Acid retention with reduced glomerular filtration rate increases urine biomarkers of kidney and bone injury

Donald E. Wesson[1,2], Jessica Pruszynski[3], Wendy Cai[4] and Jan Simoni[5]

[1]Baylor Scott and White Health, Dallas, TX; [2]Department of Medicine, Texas A&M College of Medicine, Temple, TX; [3]Department of Cardiovascular and Thoracic Surgery, University of Texas Southwestern Medical Center, Dallas, TX; [4]Department of Biostatistics, Baylor Scott and White Health, Temple, TX; and [5]Department of Surgery, Texas Tech University Health Sciences Center, Lubbock, TX

Diets high in acid of developed societies that do not cause metabolic acidosis in patients with chronic kidney disease nevertheless appear to cause acid retention with associated morbidity, particularly in those with reduced glomerular filtration rate. Here we used a rat 2/3 nephrectomy model of chronic kidney disease to study induction and maintenance of acid retention and its consequences on indicators of kidney and bone injury. Dietary acid was increased in animals eating base-producing soy protein with acid-producing casein and in casein-eating animals with added ammonium chloride. Using microdialysis to measure the kidney cortical acid content, we found that nephrectomized animals had greater acid retention than sham-operated animals when both ate the soy diet. Each increment in dietary acid further increased acid retention more in nephrectomized than in sham rats. Nephrectomized and sham animals achieved similar steady-state daily urine net acid excretion in response to increments in dietary acid but nephrectomized animals took longer to do so, contributing to greater acid retention that was maintained until the increased dietary acid was stopped. Acid retention was associated with increased urine excretion of both N-acetyl-β-D-glucosaminidase and deoxypyridinoline, greater in nephrectomized than control rats, consistent with kidney tubulointerstitial and bone matrix injury, respectively. Greater acid retention in nephrectomized than control animals was induced by a slower increase in urinary net acid excretion rate in response to the increment in dietary acid and also maintained until the dietary acid increment was stopped. Thus, acid retention increased biomarkers of kidney and bone injury in the urine, supporting untoward consequences to these two tissues.

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Correspondence: *Donald E. Wesson, Diabetes Health and Wellness Institute of Baylor Scott and White Health,4500 Spring Avenue, Dallas, TX 75210. E-mail: Donald.Wesson@BSWHealth.org*

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Although patients with reduced glomerular filtration rate (GFR) can effect steady-state urine acid (H^+) excretion sufficient to avoid progressive metabolic acidosis in response to most *ad libitum* diets,[1,2] they might do so in a setting of H^+ retention not reflected by plasma acid-base parameters.[2–4] Notably, diets in developed societies are largely H^+-producing,[5] and individuals subjected to a continuous dietary H^+ challenge cumulatively excrete less H^+ than their dietary H^+ load,[6] which is consistent with H^+ retention. Furthermore, even substantial increases in dietary H^+ lead to only modest changes in plasma acid-base parameters within accepted normal ranges,[7] yet they might be associated with significant morbidity without inducing measurable changes in plasma acid-base parameter characteristic of metabolic acidosis.[8]

Similarly, animals with reduced GFR eating H^+-producing diets and with plasma acid-base parameters comparable to control nevertheless have H^+ retention that mediates GFR decline.[9–11] Importantly, humans with reduced GFR have H^+ retention,[2–4] which might mediate GFR decline in those without metabolic acidosis.[12] Identifying mechanism(s) for induction and maintenance of H^+ retention in patients with reduced GFR but without metabolic acidosis will help design strategies to ameliorate or eliminate it and thereby help clinicians reduce its contribution to chronic kidney disease (CKD)-related morbidity.

Many CKD patients with reduced GFR without metabolic acidosis nevertheless have plasma abnormalities consistent with CKD-related bone disease[13] and might experience progressive GFR decline.[12,14] This laboratory developed an animal model of CKD with reduced GFR without metabolic acidosis as a surrogate for study of such patients.[9–11] Contrary to animals with the classic 5/6 nephrectomy that have metabolic acidosis,[15] 2/3 nephrectomized (Nx) animals have reduced GFR and no metabolic acidosis, yet, like 5/6 Nx, they have progressive GFR decline when fed standard, casein-based (i.e., H^+-producing) diets.[9–11] Their GFR decline was ameliorated when they concomitantly ate alkali with the casein or ate a soy-based (i.e., base-producing) diet.[9–11] We

used this 2/3 Nx model to explore mechanisms by which H^+ retention is induced and maintained in CKD without metabolic acidosis and to explore the potential effect of this H^+ retention and its resolution on kidney and bone health.

RESULTS

Effect of kidney mass reduction and diet on body weight and GFR

Baseline body weight of 6 matched Nx (201 ± 13 g) and sham (201 ± 12 g) animals was not statistically different before kidney mass reduction surgery or sham surgery ($P = 0.98$), but 12-week weight gain while eating soy following surgery was less in Nx than sham (138 ± 6 vs. 148 ± 7 g; $P < 0.01$). As per design, Nx had lower GFR than sham 12 weeks after surgery while eating soy (1892 ± 150 vs. 3336 ± 193 µl/min, $P < 0.01$). When these animals who had eaten soy for 12 weeks were given casein diet for an additional week, GFR was also lower in Nx than sham (2525 ± 164 vs. 4020 ± 252 µl/min, $P < 0.01$) and soy. Respective GFR was lower in animals eating soy than casein for both Nx ($P < 0.01$) and sham ($P < 0.01$).

Time to reach steady state with initiation of increment in dietary H^+

Figure 1 depicts the course of daily urine net acid excretion (UNAE) (1a and b), plasma total CO_2 ($PTCO_2$) (1c and d), and microdialysate H^+ addition (1e and f) when the indicated dietary H^+ increment was continuous throughout the 14-day study period in sham and Nx animals. For animals eating soy-based diet who then switched to casein-based diet (Soy-Cas) and animals eating casein for 1 week to which was added NH_4Cl (Cas-NH_4Cl), steady state was achieved in sham and

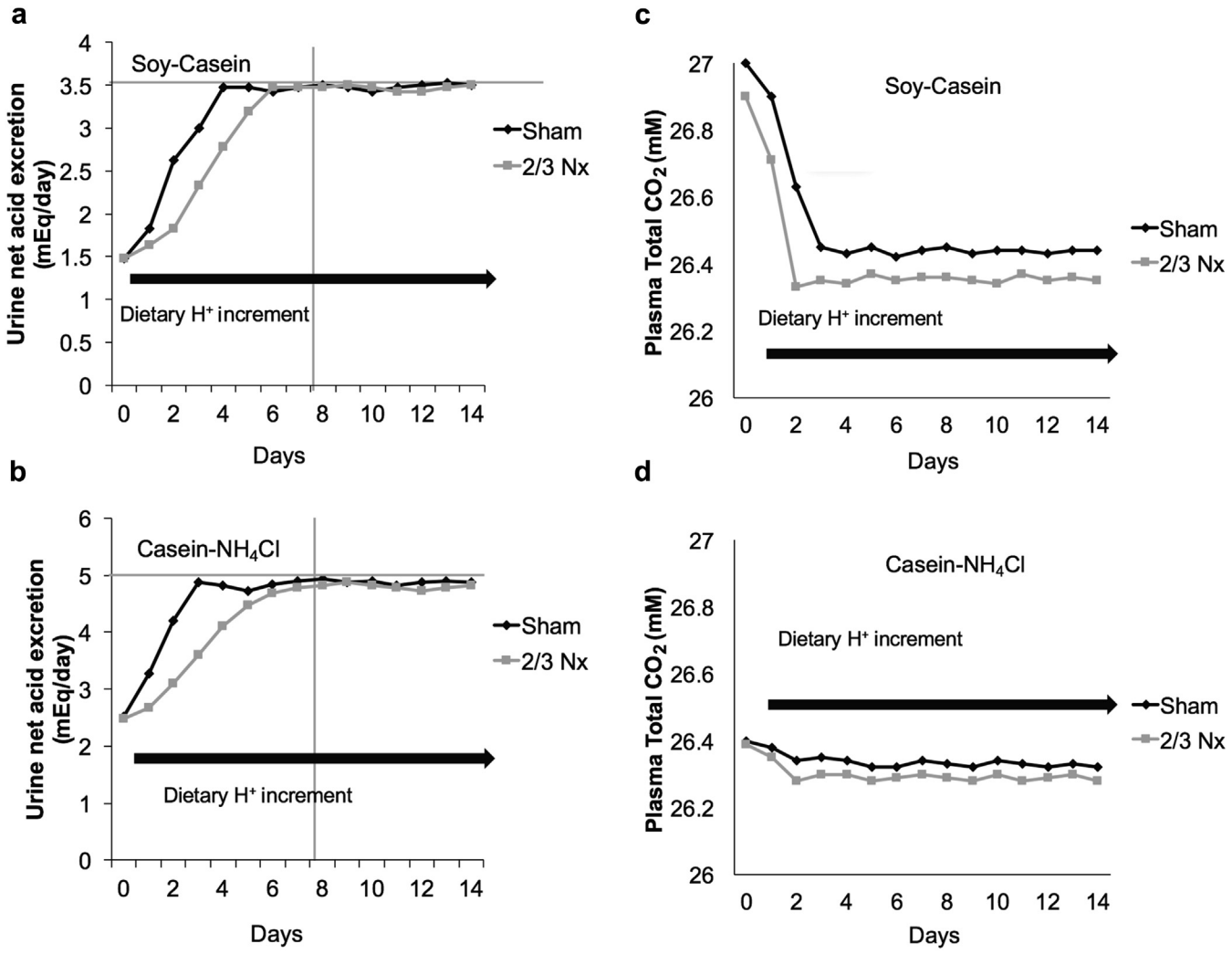

Figure 1 | Time course to attain steady state in response to 14 days of a continuous increment in dietary acid (H^+) provided as casein (H^+-producing) substituted for (a,c,e) soy (base-producing) diet (Soy-Cas) diet or as (b,d,f) baseline casein diet then casein with added NH_4Cl (Cas-NH_4Cl) for (a,b) daily urine net acid excretion, (c,d) plasma total CO_2, and (e,f) net H^+ addition to microdialysate for sham and 2/3 nephrectomized (Nx) animals. (**a,b**) The upper horizontal gray line represents the maximum, steady-state urine net acid excretion achieved for Nx and sham animals. The horizontal black line with the right arrowhead in all panels indicates duration of the dietary H^+ increment, beginning on day 1. For each dietary protocol, $n = 6$ animals each for Nx and sham. (Continued)