Do low-protein diets retard the loss of kidney function in patients with diabetic nephropathy?\textsuperscript{1,2}

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The world-wide epidemic of diabetes mellitus and the increasing numbers of patients with chronic kidney disease (CKD) and end-stage renal failure caused by diabetic nephropathy continue to stimulate the search for methods to prevent the development and progression of CKD. Therefore, the current meta-analysis by Pan et al (1) of the effects of low-protein diets (LPDs) on the progression of CKD and proteinuria is highly relevant.

After searching several databases, the authors identified 8 published randomized controlled clinical trials (RCTs) of LPDs in 519 patients with diabetic nephropathy. Data from CKD patients with type 1 or type 2 diabetes mellitus were combined, an approach that the authors contend is justified because the pathophysiology of CKD in these 2 types of diabetes is similar. For inclusion in the analyses, RCTs had to be of \( \geq 6 \) mo duration and had to provide outcome data on glomerular filtration rate (GFR) or creatinine clearance (Ccr) or albuminuria or proteinuria. Appropriate methods for weighting differences and testing for heterogeneity and publication bias appear to have been used. Crossover studies of LPDs were excluded because of possible carryover effects from one diet to the other. The authors’ analyses indicated that LPDs were not associated with a slower progression of GFR or Ccr in type 1 or type 2 diabetes mellitus, when considered together (\( P = 0.61 \)) or separately, although LPDs were associated with a decrease in glycated hemoglobin (HbA\textsubscript{1c}) concentrations (\( P = 0.005 \)). There was also a reduction in albuminuria or proteinuria with the LPDs (\( P = 0.003 \)); the latter data were associated with substantial heterogeneity.

These findings stand in contrast to meta-analyses of the effects of LPDs in nondiabetic persons with CKD. Significant prolongation of the time until the beginning of renal replacement therapy and a slowing of the loss of GFR have been described with LPDs in these patients (2–5). However, whereas the prolongation of time until renal replacement therapy was substantial (2, 3, 5), the slowing of the loss of GFR was rather small: 0.53 mL min\textsuperscript{-1} y\textsuperscript{-1} (4). These studies in persons without diabetes (2–5) do not conflict with each other, because LPDs also decrease the rate of generation of protein metabolites and, presumably, uremic toxins. Hence, CKD patients ingesting LPDs may start maintenance dialysis therapy at lower GFRs, presumably because, for any reduction in GFR, they accumulate less uremic toxins and therefore are less symptomatic (6). Another recent meta-analysis concurred that there was no significant slowing of the loss of GFR in diabetic patients prescribed LPDs, although a trend toward such a reduction was observed (\( P = 0.14 \)) (7).

Studies of the effects of LPDs on CKD patients may be deceptively difficult to evaluate. First, the actual protein intakes consumed in the LPDs evaluated in the meta-analysis by Pan et al may have been too high (1). The mean protein intakes of the subjects assigned to the LPDs ranged from 0.71 to 1.10 g kg\textsuperscript{-1} d\textsuperscript{-1}. In more than half of the patients assigned to the LPDs, the average protein intakes ranged from 0.93 to 1.10 g kg\textsuperscript{-1} d\textsuperscript{-1}. These actual protein intakes stand in contrast to the LPDs recommended by some workers in the field of 0.80 g kg\textsuperscript{-1} d\textsuperscript{-1} for nonnephrotic patients with CKD (6, 8, 9). The study by Pan et al also included patients with microalbuminuria, proteinuria, and the nephrotic syndrome; it is possible that the response to LPDs may vary in persons who have these different degrees of protein excretion. It is puzzling that, in the meta-analysis by Pan et al, although LPDs did not slow the loss of GFR, they were associated with less albuminuria or proteinuria and lower HbA\textsubscript{1c} concentrations, which are risk factors for more rapid progression of CKD (6). In this regard, it would have been helpful to analyze separately the LPD effects on the patients with greater degrees of proteinuria, including those with the nephrotic syndrome. This latter analysis was probably not possible, however, because the sample size of the patients with heavy proteinuria was probably too small for a valid statistical examination of the effects of LPDs on GFR loss; in addition, it may not have been possible to obtain individual outcome data from these latter studies.

Moreover, the duration of treatment ranged from 9 to 48 mo and was rather short in most of the studies analyzed by Pan et al; in 4 of the 8 reports, the LPD treatment lasted 6–12 mo. In some RCTs, the divergence of the GFR in the patients prescribed the LPD and that in patients prescribed higher protein intakes occurred gradually, over many months, and significant changes in GFR may not have been initially apparent (4, 10). A further confounding factor is that, when persons with normal kidneys or CKD ingest smaller amounts of protein, there is a rather abrupt but limited reduction in GFR, which is considered to be caused by hemodynamic changes (6). This phenomenon has increased the difficulties of using GFR as the key outcome measure of the

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effects of LPDs on the progression of CKD, particularly when RCTs are of short duration. There also is evidence that LPDs may decrease CrCl when the GFR does not change significantly (11); this phenomenon would argue against combining, in the same meta-analysis, RCTs using GFR and CrCl outcome measures. Another concern is that many of the patients in the meta-analysis by Pan et al had GFRs that were well above 60 mL/min. Is it possible that persons with a lower GFR may respond more effectively to LPDs?

Many of the physiologic effects of LPDs on the kidney are similar to those engendered by the classes of antihypertensive medications called angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor-2 blockers (ARBs) (10, 12, 13). ACEIs and ARBs slow the rate of progression of CKD, an effect that is partially independent of their blood pressure–reducing effects (12, 13). LPDs decrease kidney renin mRNA in rats, lower plasma renin activity in humans, and increase urinary excretion of the vasodilatory cyto-
kines prostaglandin E2 and prostacyclin in urine of normal rats and patients with glomerular disease (14–16). ACEIs also decrease the synthesis of angiotensin II and, in rats, reduce glomerular eicosanoid production (16). ARBs block the binding of angiotensin II to its receptor. It is apparent that not all of the patients in the RCTs included in the meta-analysis by Pan et al were given ACEIs and ARBs. Moreover, there is no evidence that the patients who received those medicines were given the medications in equivalent doses. Thus, it is possible that the different effects of varied doses of ACEIs and ARBs may have obscured the effects of LPDs on progression of CKD. Indeed, a highly relevant and related question is whether LPDs offer additional renal-protective benefits in patients receiving maximum doses of ACEIs or ARBs (or both), of aldosterone receptor blockers, or of the more recently available renin antagonists that also block components of the renin-angiotensin-aldosterone system (17).

Recently, some investigators have advocated high-protein, low-carbohydrate diets for the treatment of persons with diabetes mellitus without CKD (18, 19). These diets are reported to result in lower serum glucose concentrations or insulin requirements and, in some studies, greater weight loss and a more desirable serum lipid pattern. The recommended diets provide ≈20–30% of calories from protein rather than the 15–20% provided by most normal diets. It should be emphasized that the meta-analysis of Pan et al did not examine whether these higher-protein diets are safe or effective in diabetic patients with CKD.

Given the above qualifications, where does this meta-analysis leave us with regard to the treatment of diabetic patients with CKD? It seems fair to conclude that LPDs do not have a dramatic effect on slowing the loss of GFR in diabetic patients with CKD. This meta-analysis did not address the question of whether, by reducing uremic toxicity, LPDs may delay the need for renal replacement therapy. It is my opinion that, for the reasons expressed above, a small beneficial effect of LPDs against the loss of GFR has not been ruled out in diabetic patients with CKD. LPDs are unpleasant and difficult to follow for many, but not all, patients. In my experience, ≈15% of CKD patients, with or without diabetes mellitus, are able to follow these diets rather comfortably. Therefore, it does not seem unreasonable to treat diabetic patients with CKD with ACEI, ARBS, or other medications that suppress the renin-angiotensin-aldosterone system; to maintain tight control of blood pressure and glucose and HbA1c concentrations; and to ensure that patients follow health-enhancing diets. In addition, such patients could be offered treatment with LPDs providing 0.60–0.80 g protein · kg⁻¹ · d⁻¹, adjusted for nephrotic range proteinuria if present, as previously described (8). It would be important to disclose to such patients that these diets have not been proven to slow the progression of CKD or to delay the onset of renal replacement therapy. However, if the diet is followed closely and the patient’s nutritional status is monitored carefully, the risk of protein-energy wasting and other disorders associated with this dietary therapy should be very low.

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