Effect of metabolic acidosis on progression of chronic kidney disease

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METABOLIC ACIDOSIS, TRADITIONALLY defined as a reduction in serum HCO₃⁻ concentration ([HCO₃⁻]) often associated with a detectable reduction in blood pH, is a common accompaniment of progressive chronic kidney disease (CKD) (7). The metabolic acidosis even when mild is not without consequences: increased degradation of muscle protein with muscle wasting (1), reduced albumin synthesis with resultant hypoalbuminemia (2), production or exacerbation of bone disease along with stunting of growth in children (8, 9), and impairment in glucose tolerance (11), are among its major consequences. The mechanisms underlying these effects appear to be complex, involving several different pathways, although treatment of the metabolic acidosis with base usually lessens the severity of or completely reverses these abnormalities (8).

Studies performed in animals and humans have confirmed that metabolic acidosis is also a risk factor for progression of CKD (3, 8, 12–14). Administration of either citrate (5) or sodium bicarbonate (12) to rats with CKD decreased the severity of tubulointerstitial disease and/or the decline in glomerular filtration rate compared with controls receiving sodium chloride. Also, the chronic administration of base to Han.S-PRD rats, an animal model of polycystic kidney disease, decreased the cystic enlargement and prevented development of interstitial inflammation, chronic fibrosis, and severe renal failure (18).

Studies of a cohort of patients from a single medical center revealed that compared with those with a serum [HCO₃⁻] of 25–26 meq/l, the presence of a serum [HCO₃⁻] <22 meq/l was associated with a 54% increased hazard of progression of CKD (17). Moreover, the administration of bicarbonate to individuals with CKD of diverse etiology and metabolic acidosis not only slowed the progression of CKD (the decline in GFR was less than half of the control group who received sodium chloride) (3), but the number of individuals developing end-stage renal disease was reduced significantly.

Similarly, in patients with hypertensive nephrosclerosis [mean glomerular filtration rate (GFR) of 33 ml/min] and mild metabolic acidosis (mean serum [HCO₃⁻] of 20 meq/l), provision of citrate for 2 yr slowed the decline in GFR in association with a rise in serum [HCO₃⁻] to 23 meq/l (15).

The mechanism(s) underlying the decline in GFR with metabolic acidosis was examined in rats by Nath et al. (12). These investigators provided evidence for a link between acidosis-induced stimulation of renal ammonia production by the kidney and progressive tubulointerstitial injury, an effect initiated by activation of the complement cascade. Others have suggested that the stimulation of new bicarbonate production in the kidney alkalinizes the interstitium thereby encouraging precipitation of calcium in the kidney and renal injury (6).

Finally, studies in rats using the remnant kidney model of CKD indicated that the decline in GFR was mediated in part by the actions of excess aldosterone and endothelin, the latter acting via activation of endothelin A receptors (14, 20, 22).

The studies cited above suggest that metabolic acidosis when present can contribute to progression of CKD, and therefore under these circumstances base treatment is warranted. However, the magnitude of hypobicarbonatemia present in patients with CKD is variable and some patients can actually have a normal serum [HCO₃⁻] even in the face of severe renal failure (19). Therefore, the threshold for initiation of base therapy in patients with CKD is important to establish. Should patients with CKD, but a serum [HCO₃⁻] within the normal range, be treated with base?

To address this question, Wesson et al. (22) examined the effect of alkali therapy on the progression of renal failure in rats with ⅔ nephrectomy who had CKD without significant hypobicarbonatemia. Alkali therapy slowed the decline in GFR, an effect which was related to increased endothelin and aldosterone production. Renal hydrogen content in these rats was greater than that of sham-operated controls; observations consistent with tissue acid retention despite the absence of a reduced serum [HCO₃⁻]. Moreover, subsequent studies in humans with hypertensive nephrosclerosis and early CKD (mean GFR of 75 ml/min) and a normal serum [HCO₃⁻] (mean 26 meq/l) (10) revealed that administration of sodium bicarbonate for 5 yr also preserved GFR.

In an issue of the American Journal of Physiology Renal Physiology, Wesson et al. (21) examined whether humans with stage 2 CKD (GFR 60–90 ml/min) without macroalbuminemia, but not hypobicarbonatemia had evidence of hydrogen retention and increased levels of endothelin-1 and aldosterone compared with those with a GFR of >90 ml/min. They found higher plasma levels of endothelin-1 and aldosterone in individuals with CKD 2 compared with those with a GFR >90 ml/min, and levels of these hormones were reduced after 30 days of bicarbonate therapy. Because they were not able to directly assess the acid content of the kidney (as had been done in animal studies), they indirectly evaluated acid content of tissues by the impact of a bicarbonate bolus on serum [HCO₃⁻] and urinary net acid excretion. The results seem to suggest that tissue acid retention was greater in the CKD 2 group. Of course, certain assumptions were made including similar total body buffering capacity in both groups that are worth confirming to render greater support to this hypothesis. However, based on their previous elegant studies and those of other investigators, it is not unreasonable to expect hydrogen retention in humans as renal function declines even if serum [HCO₃⁻] does not appear to be perturbed.

Therefore, in both animals and humans it appears that as renal function and the ability to eliminate the daily acid load

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decline, acid retention occurs, which secondarily stimulates endothelin and aldosterone production that contributes to a further decline in GFR. The effects of excess endothelin and aldosterone on the kidney might not be the only mechanism by which metabolic acidosis contributes to a decline in GFR: Provision of dietary alkali better preserves GFR than administration of endothelin and aldosterone receptor antagonists (22).

Interestingly, these studies confirm the beneficial effects of base therapy on other organ systems in the absence of metabolic acidosis: Base therapy improves nitrogen balance (4) and bone metabolism (16) in subjects with normal renal function even in the absence of detectable hypobicarbonatemia. Furthermore, these studies that show that base therapy is beneficial even in the absence of hypobicarbonatemia raise the issue of whether the definition of metabolic acidosis should be expanded to include any process in which there is a net gain of $H^+$ in body fluids.

The current study is a natural extension of the previous research by this group. The cohort of studies accrued over the last 7 yr or so has translated findings from animal studies into the clinical sphere which have great relevance to the treatment of individuals with CKD. Although it might be too early to recommend base therapy for all individuals with some degree of renal impairment (which could be present in as much as 11% of the population) without demonstrating that base therapy is free of important adverse effects, these interesting results suggest this modality of treatment deserves important consideration. Moreover, since the daily acid load is primarily dependent on the magnitude and type of protein ingested, restricting the acid-inducing dietary protein might be complementary to base therapy in preserving renal function.

Finally, since findings based on studies performed in vitro or in vivo in animals are not always confirmed by similar studies in humans, there is a great need for rapid examination of hypotheses derived from animal studies using human subjects. It is exemplary when the same group is able to perform basic and clinical studies and is a perfect model of translational research that should be copied by other investigators.

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DISCLOSURES

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REFERENCES