

## Dietary Protein Restriction in CKD: The Debate Continues

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**D**ietary protein restriction has been one of the mainstays of nutritional intervention in patients with chronic kidney disease (CKD). The apparent benefits of such dietary manipulation include diminishing the accumulation of nitrogenous wastes and limiting the metabolic disturbances characteristic of advanced CKD (Table 1). A diet that is restricted in protein is invariably limited in the quantities of sulfates, phosphates, potassium, and sodium ingested each day, and hence leads to a more favorable metabolic profile in patients with CKD. The role of dietary protein restriction in slowing progression of CKD is more controversial, although several meta-analyses indicate a beneficial effect, albeit small.<sup>1</sup> Despite the obvious and putative benefits of protein restriction, concern has been raised by several investigators that low-protein diets (LPDs), especially ones designed to provide very low quantities of dietary protein (very-low-protein diets; VLPDs), could lead to deterioration in the nutritional status of CKD patients and hence could predispose these individuals to adverse clinical outcomes, especially after the ini-

tiation of long-term dialysis. These concerns have been mostly defied by a number of studies showing that well-designed diets planned by skilled dietitians and followed by motivated and adherent patients are effective and do not have harmful effects on nutritional condition.<sup>2</sup> In this issue of the *American Journal of Kidney Diseases*, Menon and colleagues<sup>3</sup> ignite this controversy by providing evidence that, compared with an LPD, assignment to a VLPD supplemented with keto acids and amino acids had no impact on delaying the progression to kidney failure, had no relationship with a composite outcome of kidney failure and death, but increased the risk of death in the long term.

This particular study was performed as a follow up of a subpopulation (Study B, see the following) of the Modification of Diet in Renal Disease (MDRD) Study participants.<sup>4</sup> The MDRD Study tested the effects of low protein intake and strict blood pressure control on the progression of kidney disease in more than 800 patients separated into 2 groups: Study A, comprising individuals having a glomerular filtration rate (GFR) of 25 to 55 mL/min/1.73 m<sup>2</sup> and Study B, composed of participants with a GFR of 13 to 24 mL/min/1.73 m<sup>2</sup>. In Study A, patients were randomized using a factorial design to protein intakes of 1.3 g/kg/d (corresponding to a usual-protein diet) or 0.58 g/kg/d (corresponding to LPD) and to a mean blood pressure of 107 mm Hg or 92 mm Hg. In Study B, patients were randomized using a factorial design to protein intakes of 0.58 g/kg/d (LPD) or 0.28 g/kg/d plus keto/amino acid supplementation (denoted the VLPD-KA group), and were treated to blood pressure goals comparable to those in Study A. The loss of GFR was estimated by the slope of <sup>125</sup>I-iothalamate clearance measured over 2 years. The mean follow up was only 2.2 years and actual protein intakes were 1.11 g/kg/d versus 0.73 g/kg/d in Study A (n =

**Table 1. Proven and Controversial Advantages and Disadvantages of Dietary Protein Restriction in CKD Patients**

	Advantages	Disadvantages
Proven	Decreased toxin load Slowing progression Better BP control Better phosphorus control Better H <sup>+</sup> control Improved insulin sensitivity Improved proteinuria*	Predisposition to PEM Complex diet Need for close supervision Decreased muscle mass
Controversial	Extending time to ESRD	Possible weight gain Increased mortality†

Abbreviations: BP, blood pressure; ESRD, end-stage renal disease; PEM, protein energy malnutrition.

\*In nephritic syndrome patients.

†Very-low-protein diets only.

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585), and 0.69 versus 0.46 g/kg/d in Study B ( $n = 255$ ). No difference was observed in GFR decline between groups in Study A. In Study B, there was a somewhat faster decline in GFR in the LPD group as compared with the VLPD-KA group ( $P = 0.07$ ).

The primary and secondary analyses of the MDRD Study results, especially in regard to the effects on progression of CKD or other metabolic and nutritional consequences, are still being debated. The study by Menon et al forces us to reconsider the clinical significance of this important trial, given the potential long-term risk that is attributed to one of the interventions, at least for a subgroup of patients enrolled in the study. The investigators examined the frequencies of either beginning dialysis or death in patients with GFR values less than 25 mL/min/1.73 m<sup>2</sup> who participated in the MDRD Study B and were assigned to treatment with an LPD or a VLPD-KA. Their results showed that, compared with an LPD, assignment to a VLPD-KA had increased the risk of death in the long term, most significantly after initiation of long-term dialysis. Of note, 89% of the Study B participants developed kidney failure, and assignment to the VLPD-KA group had no impact on delaying the progression to kidney failure and had no relationship with a composite outcome of kidney failure and death.

This study has several strengths. The results are based on one of the best-executed studies exploring the effects of LPDs in CKD patients, and the follow-up period is remarkably long. Equally important is the opportunity to be able to compare LPDs and VLPDs, which has not been systematically done in most other studies. The investigators use appropriate statistical techniques and there is complete ascertainment of outcome data of interest using clinical outcomes. On the other hand, certain apparent limitations require us to interpret these results with great caution. The primary limitation, acknowledged by the authors as well, is the lack of dietary protein intake and nutritional measurements during the course of the long-term follow-up period. More specifically, after the completion of study interventions in 1993, there were 2 additional assessments of dietary protein intake during the 9-month phase 5. Thereafter, protein intake and nutritional measurements are not available. Obvi-

ously, it is not known how many patients continued with the LPD or the VLPD and/or the keto/amino acids after the study finished. This is an important drawback since one of the speculative explanations for the study results is the adverse effects of keto/amino acid supplements. It is important to note that while keto/amino acid supplementation is not a common intervention in the United States, it is regularly prescribed elsewhere in the world, and there are no reports indicating an adverse event profile.<sup>5</sup> If anything, most of the published studies indicate a very favorable efficacy and side-effect profile. Nevertheless, the publication bias towards positive results cannot be excluded in terms of the efficacy and safety profile of keto/amino acid supplements.

In addition to the critically important nutritional data, information on medical management and clinical course during this long-term follow-up period is not available. In terms of the latter, it is important to note that the difference in death rate was principally in those treated by dialysis. The criteria for beginning dialysis, the inherent differences in the types of dialysis, the types of dialysis accesses used, and the pharmacological management during end-stage renal disease are fundamental to the observed outcomes in these patients. The lack of these crucial data along with the limited nutritional intake information profoundly limits our ability not only to understand the exact mechanism underlying the increased risk of death seen in the VLPD-KA group, but also confounds the possibility of ascribing these adverse outcomes to VLPD-KA treatment alone.

What are the implications of this particular study? The results of the study by Menon et al have to be considered with certain caveats. First, this particular study is designed to look at the differences between an LPD versus a VLPD-KA. Therefore, the results cannot be inferred to make comparisons between normal dietary protein intake and other dietary prescriptions. Second, the critical flaws in this study seem to outweigh its potential strengths. While the concept that VLPD-KA intervention might in fact lead to deterioration in nutritional status and hence predispose to an undesirable risk profile is intriguing, it cannot be fully proven by this particular study. If anything, available evidence from better designed studies indicates to the contrary.<sup>6,7</sup> Ob-

viously, an appropriately designed randomized clinical trial could answer this question, but given the current interest level and climate, such a study will never be performed. Therefore, we have to rely on the available data and are required to make a judgment based on our interpretation of these results. Despite its important shortcomings, Menon and colleagues have to be commended on their attempt to explore these important questions in this particular study. The availability of these and hopefully subsequent data will ultimately lead to the best care of our patients.

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#### **REFERENCES**

1. Kasiske BL, Lakatua JD, Ma JZ, Louis TA: A meta-analysis of the effects of dietary protein restriction on the rate of decline in renal function. *Am J Kidney Dis* 31:954-961, 1998
2. Fouque D, Aparicio M: Eleven reasons to control the protein intake of patients with chronic kidney disease. *Nat Clin Pract Nephrol* 3:383-392, 2007
3. Menon V, Kopple JD, Wang X, et al: Effect of a very low-protein diet on outcomes: long-term follow-up of the Modification of Diet in Renal Disease (MDRD) Study. *Am J Kidney Dis* 53:208-217, 2009
4. Klahr S, Levey AS, Beck GJ, et al: The effects of dietary protein restriction and blood-pressure control on the progression of chronic renal disease. *N Engl J Med* 330:877-884, 1994
5. Cano NJ, Fouque D, Leverve XM: Application of branched-chain amino acids in human pathological states: renal failure. *J Nutr* 136:299S-307S, 2006
6. Cianciaruso B, Pota A, Pisani A, et al: Metabolic effects of two low protein diets in chronic kidney disease stage 4-5: a randomized controlled trial. *Nephrol Dial Transplant* 23:636-644, 2008
7. Vendrely B, Chauveau P, Barthe N, et al: Nutrition in hemodialysis patients previously on a supplemented very low protein diet. *Kidney Int* 63:1491-1498, 2003