Temporal Patterns of Vascular Pathogenesis in CKD: Regional Heterogeneity in Vascular Calcium Accrual

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Conclusions

1) In early CKD, distal vessels calcify more severely compared to proximal vessels
2) When proximal vessels are not calcified, distal vessels accrue significantly greater amounts of Ca^{2+} than proximal vessels, relative to control values
3) As renal insufficiency progresses, proximal vessels calcify more severely than distal vessels

Introduction

Background: In chronic kidney disease (CKD), the leading cause of mortality is cardiovascular disease (CVD).[1] In CKD, alterations to mineral handling brought on by decreases in renal function and increased hormonal stimuli (e.g. excessive PTH) lead to hyperphosphatemia and significantly increased calcium (Ca^{2+}) levels.[2] Phosphate (PO_4^{3-}) and Ca^{2+} are vital to various physiologic functions, but significant increases in their levels may lead to pathologies.[3, 4] In CKD, the build-up of a Ca^{2+}–PO_4^{3-} product in vascular walls is common, leading to vascular calcification (VC).[2] Although many studies have examined the effects of severe VC in CKD, the handling of Ca^{2+} and PO_4^{3-} across vascular beds in both early renal insufficiency and through its progression is not well defined. Recently, our lab demonstrated distal and proximal vessels possess differentiated stoichiometric mineral accrual patterns.[5] It is likely that during the progression of CKD, Ca^{2+} and PO_4^{3-} accrue differently in proximal versus distal vessels.

Purpose: The aim of this study was to investigate differences in mineral accrual across vascular beds in a progressive model of CKD; specifically, to examine if trends of mineral accrual across vascular beds remain change as renal insufficiency progresses.

Experimental Approach

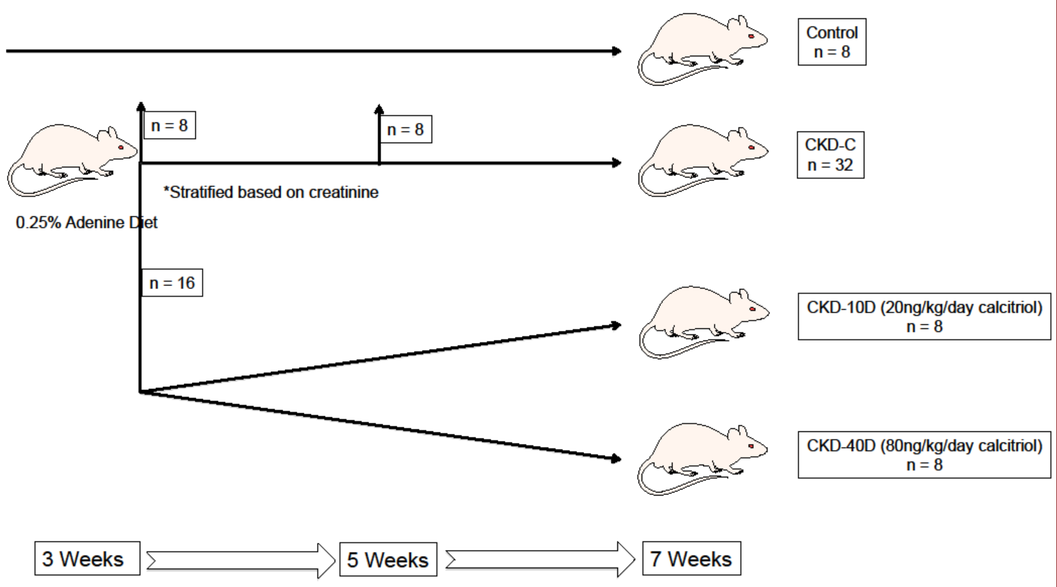

Figure 1. Male Sprague-Dawley rats were administered standard rat chow diet or a CKD-inducing diet (0.25% adenine) for 3 weeks. At 3 weeks, CKD animals were stratified based on serum creatinine levels into 3 treatment groups: CKD control (0.25% dietary adenine, CKD-C), low calcitriol (0.25% dietary adenine & 20ng/kg/day calcitriol, CKD-10D), and high calcitriol (0.25% dietary adenine & 80ng/kg/day calcitriol, CKD-40D). Animals were treated for 4 weeks. Additionally, animals from the CKD-C group were sacrificed at 3 weeks and 5 weeks.

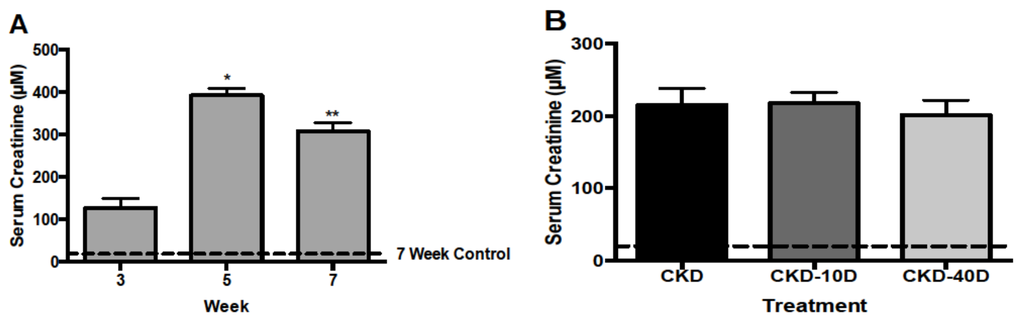

Figure 2. Time course of serum creatinine in rats treated with 0.25% adenine diet (A), and 7-week treatment groups (B).*Significantly different than 3 Week CKD, p<0.05. **Significantly different than 3 Week and 5 Week CKD, p<0.05. Data expressed as mean ± SEM.

Results

Ca^{2+} Accrual Time Course

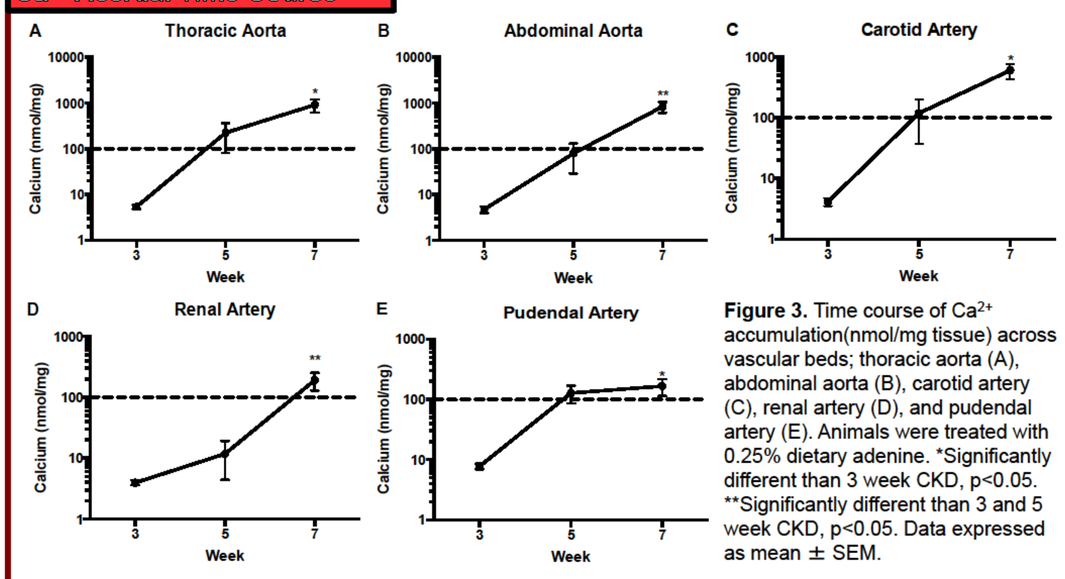

Figure 3. Time course of Ca^{2+} accumulation(nmol/mg tissue) across vascular beds; thoracic aorta (A), abdominal aorta (B), carotid artery (C), renal artery (D), and pudendal artery (E). Animals were treated with 0.25% dietary adenine. *Significantly different than 3 week CKD, p<0.05. **Significantly different than 3 and 5 week CKD, p<0.05. Data expressed as mean ± SEM.

Vascular Ca^{2+} Accrual

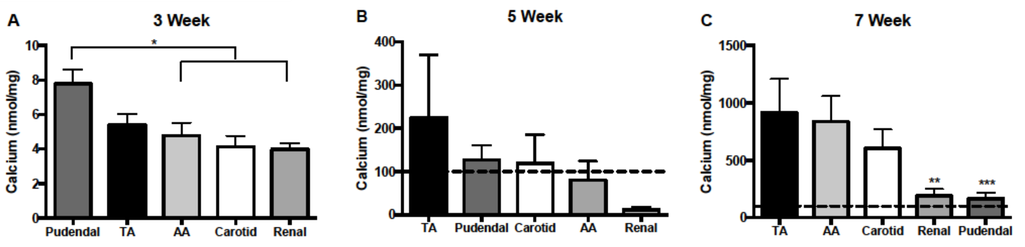

Figure 4. Differential Ca^{2+} accumulation across vascular beds at 3 Weeks (A), 5 Weeks (B), and 7 Weeks (C) of CKD (0.25% dietary adenine).Calcification defined as Ca^{2+} content > 100nmol/mg tissue. *Significantly different than abdominal aorta, carotid artery, and renal artery, p<0.05. **Significantly different than abdominal aorta, p<0.05. ***Significantly different than thoracic aorta and abdominal aorta, p<0.05. Data expressed as mean ± SEM.

Occurrence of Calcification in Vessels

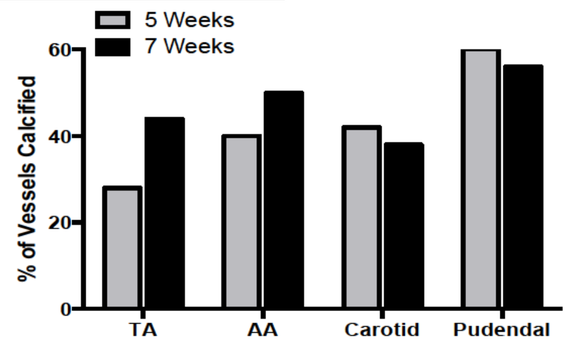

Figure 5. Percentage of animals with calcified vascular beds between 5 week and 7 week CKD groups (0.25% dietary adenine). Calcification defined as Ca^{2+} content >100nmol/mg tissue.

Peripheral Vasculature Is More Susceptible to VC in CKD

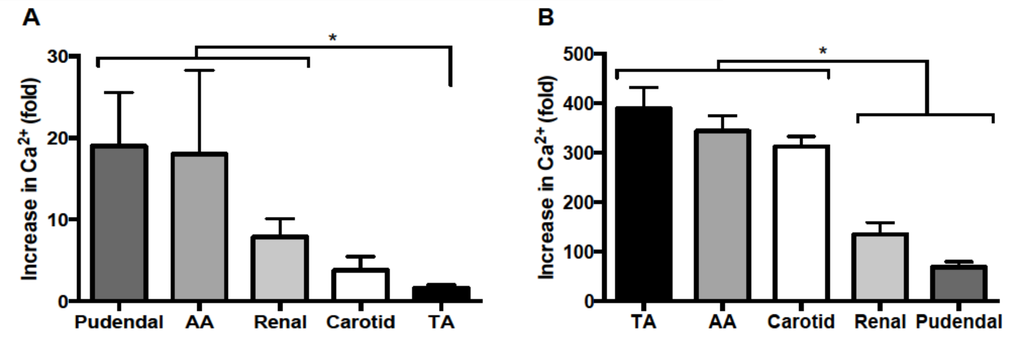

Figure 6.. Increases in vascular Ca^{2+} content relative to control levels across vascular beds in the presence (A) and absence (B) of thoracic aorta VC. CKD rats were administered calcitriol at either high dose (80ng/kg/day, n=8) or low dose (20ng/kg/day, n=8) to generate a range of VC severity. During analysis rats were stratified based on thoracic aorta calcification, defined as Ca^{2+} content > 100. *Significant within group differences, p<0.05. Data expressed as mean ± SEM.

References

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