Is Dietary Acid a Modifiable Risk Factor for Nephropathy Progression?

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Treating metabolic acidosis in chronic kidney disease (CKD) as per current KDOQI guidelines appears to slow CKD progression [1, 2] and is an added reason to treat CKD-related metabolic acidosis when serum total $[\text{HCO}_3^-]$ is <22 mEq/l [3]. This recommendation is based on ‘evidence and opinion’ [3] but cautioned that ‘more research is needed on the long-term effects of correcting acidemia on clinical outcomes...’ [3]. Since these recommendations were issued, epidemiologic studies have shown that CKD patients with ranges of plasma $[\text{HCO}_3^-]$ that include those >22 mEq/l are associated with a greater risk for and a faster rate of glomerular filtration rate (GFR) decline [4–6]. In addition, NaHCO_3 slowed the rate of estimated GFR (eGFR) decline in individuals with reduced eGFR but without metabolic acidosis [7]. Animal [8, 9] and human [10] studies support that reduced GFR is associated with acid retention, even with normal plasma $[\text{HCO}_3^-]$. Furthermore, ameliorating this apparent acid retention in animals with reduced GFR but normal plasma $[\text{HCO}_3^-]$ by adding dietary alkali or by eating diets that are base-producing rather than acid-producing slows GFR decline [8, 9]. Proposed mediators of acid-induced nephropathy progression include complement activation

[11], endothelin [10], and aldosterone [10]. Together, these studies suggest that patients with reduced GFR but no metabolic acidosis nevertheless have acid retention that might mediate nephropathy progression. Reducing acid retention with less acid-producing diets that lower net endogenous acid production (NEAP) might slow nephropathy progression in patients with reduced GFR even without metabolic acidosis.

Diets of those living in industrialized societies are largely acid-producing due to high intake of acid-producing animal protein and comparatively low intake of base-producing proteins from fruits and vegetables [12]. These acid-producing diets increase NEAP [13] and typically do so without inducing frank metabolic acidosis in individuals with relatively preserved GFR, but might induce frank metabolic acidosis in those with very low GFR [14]. Diets higher in base-producing protein like fruits and vegetables reduce NEAP [13, 14] and reduce kidney injury in subjects with reduced eGFR without metabolic acidosis [15]. In support of the importance of NEAP in nephropathy progression, high NEAP was associated with faster GFR decline in individuals with reduced GFR [16], identical to the data of Kanda et al. [17] in this issue of *Amer-*

ican Journal of Nephrology in a different population. Because total dietary protein reduction did not slow GFR decline in a large prospective study [18], data to date support that the dietary protein effect on NEAP (i.e. whether acid- or base-producing) more importantly determines nephropathy progression than amount of dietary protein.

Kanda et al. [17] make at least two new and important contributions to this evolving story of the apparent benefit of lower NEAP on nephropathy progression in patients with reduced GFR. First, the benefit was shown in an exclusively elderly population (all were ≥ 60 years of age with a mean age of 70 years), an age group that is at the highest risk for CKD and its progression [19]. These data support further studies to determine if prospectively reducing NEAP slows nephropathy progression in this comparatively high-risk group, one that has been comparatively understudied despite its high CKD prevalence and risk for progression to complete kidney failure [19]. Second, the benefit was shown in patients already on a low-protein diet (they were prescribed 0.6–0.8 g/kg body weight/day and had measured intake of 0.8–0.9 g/kg body weight/day). Despite achieving a level of total protein intake that was likely less than that ingested by CKD patients in most industrialized societies, the investigators showed detrimental effects of higher than lower NEAP on nephropathy progression within this range of NEAP that is likely lower than that for most CKD patients. The data additionally emphasize the greater importance of the character of ingested protein, i.e. whether acid- or base-inducing, rather than total protein on nephropathy progression. Unfortunately, Kanda et al. [17] did not report the types and amounts of dietary protein, but it seems safe to assume that those with higher NEAP ate a comparatively higher proportion of acid-producing compared to base-inducing protein.

The subjects reported by Kanda et al. [17] had CKD stages 3–5 eGFR with a mean eGFR of 23 ml/min/1.73 m², a level that is often associated with metabolic acidosis [20]. Nevertheless, mean serum [HCO₃] for their cohort was >25 mEq/l, consistent with the comparatively (i.e. compared to more typical patients in industrialized societies with similar eGFR) low dietary acid intake discussed earlier because patients with comparable eGFR in other settings would likely have frank metabolic acidosis [14, 20]. Although some subjects were prescribed oral NaHCO₃, its intake or level of serum [HCO₃] were not associated with nephropathy progression.

Although the study by Kanda et al. [17] makes important insights as discussed, its limitations support the need for follow-up studies to help address the important ques-

tion as to whether reduced NEAP should be standard care for subjects with reduced eGFR. Their study was observational and retrospective rather than interventional and prospective. As mentioned, they also did not report important details like the character (animal or plant source, acid- or base-producing) of ingested protein. It would have also been helpful to have compared NEAP between patients who followed the recommended diet with those with less dietary compliance. Finally, we would like to have known serum the pH and PCO₂ to better assess patient acid-base status. Despite these limitations, Kanda et al. [17] have helped identify important research directions that will lead to much-needed additions to available kidney protective therapies.

CKD is an increasing health burden, evidenced by an increase in CKD-related deaths and in years of life lost due to CKD between 1990 and 2010 [21]. This analysis supported diet as the single largest CKD-related death and disability risk factor [21], but further studies will better identify important dietary aspects that contribute to nephropathy progression. Analysis of contributing factors to CKD progression due to type 2 diabetes mellitus, the single largest CKD cause in the USA, showed that 'healthier' diets lower risk for nephropathy progression due to type 2 diabetes mellitus [22]. The analysis suggested that diets high in fruit, fruit juices, and leafy green vegetables reduce the risk for progression of CKD due to type 2 diabetes mellitus [22]. Because such diets reduce NEAP [13, 14], the data reported by Kanda et al. [17] are consistent with these two studies.

Future Research Directions

If larger-scale, prospective studies confirm that low NEAP slows nephropathy progression, additional questions need to be answered. Are reducing NEAP by adding alkali such as NaHCO₃ or substituting base-producing for acid-producing dietary protein equally effective? When in the course of CKD should efforts to reduce NEAP begin? Should NEAP begin when GFR reduction is associated with metabolic acidosis, when GFR is reduced but before metabolic acidosis appears, or with signs of kidney injury, such as albuminuria, even when GFR and acid-base status are normal? Answers to these important questions will not only lead to better treatment strategies, but more importantly, to preventive strategies for CKD.

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