloproteinases 2 and 9 (MMP2, MMP9) is implied as a critical initiating and propagating step of VC.[4] Inhibition of MMP2/9 has shown to reduce VC in severe models of CKD; however, their effects on mild CKD are yet unknown. It is likely that even with mild alterations to systemic mineral levels, inhibition of MMP2/9 can significantly alter pathological mechanisms.

Purpose: The study's aim was to investigate the effects MMP2/9 inhibition on VC in a progressive mild model of CKD; specifically, to examine alterations to how the minerals accrue and identify any heterogeneity across vascular beds.

Methods

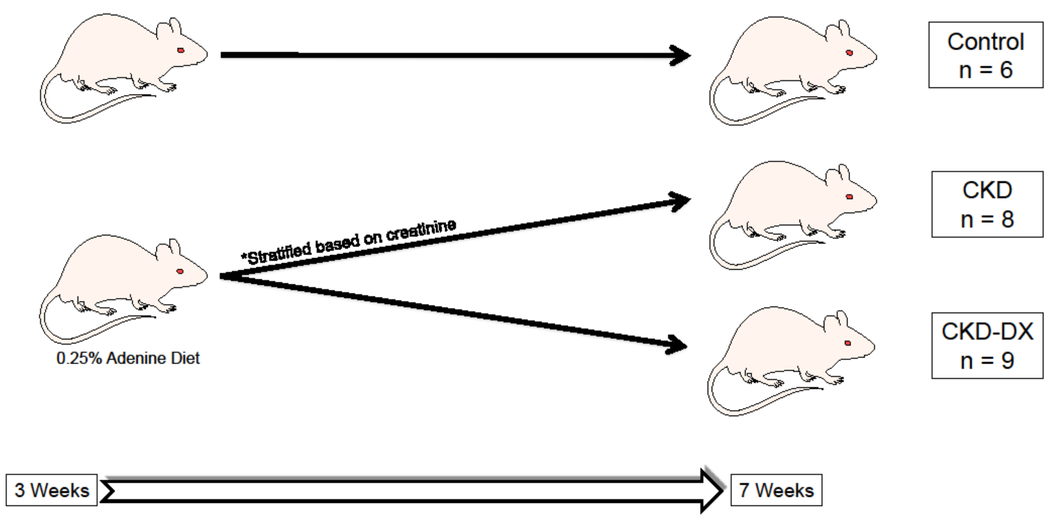

Figure 1. ***In vivo CKD rat model.*** Male Sprague-Dawley rats were administered standard rat chow or a CKD-inducing diet (0.25% adenine, 1% PO_4^{3-}) for 3 weeks. At 3 weeks, animals were stratified based on serum creatinine levels (μM) into 2 groups: CKD (0.25% dietary adenine, CKD) and CKD with doxycycline (0.25% dietary adenine & 0.30 mg/kg doxy. given twice daily intragastrically, CKD-DX). Animals were treated for 4 weeks and then sacrificed.

Results

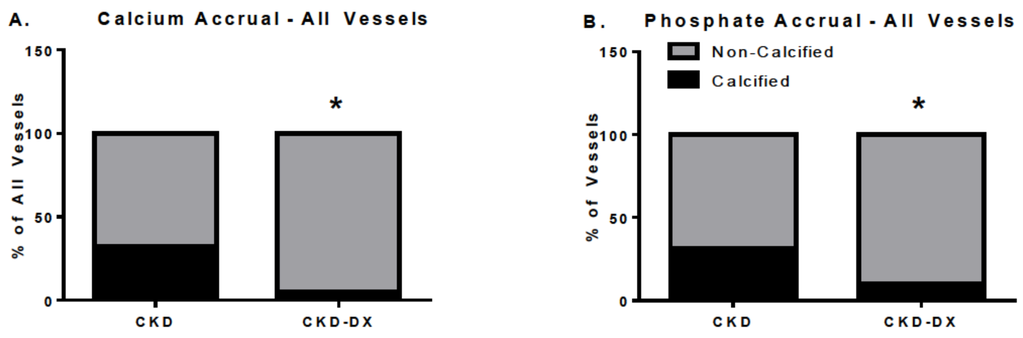

Figure 2. MMP2/9 inhibition reduces proportion of calcifying vessels. Doxycycline-induced suppression of calcification in vascular segments (Ca^{2+} > 30 nmol/mg tissue and/or PO_4^{3-} > 18 nmol/mg tissue). * Significantly different than CKD, p<0.05. Data expressed as mean SEM.

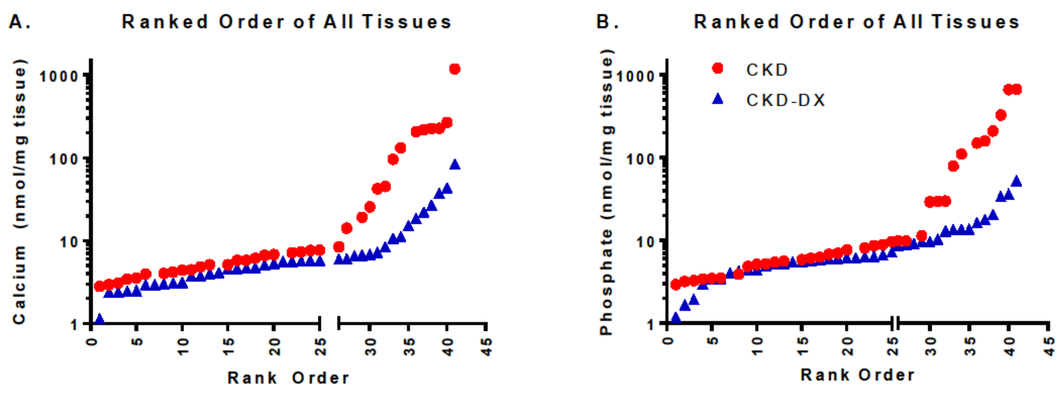

Figure 3. MMP2/9 inhibition alters pattern of mineral accrual. Alterations in (A) Ca^{2+}, and (B) PO_4^{3-} accrual from doxycycline treatment. Significant accrual differences (p<0.05) in (A) all Ca^{2+} levels, and (B) PO_4^{3-} > 9 nmol/mg tissue.

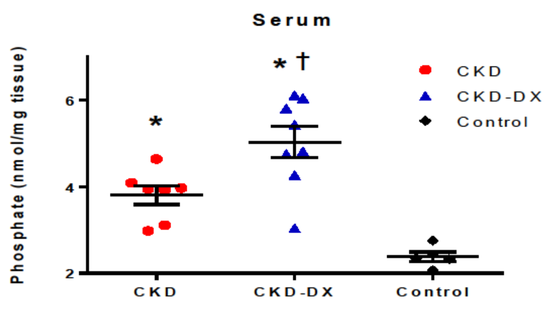

Figure 4. Inhibition of MMP2/9 alters serum phosphate content. Differences in serum PO_4^{3-} levels across treatment groups. * Significantly different than Control, p<0.0001. † Significantly different than CKD, p<0.05. Data expressed as mean SEM.

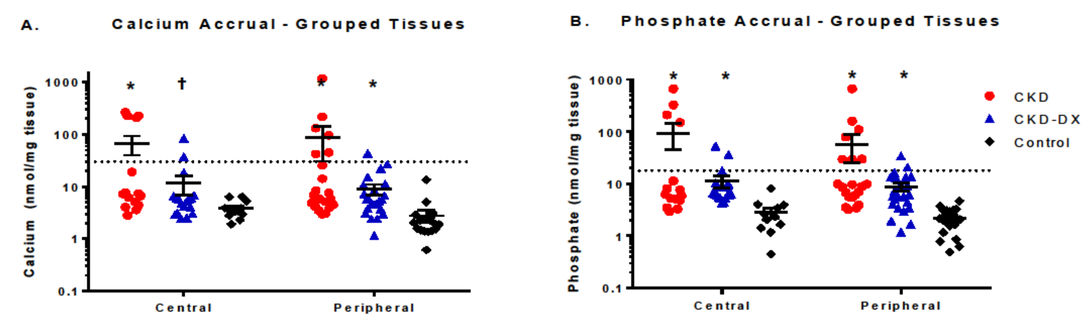

Figure 5. Differences in the effects of doxycycline on arteries based on anatomical location. Treatment effects to (A) Ca^{2+}, and (B) PO_4^{3-} accrual in tissues grouped based on anatomical location. * Significantly different than Control, p<0.01. † Significantly different than CKD, p<0.05. Data expressed as mean SEM.

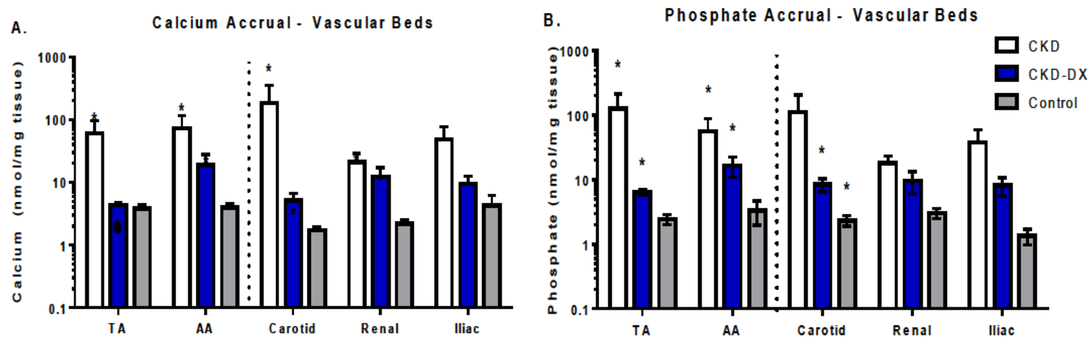

Figure 6. Doxycycline administration differentially affects mineral accrual across vascular beds. Treatment effects to (A) Ca^{2+}, and (B) PO_4^{3-} accrual across vascular beds. * Significantly different than Control, p<0.01. θ Significantly different than CKD, p<0.05. Data expressed as mean SEM.

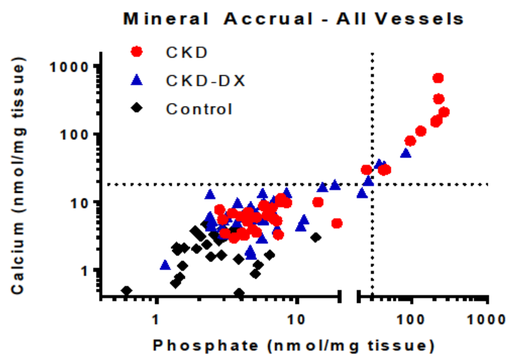

Figure 7. Doxycycline administration reduces vessel calcification. Doxycycline-induced suppression of mineral accumulation in vascular segments (Ca^{2+} > 30 nmol/mg tissue and/or PO_4^{3-} > 18 nmol/mg tissue).

Summary and Conclusions

1. Doxycycline reduces propensity for vessels to calcify
2. Doxycycline induces changes to mineral accrual in vessels
3. Inhibition of mineral accrual shows heterogeneity across vascular beds
4. Inhibition of vessel phosphate accrual coincides with significant serum phosphate increases

References

1. Go AS, Chertow GM, Fan D, McCulloch CE, Hsu CY. Chronic kidney disease and the risks of death, cardiovascular events, and hospitalization. The New England journal of medicine. 2004;351(13):1296-305.
2. Ikeda R, Imai Y, Maruyama W, Mizoguchi K. Systemic disorders of calcium dynamics in rats with adenine-induced renal failure: implication for chronic kidney disease-related complications. Nephrology. 2010;15(1):54-62.
3. Shobeiri N, Adams MA, Holden RM. Phosphate: an old bone molecule but new cardiovascular risk factor. British journal of clinical pharmacology. 2014;77(1):39-54.
4. Moe SM, Chen NX. Pathophysiology of vascular calcification in chronic kidney disease. Circulation research. 2004;95(6):560-7.

Acknowledgements

CIHR IRSC · The Kidney Foundation of Canada · NSERC CRSNG · Heart & Stroke Foundation

91--SP
53 ERA
Hypertension. Experimental.
Bruno Svajger
DOI: 10.3252/pso.eu.53era.2016
ePosters supported by F. Hoffmann- La Roche Ltd.
53rd Congress ERA-EDTA Vienna Austria May 21st-24th, 2016
PosterSessionOnline.com