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Urine pH and NH4+ as Biomarkers of Kidney Disease

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Background: Urinary acidification is a crucial aspect of kidney tubular function that helps maintain the body's acid-base balance. The primary component of net acid excretion is ammonium (NH_4^+), which is formed when hydrogen ions (H^+) secreted from the tubule combine with the major urinary buffer, ammonia (NH_3). Consequently, both H^+ and NH_3 influence urine NH_4^+ excretion. While urine NH_4^+ is the standard measure of renal acid excretion, urine pH is also valuable for assessing urinary acidification, as it reflects the extent of H^+ secretion from the collecting duct. Urine pH can be accurately measured using a pH meter, and urine NH_4^+ can be quantified through an enzymatic method adapted from plasma ammonia assays. Summary: A low urinary NH_4^+ excretion < 40 mmol/day is a hallmark of renal tubular acidosis (RTA) and is essential for excluding non-renal causes of hyperchloremic metabolic acidosis. Urine pH is valuable in the differential diagnosis of RTA; Type 1 distal RTA is characterized by a urine pH > 5.3, while Type 4 RTA is characterized by a urine pH < 5.3. In Type 2 proximal RTA, urine pH is variable and depends on the serum HCO_3^- level. Low urine NH_4^+ levels in patients with chronic kidney disease (CKD) may indicate that acid is retained in the kidneys, leading to tubulointerstitial inflammation and fibrosis. A post-hoc analysis of the AASK trial found that low urinary NH_4^+ excretion < 20 mmol/day was associated with end-stage kidney disease (ESKD) even before metabolic acidosis developed. In the NephroTest cohort, lower tertile urinary NH_4^+ excretion was linked to ESKD during a median follow-up of 4.3 years. Typically, CKD patients exhibit acidic urine pH, indicative of renal acid retention. A Japanese observational study found that lower urine pH was associated with the incidence of CKD. When urine pH was considered alongside urine NH_4^+, the prognostic value for CKD progression was significantly enhanced. Key Messages: Urine pH serves as a valuable tool for the differential diagnosis of RTA, but direct measurement of urine NH_4^+ is essential. In CKD, low urine NH_4^+ levels may indicate a diminished capacity for acid excretion or suggest renal acid retention, which can contribute to the progression of CKD. Additionally, the low urine pH

observed in CKD reflects renal acid retention and may be associated with both incident and prevalent CKD. The integration of urine pH and NH_4^+ measurements would enhance the predictability of CKD progression.

Keywords: acidosis, biomarker, chronic kidney disease, urine ammonium, urine pH