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EDITORIAL

Nutrition in CKD: Songgaar | Burungaar

This issue of *Advances in Chronic Kidney Disease* provides equipoise regarding dietary therapy in CKD. The guest editors, Drs. Holly Kramer and Julie Lin, have patiently plaited together a series of up-to-date reviews regarding the whys and wherefores of nutritional intervention in patients with nondialysis-dependent CKD and those with ESRD. Kramer and Lin challenge you, the reader, to examine current views of medical nutritional therapy issues relevant to kidney patients, with the overarching mission of undergirding you with greater knowledge, so that you may take action with timely, structured decision-making on behalf of CKD patients with nutritional issues, possibly the area that receives the least volume of formalized training in nephrology.

The Tuvan word for "the past" and "go forward" is "burungaar."[1] The word "songgaar" means "the future" and to "go back". These concepts are opposite to the Western model of forward-peering to the future and backward-looking to the past, but using the Tuvan concept of time facilitates our understanding of why we simply do not deliver adequate nutritional content and care in CKD. To determine the value of medical nutritional therapy in CKD mandates both.

Excessive dietary protein has long been considered to facilitate kidney demise in individuals with CKD, by Beale in 1869 and Smith afterward in 1926, who successfully enforced severe protein restriction (0.26 mg/kg) in an azotemic patient for 6 months.[2] However, therapeutic nutritional privation and the negative consequences of protein restriction forced this dietary alternative to fall into disfavor. In the early to mid-1960s, Giordano, who advised 2 to 3 g of nitrogen daily, and Giovanetti and Maggiore, who advocated for a high biological value protein-restricted diet combined with calorie sufficiency from wheat starch pasta and cornstarch wafers, demonstrated the possibility of lifesaving nutritional therapy in advanced CKD patients.[3] Later, other kidney nutritional devotees increased the amounts of protein to stave off the possibility of protein-energy wasting, and protein intake levels were adjusted to prevent uremic symptoms. Ketoacid administration was shown later to demonstrate a salutary, protein-sparing effect, but was minimally adopted in the United States.[4]

Protein, phosphorus (calcium-phosphate precipitation hypothesis), and caloric controls were not simultaneously implemented in any of these investigations because acceptance of the various toxicities of each were at differing points in their respective evolutions of acknowledgement. Therefore, definitive conclusions could not be drawn from many of them. Intact animals with normal kidneys developed kidney hypertrophy with high dietary protein loads. In animals with prior glomerular injury or near-total kidney ablation (5/6 nephrectomy), glomerulosclerosis occurred in the face of relatively excessive protein intake. Severe protein restriction prevented progression of their acutely derived CKD.[5] Severe protein restriction led to the animals' demise, and severe protein restriction in man would never again be contemplated, akin to the protein-energy wasting incurred by some individuals with advanced CKD and ESRD.

It is important to note that in contradistinction to the protein-hyperfiltration hypothesis, the group of Venkatachalam had posited that the presence of high protein was not requisite to the acquisition of glomerulopathy; excessive caloric intake was.[6] In his work, total caloric consumption provided the impetus for kidney injury, not protein. This body of work adumbrated what has been reported in obese persons by Kambham, obesity-related glomerulopathy (ORG), presumably the consequence of glomerular hyperfiltration. It is important to note that ORG appears less to follow a less pernicious course than classical focal and segmental glomerulosclerosis.[7]

More recently, the *Sirt1* gene (nicotinamide adenine dinucleotide–dependent deacetylase sirtuin 1) has been

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implicated in the pathogenesis of obesity-induced proteinuria, during which time adiponectin levels are simultaneously depressed. Via Sirt1's deacetylase activity, downregulation of oxidative stress occurs through FoxO1 activation, which in turn raises adiponectin levels.[8,9] In obese African Americans, reduced adiponectin was associated with albuminuria. In diabetic, adiponectin null mice, podocyte effacement and proteinuria were present with increases in oxidative stress via enhanced NADPH oxidase Nox4 activity.[10]

As forewarned by Kambham, with obesity at epidemic proportions—nearly one third of the United States is obese, and 33 states have obesity rates greater than 25 percent—the ORG population will commensurately expand.[11] This problem is not a national one; it is global. Of the 1.4 billion overweight persons worldwide, in 2008, 1.5 billion persons were considered obese, and the proportion of children less than 5 years old who were overweight or obese was increasing. Per Hsu and colleagues, this weighty factor explains much of the reason for the global epidemic of diabetes, which is strongly associated with proteinuria and ESRD.[12]

However, diabetes may only represent part of the end of the chain initiated by the addition of high fructose corn syrup-containing foods (~5.2 tablespoons pure fructose or ~2.5 sugar-sweetened beverages daily), which may foster elevated blood pressure and hyperuricemia.[13,14] The pathogenesis of uric acid lithiasis, of which hyperuricemia is not a requisite because fractional excretions of urate are highly variable in diabetics, occurs principally because of low urine ammonium and pH. This pathogenetic sequence derives from obesity-related insulin resistance, and the observation that uric acid stone-formers "run in families" may be explicated by the prevalence of obesity within families.[15,16] The relatively low urinary citrate and pH of insulin-resistant patients is most effectively combated in this circumstance by ingestion of a proportionally higher alkaline diet, namely one that is more vegetarian in composition and ideally with a lesser caloric intake, which could reduce insulin resistance through weight loss. This strategy complements a diet of enhanced intake of citrate-containing fluids and reduction of animal protein ingestion and, hence, purine intake. In addition to its role in kidney stone formation, uric acid has been linked to kidney disease onset and progression. Although it remains controversial if this link is causal, recent clinical studies suggest that lowering uric acid levels might delay the need for kidney replacement therapy.[17] Notwithstanding their limitations, such studies suggest that dietary modifications that lower serum uric acid levels could reduce incident CKD and retard its progression.

The reasons for the inability of kidney nutritional therapy to penetrate each practitioner's medical armamentarium are painstakingly enumerated by a former mentor of mine (A.G. Wasserstein, MD) as a series of responses to a multitude of seemingly disparate forces.[18] These included personalities, philosophic orientations, economics, cultural dissimilarities, medical knowledge, the evolution of medical practice, and the medical school curriculum. Nevertheless, whether intact nephrons that hyperfilter under the injurious load of excessive protein represented the final common pathway toward glomerular and then nephronal obsolescence was to be definitively determined by the multicenter trial, the Modification of Diet in Renal Disease; it was not. The study was marred at the outset by the protein-restricted patients' nonadherence with the prescribed dietary intervention. After all, the conduct of this randomized, controlled trial occurred in the USA, one of the highest protein-consuming countries worldwide.[19] Thus, one might conclude that the actual study has never been done.

Dr. Wasserstein abjured "paternalism" between interactions of nephrologists with kidney dietitians. To ignore the kidney dietitian's recommendations principally because of one's own ignorance of adequate nutritional training is wrong, and patients potentially lose the benefits of kidney nutritional therapy. Therefore, to prolong the patient's time before ESRD, seek and use the advice of those unheralded caregivers, kidney nutritionists. In fact, consider renewing your knowledge base and that of those health-care workers with which you are involved by reviewing the excellent, medical nutrition therapy materials available from the National Kidney Disease Education Program.[20] Reducing calories, protein, sodium, potassium, and phosphate harms neither the patient nor the practitioner because inaction may inure more complications of CKD and/or its progression. It is time to move forward from the past so that we may look back at our future, which shall show that we have improved CKD care through scientific and far-reaching nutritional intervention(s).

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References

1. Rymer R. Vanishing voices. *Natl Geogr.* 2012;222(1):60-93.
2. Hensley M. Kidney function in health and disease. In: Byham-Gray LD, Burrows JD, Chertow GD, eds. *Nutrition in Kidney Disease. Part 1: Foundations for Clinical Practice and Overview.* New York, NY: Humana Press; 2008:21-22.
3. Koulouridis E, Koulouridis I. Is the dietary protein restriction achievable in chronic kidney disease? The impact upon quality of life and the dialysis delay. *Hippokratia.* 2011;15(suppl 1):3-7.
4. Feiten SF, Draibe SA, Watanabe R, et al. Short-term effects of a very-low-protein diet supplemented with ketoacids in nondialyzed chronic kidney disease patients. *Eur J Clin Nutr.* 2005; 59(1):129-136.
5. Nath KA, Kren SM, Hostetter TH. Dietary protein restriction in established renal injury in the rat. Selective role of glomerular capillary pressure in progressive glomerular dysfunction. *J Clin Invest.* 1986;78(95):1199-1205.
6. Tapp DC, Wortham WG, Addison JF, Hammonds DN, Barnes JL, Venkatachalam MA. Food restriction retards body growth and

prevents end-stage renal pathology in remnant kidneys of rats regardless of protein intake. *Lab Invest.* 1989;60(2):184-195.
7. Kambham N, Markowitz GS, Valery AM, Lin J, D'Agati VD. Obesity-related glomerulopathy: an emerging epidemic. *Kidney Int.* 2001;59(4):1498-1509.
8. Nakae J, Cao Y, Daitoku H, et al. The LXXLL motif of murine forkhead transcription factor FoxO1 mediates Sirt1-dependent transcriptional activity. *J Clin Invest.* 2006;116:2473-2483.
9. Schug TT, Li X. Sirtuin 1 in lipid metabolism and obesity. *Ann Med.* 2011;43(3):198-211.
10. Sharma K, Ramachandrarao S, Qiu G, et al. Adiponectin regulates albuminuria and podocyte function in mice. *J Clin Invest.* 2008;118(5):1645-1656.
11. Freedman DH. How to fix the obesity crisis. *Sci Am.* 2011;304:40-47.
12. Hsu CY, Iribarren C, McCulloch CE, Darbinian J, Go AS. Risk factors for end-stage renal disease: 25-year follow-up. *Arch Intern Med.* 2009;169(2):342-350.
13. Jalal DI, Smits G, Johnson RJ, Chonchol M. Increased fructose associates with elevated blood pressure. *J Am Soc Nephrol.* 2010;21:1543-1549.
14. Choi HK, Ford ES. Sugar-sweetened soft drinks, diet soft drinks, and serum uric acid level: the Third National Health and Nutrition Examination Survey. *Arthritis Rheum.* 2008;59(1):109-116.
15. Price RA, Lee JH. Risk ratios for obesity in families of obese African-American and Caucasian women. *Hum Hered.* 2001;51:35-40.
16. Maalouf NM, Sakhaee K, Parks JH, Coe FL, Adams-Huet B, Pak CY. Association of urinary pH with body weight in nephrolithiasis. *Kidney Int.* 2004;65(4):1422-1425.
17. Jalal DI, Chonchol M, Chen W, et al. Uric Acid as a Target of Therapy in CKD. *Am J Kidney Dis.* 2013;61(1):134-146.
18. Wasserstein AG. Changing patterns of medical practice: protein restriction for chronic renal failure. *Ann Intern Med.* 1993;119(1):79-85.
19. Charts Bin. Daily protein intake per capita. Available at: http://chartsbin.com/view/1155. Accessed December 31, 2012.
20. National Kidney Disease Education Program. CKD & nutrition. Available at: http://nkdep.nih.gov/identify-manage/ckd-nutrition.shtml. Accessed December 31, 2012.