Urinary ammonia and long-term outcomes in chronic kidney disease

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Recent studies suggest that alkalinizing treatments improve the course of chronic kidney disease (CKD), even in patients without overt metabolic acidosis. Here, we tested whether a decreased ability in excreting urinary acid rather than overt metabolic acidosis may be deleterious to the course of CKD. We studied the associations between baseline venous total CO_2 concentration or urinary ammonia excretion and long-term CKD outcomes in 1065 patients of the NephroTest cohort with CKD stages 1–4. All patients had measured glomerular filtration rate (mGFR) by ^{51}Cr-EDTA renal clearance. Median mGFR at baseline was 37.6 ml/min per 1.73 m^2. Urinary ammonia excretion decreased with GFR, whereas net endogenous acid production did not. After a median follow-up of 4.3 years, 201 patients reached end-stage renal disease (ESRD) and 114 died before ESRD. Twenty-six percent of the patients had mGFR decline rate greater than 10% per year. Compared with patients in the highest tertile of urinary ammonia excretion, those in the lowest tertile had a significantly increased hazard ratio for ESRD, 1.82 (95% CI, 1.06–3.13), and a higher odds ratio of fast mGFR decline, 1.84 (0.98–3.48), independent of mGFR and other confounders. Patients in the lowest tertile of venous total CO_2 had significantly increased risk of fast mGFR decline but not of ESRD. None of these biomarkers was associated with mortality. Thus, these results suggest that the inability to excrete the daily acid load is deleterious to renal outcomes.

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In chronic kidney disease (CKD), the ability of the kidney to excrete the daily acid load declines[1–3] and the prevalence of metabolic acidosis increases with the severity of the disease.[4,5] The results of prospective studies suggest that alkali-based therapy efficiently delays CKD progression in patients with[6,7] or without overt metabolic acidosis.[8,9] In cohort studies, a low plasma bicarbonate concentration is associated with increased mortality.[10–12] However, whether a low plasma bicarbonate level is a risk factor for a faster decline in the glomerular filtration rate (GFR) remains uncertain.[11,13–15] Scialla *et al.*[16] have recently studied in the AASK trial the association between net endogenous acid production (NEAP), the balance between fixed acid and alkali precursors in diet, and CKD progression. A higher NEAP was associated with a significantly faster decline in GFR. This could indicate that the daily acid load itself and/or the inability of the kidney to cope with the acid load is a risk factor for disease worsening in CKD patients. So far, most of the published studies have focused on the link between plasma bicarbonate level, a surrogate marker of the status of acid balance, and the decline in GFR. None has tested whether the impaired ability of the kidney to excrete the daily net acid load is an independent risk factor for the progression of CKD.

Kidneys excrete the daily acid load mainly by generating and excreting ammonia (ammonia refers to the sum of NH_4^+ and NH_3; as NH_3 concentration is negligible in urine, ammonia concentration virtually equals that of NH_4^+) and to a lesser extent by excreting hydrogen ions as titratable acid (TA). Urinary excretion of ammonia decreases in parallel to GFR, whereas TA excretion is maintained until very advanced CKD stages.[2,3,17]

We made the assumption that a low urinary ammonia excretion might be an earlier marker of the propensity to develop a positive acid balance (and hence metabolic acidosis) compared with plasma bicarbonate concentration. Therefore, we calculated the balance of fixed acid and compared the associations between plasma total CO_2 (tCO_2) level or urinary ammonia excretion and long-term outcomes including the rate of decline in GFR, the incidence of end-stage renal disease (ESRD), and mortality, in the NephroTest study cohort.

RESULTS

Baseline characteristics of the study cohort

Patients' mean age was 60 ± 15 years and most were men (70.6%) (Table 1). Eighty per cent were on angiotensin-converting enzyme inhibitor/angiotensin receptor blockers treatment at baseline. Median measured glomerular filtration rate (mGFR) was 37.6 ml/min per 1.73 m^2 (interquartile range (IQR) 27.6–51.4). Fifty-four percent of the patients had CKD stage 3 and 31% had stage 4. Mean venous tCO_2 concentration was 26 ± 3 mmol/l, and only 8.3% of the patients had overt metabolic acidosis (defined by a venous tCO_2 concentration below 22 mmol/l). Median NEAP was 56.3 mEq/24 h (IQR 44.4, 73.7). Median urinary 24-h ammonia excretion was 1.70 mEq/mmol creatinine (IQR 1.17–2.42) and median fasting ammonia concentration was 12.3 mEq/l (IQR 7.5–20.0). NEAP was not associated with mGFR, whereas 24-h ammonia excretion and fasting urinary ammonia concentration significantly decreased with decreasing baseline mGFR (Figure 1). Fasting urinary pH was inversely related to urinary ammonia excretion. No relation between body mass index (BMI), urinary phosphate or urinary urea nitrogen, and 24-h urinary ammonia excretion was observed in our study population.

Cross-sectional analysis of acid balance in CKD patients

In a subset of our study population ($n = 160$, Table 1), we measured 24-h net acid excretion (NAE) and calculated acid balance (Figure 2). Both urinary ammonia and TA excretions decreased with mGFR ($r = 0.30$, $P < 0.0001$ and $r = 0.16$, $P = 0.05$, respectively). NAE also significantly decreased with mGFR ($r = 0.22$, $P = 0.004$), mainly because of the decrease in ammonia excretion. Acid balance was not

Table 1 | Population characteristics, mean ± s.d., median (Q1–Q3), or % (*n*)

	All patients	Sub-group of patients with ≥ 2 visits	Sub-group of patients with 1 visit	Sub-group of patients with acid balance
N	1065	711	354	160
Demographic				
Men	70.6 (752)	69.9 (497)	72.0 (255)	70.6 (113)
Age, year	60.1 ± 14.9	58.9 ± 14.8	62.4 ± 14.7	62.2 ± 13.9
Sub-Saharan African origin	11.5 (118)	11.4 (80)	11.5 (38)	9.4 (15)
BMI	26.5 ± 5.0	26.2 ± 4.9	27.0 ± 5.0	26.1 ± 4.1
Systolic/Diastolic BP, mm Hg	138 ± 21/75 ± 12	137 ± 21/75 ± 11	139 ± 21/75 ± 12	139 ± 21/76 ± 11
Diabetes	29.0 (309)	27.0 (192)	33.1 (117)	18.1 (29)
History of cardiovascular disease	20.5 (216)	18.7 (131)	24.1 (85)	14.5 (23)
History of smoking, past/current	35.4 (377)/16.0 (170)	36.1 (257)/17.0 (121)	33.9 (120)/13.8 (49)	40.6 (65)/13.1 (21)
Renal function				
mGFR, ml/min per 1.73 m^2	37.6 (27.6–51.4)	37.7 (27.6–50.6)	37.4 (27.5–53.4)	39.1 (26.7–49.5)
≥60	15.4(164)	14.3 (102)	17.5 (62)	13.8 (22)
45–59	20.8(221)	21.7 (154)	18.9 (67)	21.3 (34)
30–44	32.7(348)	33.9 (241)	30.2 (107)	31.9 (51)
15–29	31.2(332)	30.1 (214)	33.3 (118)	33.1 (53)
ACR, mg/mmol	9.0 (1.8–47.9)	9.8 (2.0–44.0)	7.5 (1.7–60.4)	7.2 (1.4– 31.7)
PCR, mg/mmol	30.0 (11.1–110.0)	30.0 (11.8–102.3)	29.0 (10.0–120.0)	18.3 (9.9–60.2)
Acid-base homeostasis				
Fasting urinary NH_4 concentration, mEq/l	12.3 (7.5–20.0)	12.1 (7.3–19.8)	13.0 (7.6–20.7)	13.6 (8.7–18.9)
Fasting urinary osmolality, mOsm/kgH_2O	487 ± 139	489 ± 138	483 ± 143	472 ± 134
24-h urinary NH_4 excretion, mEq/24 h	18.5 (12.1–27.2)	18.2 (12.0–26.6)	18.9 (12.4–27.7)	20.7 (15.7–29.1)
24-h urinary creatinine excretion, mmol/24 h	11.6 ± 4.3	11.8 ± 4.2	11.1 ± 4.4	12.9 ± 5.4
24-h urinary NH_4/creatinine mEq/mmol	1.70 (1.17–2.42)	1.66 (1.11–2.33)	1.80 (1.28–2.53)	1.74 (1.32–2.37)
Venous total CO_2, mmol/l	26.0 ± 3.0	26.0 ± 2.9	26.1 ± 3.1	25.9 ± 3.0
Acidosis, $tCO_2 < 22$ mmol/l	8.3 (88)	7.5 (53)	9.9 (35)	8.8 (14)
Treatments				
Loop diuretics treatment	33.9 (361)	32.9 (234)	35.9 (127)	18.8 (30)
Phosphate binders treatment	1.0 (11)	1.1(8)	0.8(3)	0.6 (1)
ACEi or ARB treatment	80.2 (854)	82.7 (588)	75.1 (266)	91.3 (146)

Abbreviations: ACEi, angiotensin-converting enzyme inhibitor; ACR, urinary albumin-creatinine ratio; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; mGFR, measured glomerular filtration rate; PCR, urinary protein-creatinine ratio; tCO_2, total CO_2.