High-protein diet in diabetic nephropathy: what is really safe?1,2

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The well-trod controversy concerning the risks and benefits of limiting protein in the diet of patients with chronic kidney disease (CKD)1 has been raised again. In this issue of the Journal, Jesudason et al (1) have published their results from a comparison of 2 dietary prescriptions in subjects with suspected diabetic nephropathy, one prescription being higher in protein than the other. The controversies about dietary protein have centered on 2 topics: first, there is the potential that protein-restricted diets might slow the progression of kidney failure; and second, there is concern that protein-restricted diets might cause loss of protein stores in patients with CKD. The genesis of the first topic extends back at least to the first half of the 20th century when Thomas Addis developed a theory to explain the progressive loss of kidney function in CKD. He showed that the loss of kidney mass actually stimulated hypertrophy of the remaining kidney tissue and pointed out that the degree of hypertrophy depended on the amount of protein in the diet (2). He proposed that the loss of kidney function in CKD arose from the work required to maintain osmolality and that this was the stimulus for kidney growth. Similar experiments conducted in other animal models of CKD led to the general conclusion that animals fed a high-protein diet develop more serious kidney injury compared with those fed a protein-restricted diet (3). Decades later, it was revealed that an excess of dietary protein increases glomerular capillary pressure by increasing the resistance of efferent arterioles of the glomerulus more than that of afferent arterioles (4). Brenner et al (5) proposed that these hemodynamic responses led to glomerular damage and ultimately to progressive CKD. Their reports culminated in proposing a hyperfiltration theory of progressive kidney disease; they concluded that increasing glomerular filtration causes progressive CKD. It was proposed that treatment strategies that suppress hyperfiltration (eg, reducing hypertension and, especially, blocking the renin-angiotensin system pharmacologically or with low-protein diets) would preserve kidney function. Ever since, the merits of dietary protein restriction in terms of slowing progression of CKD have been debated, but well-done randomized controlled trials on the issue are few.

With regard to the report by Jesudason et al (1), the authors examined differences in measured glomerular filtration rate (GFR; the definer of hyperfiltration) in response to the prescription of a moderate (MP) compared with a standard (SP) amount of daily protein intake in patients with presumed diabetic nephropathy. Their results show that, before the study, patients had an estimated GFR of $\geq 40$ mL/min and were prescribed a protein intake of 90–120 g/d in the MP group and 55–70 g/d in the SP group. The actual intake was not so precise; MP patients increased their mean (±SD) protein intake minimally from 106 ± 31 to 110 ± 38 g/d (1.22 g/kg), whereas the SP patients reduced their protein intake from 112 ± 33 to 97 ± 25 g/d (0.93 g/kg). The results of the trial, however, showed an average difference in protein intakes of 19 ± 6 g/d during the 12-mo period. On average, both treatment groups lost weight: 9.7 ± 13.4 kg in the MP group and 6.6 ± 7.1 kg in the SP group. Notably, there was no significant difference in GFR values determined at the beginning and end of the study (143 ± 59 to 129 ± 49 mL/min in MP patients and 112 ± 39 to 113 ± 40 mL/min in SP patients). The authors concluded that higher-protein diets are not harmful for patients with early diabetic nephropathy.

Long-term clinical investigations, especially those requiring nutritional intervention, are extremely difficult to execute, and the authors are commended for their efforts. But have they uncovered new insights? First, a difference in protein intake of 1.22 g/kg compared with 0.93 g/kg between the 2 groups is too small to assign a cause-effect response. More important, the daily protein intake in the SP group would not be considered a “low protein” diet and certainly not an amount that would be considered as dietary therapy for CKD. On the other hand, the authors’ intent was to show that a high-protein diet consumed by patients with signs of early diabetic nephropathy would not affect GFR adversely. We believe they reached their goal, but there must be a word of caution about the conclusions because, without histologic evidence, the reduction in GFR from 143 to 129 mL/min determined isotopically may represent loss of kidney function rather than simply correction of hyperfiltration. We believe this should be pointed out because the CV of clearance methods ranges up to 10 mL/min per 1.73m² under ideal circumstances, and the variability is higher in patients with CKD, especially because the number of blood samples for calculating the GFR was minimal—2 time points (6). Last, it should be pointed out that a GFR of 40 mL/min can occur in patients with advanced CKD.

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3 Abbreviations used: CKD, chronic kidney disease; GFR, glomerular filtration rate; MP, moderate amount of daily protein intake; SP, standard amount of daily protein intake.

What about the flip side? Namely, does restriction of dietary protein affect the progression of CKD? First, there are the results from the Modification of Diet in Renal Disease (7). Diabetic patients were excluded from that trial, but secondary analyses of the outcome of the Modification of Diet in Renal Disease trial showed that there were slower losses of residual kidney function among patients who were consuming low-protein diets (8). The longest randomized trial of dietary manipulation in patients with type 1 diabetes and CKD was reported by Hansen et al (9): patients were divided into a group who consumed their usual diet or another group who was prescribed a diet containing 0.6 g protein · kg⁻¹ · d⁻¹ (actual protein intakes were 1.02 and 0.89 g · kg⁻¹ · d⁻¹). After a 4-y trial, the frequency of end-stage kidney disease was 36% lower in patients consuming the protein-restricted diet; and after adjustment for cardiovascular disease, the “risk reduction” for developing end-stage kidney disease in those assigned to the low-protein diet was even more significant. Zeller et al (10) studied 36 type 1 diabetic patients with CKD while they were prescribed a diet containing 1 g protein · kg⁻¹ · d⁻¹ or 0.6 g protein · kg⁻¹ · d⁻¹. After an average of 35 mo, the low-protein diet significantly reduced the decrease in the GFR compared with results with the control diet. There was no indication that nutritional status was compromised by the low-protein diet. Finally, Walker et al (11) studied the responses to a low-protein diet on the progression of CKD in diabetic patients and found the following: 1) no adverse effects on nutritional status, 2) no increase in glycated hemoglobin, 3) improved control of mean blood pressure, 4) reduced proteinuria, and 5) slowing of the decrease in GFR. These reports largely deal with patients who have had more established disease than those reported by Jesudason et al, but they do provide reassurance for the safety of low-protein diets in patients with CKD, including diabetic nephropathy.

The second contentious issue is the safety of low-protein diets for patients with CKD. Specifically, some patients with CKD may spontaneously reduce the amount of protein in their diets, leading to loss of protein stores because of an inadequate amount of protein. This concern has been dispelled, and in fact, there is evidence that reducing dietary protein in patients with CKD not only produces neutral or positive nitrogen balance but also maintains body weight and serum albumin and other characteristics, even in elderly subjects (12, 13). What could account for the difference in outcomes? Jesudason et al (1) examined blood pressure and noted that it was unchanged in both of the treatment groups. But part and parcel of consuming high-protein diets is that the intake of salt rises sharply, a response that would increase the blood pressures of hypertensive CKD patients. Thus, blood pressure must be repeatedly assessed in patients undertaking a high-protein diet to lose weight. Increasing salt intake is not the only problem that can arise from a high-protein diet: there are many metabolic products that exert toxic properties, including phosphates and uric acid. As indicated above, blocking the renin-angiotensin system can slow the loss of residual kidney function in patients with CKD. Traditionally, blockade of the system is accomplished by administering angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, especially in patients with diabetes (14, 15). But it has been reported that the beneficial influence of angiotensin-converting enzyme inhibitors on slowing the progression of CKD was reversed in patients who consumed excessive amounts of salt or phosphates (16, 17). In addition to these ions, there are effects from the retention of many other products of protein and amino acid metabolism. As one example, Kang et al (18) pointed out that hyperuricemia predisposes adults and children to the development of hypertension. In short, if kidney function is impaired, it follows that products arising from the metabolism of dietary protein will accumulate in patients in direct proportion to the amount of protein consumed and in inverse proportion to the degree of kidney failure. This is relevant because it is axiomatic that these unexcreted compounds can damage the injured kidney.

What lessons are there for modifying the diet of patients with CKD and especially those with diabetic nephropathy? First, Jesudason et al (1) have inferential evidence that consuming a high-protein diet does not appreciably affect measured GFR and that such a diet can help diabetic patients lose weight. Second, there is evidence that dietary protein is not only a source of amino acid precursors but also the source of toxic solutes that interfere with the treatment of patients with impaired kidney function. Third, for patients with more advanced CKD, there is evidence that attention to the diet can avoid at least some of the complications of CKD. These considerations suggest that encouraging diabetic or nondiabetic patients with CKD to consume high-protein diets, albeit beneficial for losing weight, is unwise and especially so in patients with low GFR values. These individuals do not have the ability to prevent the accumulation of potential toxins and ions.

Neither author had any financial interests, direct or indirect, in the subject matter or materials discussed in this editorial.

REFERENCES


