Correlation of Urine Ammonium and Urine Osmolal Gap in Kidney Transplant Recipients

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Low urinary ammonium (NH_4^+) excretion is a risk factor for kidney failure and death in CKD (1). Few clinical laboratories measure urine NH_4^+, limiting clinical application. The urinary anion gap (UAG) and urine osmolal gap (UOG) have been used to estimate urine NH_4^+. Unfortunately, the UAG had a poor correlation with NH_4^+ in CKD unless urine sulfate and phosphate were included in the calculation (2). Thus, unmeasured anions significantly affect UAG's performance as an NH_4^+ surrogate. Less is known about the utility of the UOG as an NH_4^+ surrogate. The UOG is determined by subtracting the calculated urine osmolality (Osm_{CALC})—determined from concentrations of urine Na^+, K^+, urea nitrogen, and glucose—from the measured urine osmolality (Osm_{MEAS}). A parallel problem could occur for the UOG as with UAG because of unmeasured cations such as magnesium and calcium, as considerable interindividual differences in these cations have been observed (3,4). The UOG has been reported to have strong correlation with NH_4^+ in persons with diabetic ketoacidosis, in patients with CKD both with and without metabolic acidosis (MA), and in healthy individuals without MA (5,6). However, others have reported poor agreement between UOG and NH_4^+ (7). Crude inspection of data from these studies revealed that 10%–20% of individuals had a negative UOG (5–7), which is troublesome as the UOG conceptually represents unmeasured osmoles and should theoretically always have positive values. The negative UOG might be because the Osm_{CALC} assumes that Na^+ and K^+ are completely dissociated from their accompanying anions in urine, which may be incorrect because the osmotic coefficient (φ) of molecules such as NaCl are influenced by the osmolality of, and other constituents in the solution (8,9). If incompletely dissociated, doubling Na^+ and K^+ will overestimate their contributions to the urine osmolality, which may also render the UOG as a poor NH_4^+ surrogate.

We determined the correlation between urine NH_4^+ and UOG in 70 overnight urine collections (range, 6–12 hours) obtained from 28 kidney transplant recipients in a randomized study to determine the effect of sodium bicarbonate on kidney injury markers (Clinicaltrials.gov identifier NCT01225796). Up to three collections were obtained from each individual over 6 months. Osm_{CALC} was determined using the equation [2(Na^+ + K^+ (mEq/L))+ urea nitrogen (mg/dl)/2.8+ glucose (mg/dl)/18]. UOG was calculated by subtracting Osm_{CALC} from Osm_{MEAS} (5); the latter was determined by freezing point depression. Urine NH_4^+ was measured by the formalin titration method (10). The mean (SD) age of the study sample was 48 (14) years, 16 (57%) were women, and 27 (96%) were white. Mean (SD) eGFR was 68 (16) ml/min per 1.73 m^2. Sixteen measurements were performed in the setting of MA (serum bicarbonate <22 mEq/L). Table 1 shows laboratory data for the entire sample and the MA subset. In the entire sample, the mean (SD) UOG was −29 (109) mOsm/L and 28 (40%) had a negative UOG. In the MA subset, five out of 16 (31%) had a negative UOG and the mean (SD) UOG was −21 (85) mOsm/L. There was no correlation between UOG and urine NH_4^+ concentration in the entire cohort, in the MA subset (Figure 1), or in the 16 measurements performed at baseline ($r=-0.05$), before treatment with sodium bicarbonate.

We posit that the poor correlation between UOG and NH_4^+ may be because Na^+ and K^+ incompletely dissociate from their accompanying anions in urine.

Table 1. Serum and urine laboratory characteristics among study participants

Laboratory Data	All Measurements, $n=70$	Metabolic Acidosis, $n=16$
Serum, mEq/L		
Sodium	139 (3)	139 (2)
Potassium	4.3 (0.4)	4.1 (0.4)
Chloride	105 (3)	107 (2)
Bicarbonate	23 (3)	20 (1)
Urine		
Ammonium, mEq/L	16 (12)	19 (14)
Sodium, mEq/L	78 (43)	80 (46)
Potassium, mEq/L	21 (14)	19 (13)
Urea nitrogen, mg/dl	535 (369)	572 (355)
Glucose, mg/dl[a]	103 (205)	29 (62)
Measured osmolality, mOsm/kg	361 (234)	382 (245)
Calculated osmolality, mOsm/L	390 (229)	403 (232)
Osmolal gap, mOsm/L	−29 (109)	−21 (85)

Data are presented as mean (SD).
[a]Shown are the mean (SD) glucose concentrations for samples in which glucose was detected; $n=19$ for all measurements and $n=7$ for metabolic acidosis.

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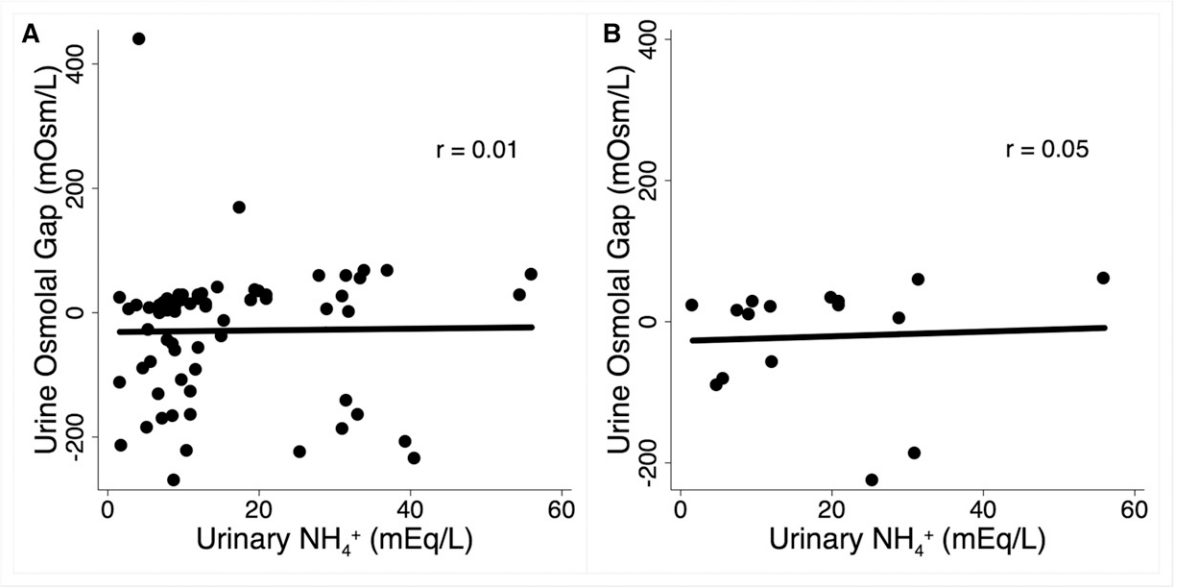

Figure 1. | Urine osmolal gap is a poor estimate of urine NH_4^+ concentration. Urinary ammonium versus urine osmolal gap in (A) all measurements (n=70) and (B) the subset with metabolic acidosis (n=16). NH_4^+, ammonium.

Therefore, doubling Na^+ and K^+ overestimated their contributions to the urine osmolality, as evidenced by a negative UOG in 40% overall and in one third with MA in our sample, resulting in an UOG that unreliably estimates unmeasured osmoles, including NH_4^+. In NaCl solutions with osmolality in the physiologic range of serum, the φ of NaCl is 0.93, indicating that 7% of Na^+ is not dissociated from Cl^- (8,9). Furthermore, the φ of NaCl decreases with increasing osmolality (φ=0.91 at 600 mOsm/kg) and is affected by other constituents in the solution (8). In fluids with many solutes and a wide range of osmolalities, such as urine, the dissociation of Na^+ and K^+ from their accompanying anions is unlikely to be complete and is difficult to predict. With respect to calculating serum osmolality, doubling Na^+ works reasonably well because the φ of 0.93 is partly offset by the water content of plasma, which is 93% (9). Including unmeasured urinary cations such as calcium and magnesium would raise Osm_{CALC}, resulting in an even lower UOG. Hence, excluding urinary cations is not the main reason why the UOG unreliably estimated NH_4^+ in our sample.

The poor correlation between UOG and NH_4^+ shown here is different from some prior studies, and we observed a higher proportion with a negative UOG (5,6); the reasons for these findings are unclear. We do not think that the discrepancy is related to kidney transplantation, as a negative UOG has been observed in healthy individuals and in CKD (5,6). In another study evaluating the correlation between Osm_{CALC} and Osm_{MEAS} in five European cohorts, a large proportion of individuals had Osm_{CALC} higher than Osm_{MEAS}. For example, mean Osm_{CALC} was 7 mOsm/L higher than mean Osm_{MEAS} in the largest cohort (n=2305) (11). Hence, the large proportion with a higher Osm_{CALC} than Osm_{MEAS} is not unique to our study, and supports the notion that the difference between Osm_{CALC} and Osm_{MEAS} is an unreliable estimate of unmeasured osmoles, including NH_4^+.

In summary, we found no correlation between UOG and NH_4^+. We believe this is because of an incorrect assumption that Na^+ and K^+ completely dissociate from their accompanying anions in urine. These factors render the UOG an unreliable estimate of unmeasured urinary osmoles, including NH_4^+.

This study was approved and overseen by the Institutional Review Board of the University of Utah and was performed under the principles embodied in the Declaration of Helsinki. The clinical and research activities being reported are consistent with the Principles of the Declaration of Istanbul as outlined in the "Declaration of Istanbul on Organ Trafficking and Transplant Tourism."

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Disclosures

None.

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