

Temporal Characterization of Mineral and Hormone Biomarker Profiles in Adenine-Induced CKD

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INTRODUCTION

- The rat adenine model is a progressive model of Chronic Kidney Disease (CKD) whereby adenine overload causes direct adenine toxicity as well as tubular obstruction and damage from the deposition of 2,8-DHA crystals resulting in perturbations in renal function and development of renal interstitial inflammation and fibrosis.
- One prevalent complication of advanced CKD is the development of CKD-Mineral and Bone Disorder (CKD-MBD) which is characterized by an imbalance of minerals and hormones, bone abnormalities, and vascular calcification – seen in 70%+ of patients with Stage 4 kidney disease.

AIM

- The purpose of this study was to temporally characterize the mineral and hormone biomarker profiles in a 56-day 0.25% adenine-induced CKD rat model.

METHODS

- Male Sprague-Dawley rats (~ 330g) were fed *ad libitum* either control diet (0.9% Pi, 0.6% Ca) or 0.25% adenine diet (Inotiv) from Day 0 – Day 56.
- Serial blood samples were collected via tail vein under conscious conditions between 2-3pm on Days 0, 3, 7, 10, 14, 17, 21, 28, 35, 42, 49, & 56.
- Serial 6-hour urine output volumes were measured, and urine samples were collected via metabolic cage housing on Days 7, 14, 21, 28, 35, 42, 49, & 56.
- Urea, creatinine, inorganic calcium, inorganic phosphorous, and sodium were determined using standard clinical chemistry procedures.
- Kidney injury molecule 1 (KIM-1), neutrophil gelatinase-associated lipocalin (NGAL), parathyroid hormone (PTH), fibroblast growth factor 23 (FGF-23), and 1,25-dihydroxyvitamin D3 concentrations were determined in using commercially available rat-specific ELISA kits.

SUMMARY

- Adenine overload via 0.25% diet admix in rats elicited several key biochemical and humoral abnormalities observed in clinical CKD-MBD, specifically progressive perturbations in renal injury biomarkers, hyperphosphatemia, hypocalcemia, hyperparathyroidemia, and elevated plasma FGF-23.
- To induce decreases in plasma Vitamin D3 levels a longer duration and/or a higher concentration of adenine consumption may be needed.

Acknowledgments

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RESULTS

Renal Injury Biomarkers

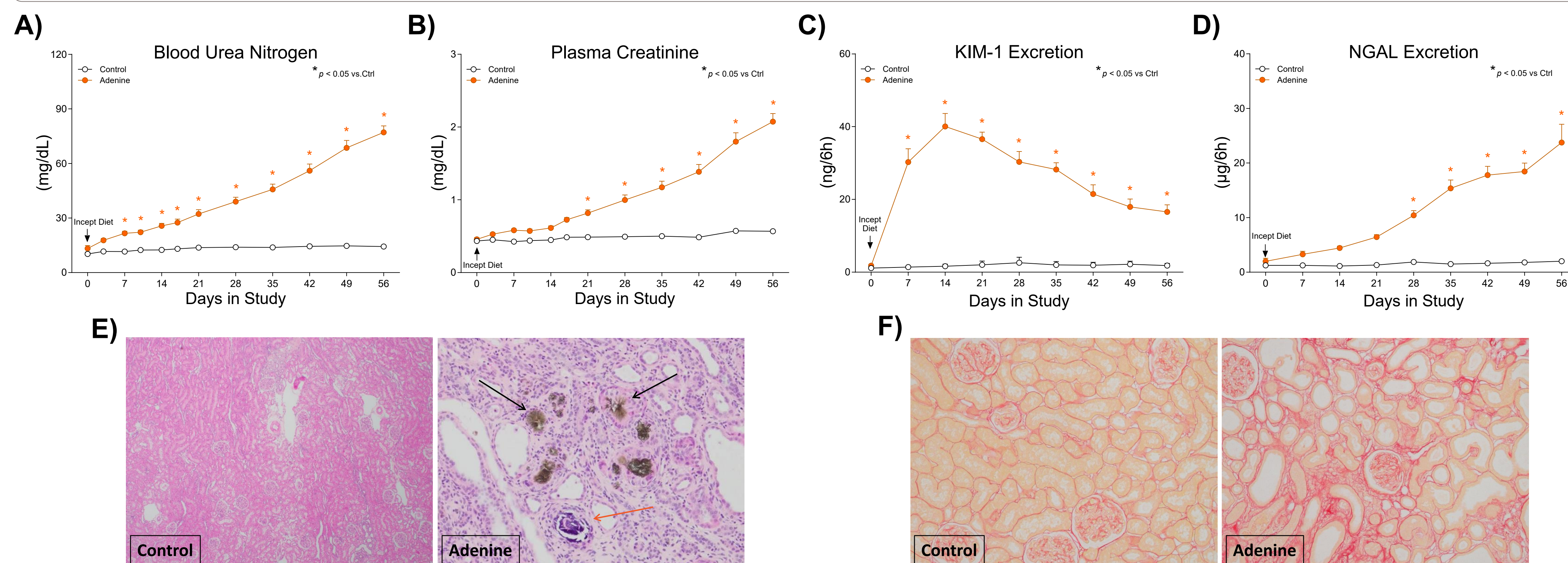


Figure 1. 0.25% adenine-induced perturbations in renal injury biomarkers over time. 0.25% adenine overload increased (A) BUN, (B) Plasma Creatinine, (C) Urinary KIM-1 Excretion, and (D) Urinary NGAL Excretion relative to control. (E) Endpoint (Day 56) representative H&E-stained kidney section at 10X from Control (left panel) and Adenine (right panel). Average histopathology scores for adenine group (0-5 scale): interstitial fibrosis = 3.8, basophilic tubules = 3.8, tubule dilation = 3.6, granulomatous inflammation - crystals (black arrows) = 3.6, thickened basement membrane = 2.5, and mineralization (orange arrow) = 1.8. (F) Endpoint (Day 56) representative PSR-stained kidney section at 100X from Control (left panel) and Adenine (right panel). Adenine overload increased renal cortical Collagen Volume Fraction (% area positive for PSR-staining) 3.7±0.2-fold compared to control.

Mineral & Hormone Biomarkers

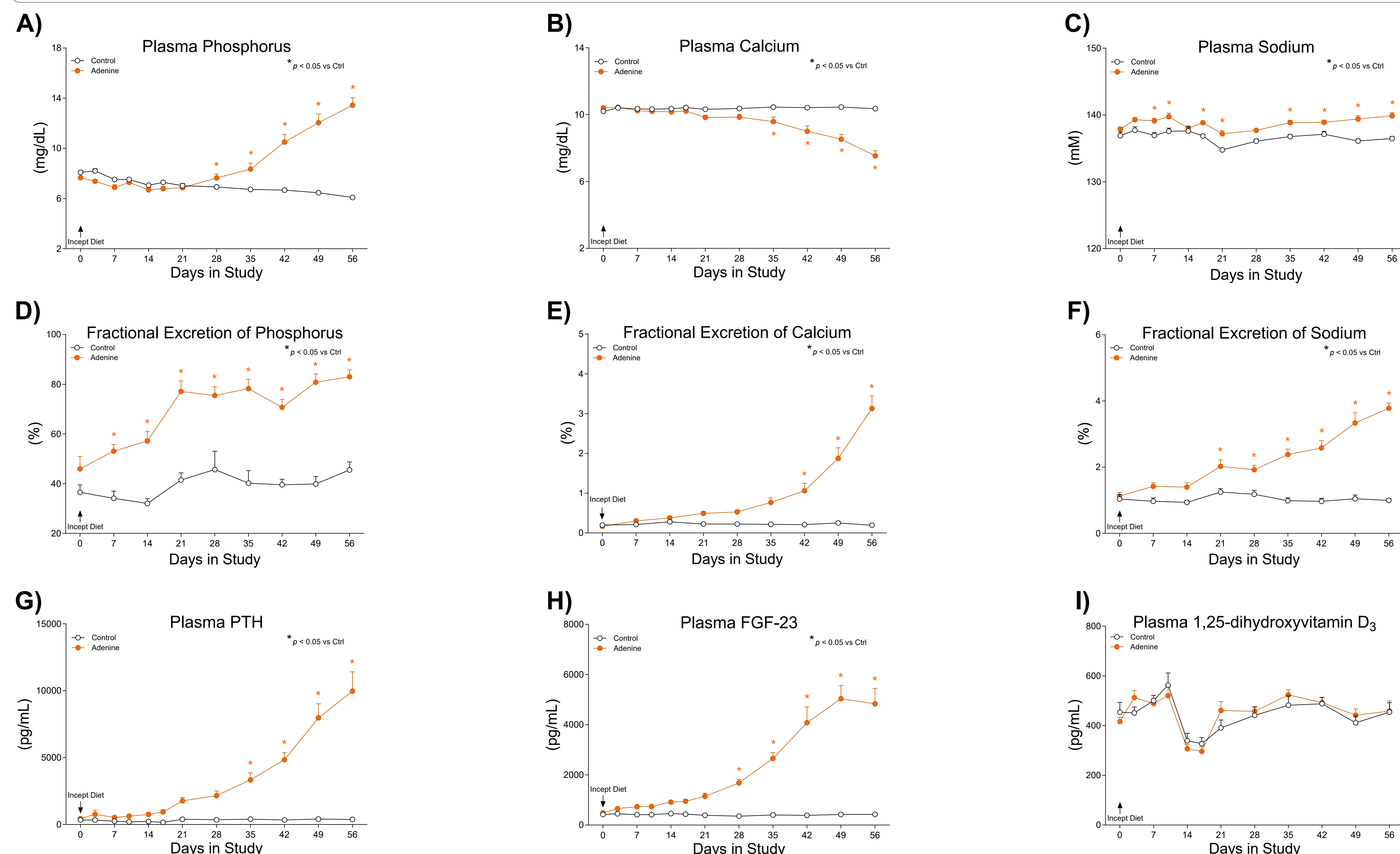


Figure 2. 0.25% adenine-induced perturbations in mineral and hormone biomarkers over time. Adenine overload increased (A) plasma phosphorus and (C) plasma sodium and decreased (B) plasma calcium relative to control. Adenine overload increased fractional excretion, measures the % of filtered analyte that is excreted in the urine, of (D) phosphorus, (E) calcium, and (F) sodium compared to control. Adenine overload progressively increased (G) plasma PTH and (H) plasma FGF-23 but did not affect (I) plasma Vitamin D relative to control.