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Nutritional Management of Chronic Kidney Disease

TO THE EDITOR: In their review article on the nutritional management of chronic kidney disease, Kalantar-Zadeh and Fouque (Nov. 2 issue)[1] make some statements about daily acid production resulting from bicarbonate losses in the gut that may contain errors, in my view. Normally, there are no losses of bicarbonate in the gut unless a person has diarrhea. Furthermore, although the metabolism of carbohydrates and fats generates organic acids, these are eventually converted back to bicarbonate and do not add net acid to the body unless the organic anions are excreted in urine.

The authors advise a daily dietary protein intake of 1.2 to 1.4 g per kilogram of body weight in patients undergoing dialysis. In my opinion, this would provide excessive protein consumption that is unsupported by data and, therefore, not warranted. A protein intake of approximately 1 g per kilogram per day has been reported as being sufficient to maintain a positive nitrogen balance in stable patients undergoing dialysis.[2] The idea that patients undergoing dialysis should have a higher protein intake derives from observational data that have shown an association between higher protein intake and better outcome and that have not been tested in interventional trials[3] and from the belief that dialysis is a catabolic event beyond dialytic losses of amino acids and proteins.[4,5]

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Kalantar-Zadeh and Fouque discuss an epidemiologic study in which higher urinary potassium excretion (as a proxy for intake) was associated with a higher risk of progression of chronic kidney disease.[1] However, there is accumulating evidence from several studies that indicates otherwise (Table S1 in the Supplementary Appendix, available with the full text of this letter at NEJM.org). In the studies listed in the table, higher urinary potassium excretion was associated with better renal outcomes or lower all-cause mortality but not with hyperkalemia. Experimental data also suggest that potassium is renoprotective by reducing blood pressure, vascular calcification, and inflammation.[2-4] An ongoing multicenter, double-blind, placebo-controlled study, in which the effect of potassium supplementation on renal outcomes is being evaluated in patients with stage 3 or 4 chronic kidney disease (ClinicalTrials.gov number, NCT03253172), is investigating whether potassium repletion is renoprotective in patients with chronic kidney disease and whether repletion outweighs the risk of hyperkalemia. Because patients with chronic kidney disease generally consume a low-potassium diet (approximately 2 g per day), supplementation in the study (1.5 g per day) is provided

to achieve the recommended daily potassium intake (3.5 g per day).[5]

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No potential conflict of interest relevant to this letter was reported.

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TO THE EDITOR: Kalantar-Zadeh and Fouque address the possible, although still debated, role of restricting dietary protein intake in reducing proteinuria and slowing the progression of chronic kidney disease. Not discussed, however, is whether there is a role for low-protein diets in the modern era of treatment with angiotensin-converting–enzyme (ACE) inhibitors and angiotensin-receptor blockers (ARBs). Data regarding the additive effect of a low-protein diet and these two drug classes on proteinuria are limited.[1,2] It is unclear how low-protein diets compare with appropriate use of ACE inhibitor or ARB treatment or whether the combination of a low-protein diet and drugs that block the renin–angiotensin–aldosterone system confers any added benefit in slowing the progression of chronic kidney disease. Low-protein diets may alleviate metabolic disturbances in some patients with chronic kidney disease, but whether such diets are effective in patients who are already receiving medications that interfere with the renin–angiotensin–aldosterone system is unknown.

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No potential conflict of interest relevant to this letter was reported.

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THE AUTHORS REPLY: Uribarri writes that there is normally no fecal bicarbonate excretion. However, in one stool-measurement study,[1] the mean (±SD) fecal bicarbonate excretion in healthy adults was 34.6±12.3 mmol per liter, and another study reported a value of 30 mmol per liter.[2] Hence, the minimum daily loss of gastrointestinal bicarbonate is 10 to 15 mmol per day. The incomplete oxidation of fats and carbohydrates leads to the generation of ketoacids and lactic acid. The bulk of these acids is recycled, but the resultant net hydrogen ion residue is added to the daily acid production.

We recommended a daily dietary protein intake of 1.0 g or less per kilogram in persons at high risk for chronic kidney disease and 0.6 to 0.8 g per kilogram in those with more advanced stages of chronic kidney disease or proteinuria, including patients who are transitioning to dialysis therapy. For patients undergoing established maintenance dialysis who have minimal residual kidney function and undergo hemodialysis three times or more per week, we recommend a higher daily dietary protein intake of more than 1.0 g per kilogram, which is a range that appears to be associated with the lowest mortality.[3] This amount is consistent with the average protein intake in the general population.

In response to Hoorn et al.: in our review article, we discuss that overzealous restrictions in dietary potassium intake should be avoided, since many potassium-rich foods, such as fresh fruits and vegetables with high fiber and vitamin content and low acidogenicity, are heart-healthy and less atherogenic than most low-

potassium foods. As shown in Table 2 of our article (available at NEJM.org), we reiterate the recommended dietary allowance of potassium of 4.7 g per day both in persons at high risk for chronic kidney disease and in patients with mild-to-moderate chronic kidney disease (stage 1, 2, or 3). However, in patients with advanced chronic kidney disease (stage 4 or 5) or frequent hyperkalemic episodes, we recommend a lower dietary potassium intake of less than 3 g per day. At this juncture, we do not recommend higher dietary potassium goals or potassium supplements, pending the results of clinical trials.

In response to Berns: in most studies of low-protein diets, participating patients with chronic kidney disease have received concurrently, beyond the diets studied, state-of-the-art therapies for chronic kidney disease, including angiotensin-pathway–modulating medications. Such trials have confirmed the beneficial effects of restricted protein intake (Table S2 in the Supplementary Appendix of our article), as have several meta-analyses, including a recent meta-analysis of the trials listed in that supplementary table.[4] In addition, we are aware of at least three focused studies in humans that have confirmed an additive effective of a low-protein diet, including the two studies cited by Berns — by Gansevoort et al. and Ruilope et al. (studies in which additive antiproteinuric effects of a low-protein diet and enalapril are reported) — and a study by Chin et al.[5] (in which higher protein intake, reflected by higher urinary level of urea nitrogen, was associated with a reduced antiproteinuric effect of olmesartan).

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Since publication of their article, the authors report no further potential conflict of interest.

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Acute Graft-versus-Host Disease

TO THE EDITOR: In their review of acute graft-versus-host disease (GVHD), Zeiser and Blazar (Nov. 30 issue)[1] identify the use of peripheral-blood stem-cell grafts as a risk factor for acute GVHD. Retrospective studies have shown that the effects of stem-cell source on acute GVHD are either inconsistent or null,[2,3] and two large, prospective, randomized, clinical trials in which bone marrow was compared with mobilized peripheral-blood allografts both showed that stem-cell source had no significant effect on the incidence of acute GVHD.[4,5] Although stem-cell source does affect the incidence of chronic GVHD after allogeneic transplantation from unrelated donors,[3] the best available evidence suggests that stem-cell source does not alter the risk of acute GVHD.

The article also describes positive results when antithymocyte globulin (ATG) is used for the prevention of acute GVHD on the basis of open-label, randomized, clinical trials. It is important to note that a recent large, multicenter, prospective, placebo-controlled, double-blind, randomized clinical trial showed that prophylactic use of ATG significantly increased the risk of death; at 2 years, overall survival was 74% in the placebo group but only 59% in the group receiving ATG. Prophylactic use of ATG for the preven-