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ROLE OF NUTRITION IN PREVENTION OF THE PROGRESSION OF RENAL DISEASE

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ABSTRACT

In rats with renal disease, low-protein diets slow the decline in renal function, histologic damage, and mortality. Low-protein (and phosphorus) diets can also ameliorate uremic symptoms, secondary hyperparathyroidism, and metabolic acidosis in patients with chronic renal failure. Albeit controversial, evidence also suggests that dietary protein restriction can slow the rate of progression of renal failure and the time until end-stage renal failure. These dietary regimens appear to be safe and patients with chronic renal failure are able to activate normal compensatory mechanisms designed to conserve lean body mass when dietary protein intake is restricted. When low-protein diets are prescribed, patients should be closely monitored to assess dietary compliance and to ensure nutritional adequacy. Evidence that the spontaneous intake of dietary protein decreases in patients with progressive chronic renal failure who consume unrestricted diets should not be construed as an argument against the use of low-protein diets. Rather, it is a persuasive argument to restrict dietary protein intake in order to minimize complications of renal failure while preserving nutritional status.

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INTRODUCTION

A protein-restricted diet can ameliorate many uremic symptoms. It also prevents some of the complications of chronic renal failure (CRF), including renal osteodystrophy, hypertension, and metabolic acidosis, because a low-protein diet invariably restricts the intake of phosphates, sodium, potassium, and acid. Although controversial, evidence suggests that low-protein diets may also slow the progressive loss of renal function.

An alarming feature of CRF is that the loss of renal function continues even when the initial disease damaging the kidney is no longer active (i.e. CRF progresses toward end-stage renal disease). For more than 50 years it has been known that in rats induced with CRF, a high-protein diet leads to increasing proteinuria, renal histologic damage, and mortality, whereas dietary protein restriction protects the kidney from further damage (11, 19). In 1976, it was shown that the rate of loss of renal function in an individual with progressive chronic renal insufficiency is predictable (46). The benefit of a low-protein diet in slowing renal progression in animals and the ability to assess changes in renal function in humans prompted investigators to examine whether restricting dietary protein might ameliorate renal damage and delay the loss of residual renal function in CRF patients.

When evaluating reports that dietary manipulation slows the loss of renal function in CRF patients, three questions should be considered. First, does the diet maintain nutritional status? Second, has dietary adequacy been monitored and has compliance been achieved? Third, has restricting the diet changed the rate of loss of renal function?

Before addressing these questions, two facts should be emphasized. First, despite intensive investigation, the mechanism(s) causing the progressive loss of renal function have not been identified. Possibilities include (*a*) a reduction in the level of an unidentified nephrotoxin arising from the metabolism of protein (52), (*b*) a decrease in the damaging influence of proteinuria (7), and (*c*) improved control of hypertension (33, 40). Thus, the complex interplay of the factors contributing to progression makes it more difficult to evaluate the impact of dietary manipulation. Second, multi-center trials testing whether a low-protein diet slows progression have not demonstrated effectiveness, at least when an "intention-to-treat" analysis was used (i.e. analysis of outcomes

regardless of whether patients complied with the diet). In contrast, results from several studies of small groups of CRF patients have shown that a low-protein diet can slow the loss of renal function. Because the mechanism(s) underlying the progressive loss of renal function (progression) have not been identified, studies with animals are not reviewed.

DO LOW-PROTEIN DIETS CAUSE MALNUTRITION?

Recently, concern has been raised that low-protein diets cause malnutrition, and it has been suggested that these diets be used cautiously in CRF patients (23, 25). This fear arises from two observations: evidence of a spontaneous decrease in protein intake and some indices of nutritional status when CRF patients consume unrestricted diets (25); and the association between hypoalbuminemia and increased mortality in hemodialysis patients (36). Concern about both issues in misplaced. First, it is clear that proper implementation of a low-protein diet yields neutral nitrogen balance and maintenance of normal serum proteins and anthropometric indices during long-term therapy (42, 45, 64, 68). Second, the mechanism causing hypoalbuminemia in hemodialysis patients may be more closely related to inflammation than to an inadequate diet (27). More importantly, use of a low-protein diet was associated with improved survival in CRF patients who subsequently began dialysis therapy (14).

Clearly, success with a protein-restricted diet depends on providing the requirements of different nutrients (38) while regularly assessing nutritional adequacy to avoid malnutrition. Monitoring nutritional adequacy is difficult (18), but most reports indicate that long-term therapy with low-protein diets can be performed safely. For example, Maroni and colleagues reported that patients treated with a very-low-protein diet (~0.3 g protein/kg per day) supplemented with an amino acid/ketoacid mixture were in neutral nitrogen balance and sustained stable anthropometrics as well as serum albumin and transferrin levels (indices of visceral protein stores) during more than one year of dietary therapy (42, 64). Walser achieved similar results when the same diet was supplemented with ketoacids or essential amino acids (EAA) (68). In fact, this regimen led to an increase in serum proteins concentrations in some patients who had subnormal values at the initiation of dietary therapy. Obviously, if the diet is inadequate or if nutritional adequacy is not monitored, patients are at risk of losing lean body mass (18, 37).

MONITORING CHANGES IN RENAL FUNCTION

The functional mass of the kidney is judged by the glomerular filtration rate (GFR) (normal range 90–110 ml/min); thus, measuring changes in GFR

provides an estimate of the loss of renal mass. Detailed discussions of the methods for measuring the rate of loss of renal function are available (31, 43, 67). Most studies used serial measurements of GFR (e.g. the renal clearance of [^{125}I]iothalamate, or ^{99m}Tc-DTPA) or indirect estimates of GFR such as the serum creatinine (Scr) or creatinine clearance (Ccr). Since nutritional factors can affect creatinine production, the problems with using serum creatinine and creatinine clearance to monitor renal function are worth noting.

A single value of Scr is a crude estimate of Ccr (or GFR) because it depends on the rate of creatinine production, the volume of distribution of creatinine, the degree of renal tubular creatinine secretion, and the rate of extrarenal creatinine clearance. Nevertheless, Scr is widely used in clinical practice to monitor changes in renal function because it is inexpensive and the day-to-day coefficient of variation in patients with renal disease is only 6.5% (21). Since the coefficient of variation in Ccr is substantially greater, most conclude that Ccr should be abandoned in favor of measuring changes in Scr (50, 55).

The most important reason to measure Scr is that its reciprocal (Scr^{-1}) declines linearly with time in most untreated CRF patients (46). The decline in Scr^{-1} in individual patients varies widely. In 34 patients reported initially, the rate of decline in Scr^{-1} varied from 0.0011 to 0.0152 dl/mg per month but was linear in all but three subjects (46). The percentage of patients exhibiting a linear decline in Scr^{-1} in other reports varies from 60 to 80% (53, 62). All reports emphasize the variability in the rate of loss of renal function among CRF patients [e.g. in patients with diabetic nephropathy, there is as much as a 40-fold difference in the rate of progression (26)].

Levey has raised four theoretical problems with the use of Scr to assess the rate of progression (31). First, Scr is a relatively crude index of GFR, and consequently, a linear decline in Scr^{-1} may not mean that GFR is lost in a constant fashion. Second, creatinine excretion varies with the amount of well-cooked meat in the diet. Third, creatinine production may be impaired in CRF patients. And fourth, extrarenal creatinine clearance could change in CRF, yielding a false estimate of the loss of GFR. The first objection is correct because Scr is an imprecise estimate of GFR (10, 51, 58, 63). Still, an increase in Scr always indicates a loss of renal function unless there has been a dramatic increase in dietary protein.

A meat-restricted diet decreases Scr because the contribution of dietary creatinine falls (44). Regardless, any decrease or stabilization of Scr resulting from a change in the diet can only persist as long as renal function remains stable. Since the half-life of creatine is $\sim$41 days (48), judgements about the slowing or halting of the progression of CRF cannot be based on a change in Scr for $\sim$4 months (i.e. more than three half-lives) (44). If Scr then rises (or Scr^{-1} declines), the explanation must be that renal insufficiency has progressed; if Scr and Scr^{-1} do not change, then progression has slowed.

The conclusion that CRF reduces creatinine production is probably incorrect. When measured by isotope dilution techniques, Mitch et al found that creatinine production was not different from the value predicted for subjects of the same age, weight, and sex (47). Moreover, the creatine concentration in muscle of CRF patients is normal (15, 34, 66). Regarding extrarenal creatinine clearance (47), the critical issue is whether extrarenal clearance changes over time or with the severity of renal insufficiency. This has not been tested.

In summary, measures of Scr and Scr^{-1} are useful clinically for assessing changes in renal function, and an increase in Scr must mean that renal function has declined unless dietary protein intake has increased dramatically. Ideally, a more precise estimate of GFR (e.g. the renal clearance of inulin, [^{125}I]iothalamate, or ^{99m}Tc-DTPA) should be used in intervention trials to assess changes in renal function.

NUTRITIONAL ADEQUACY OF LOW-PROTEIN DIETS

Three types of dietary regimens have been used to slow the progression of CRF: (*a*) a low-protein diet providing 0.6 g of protein/kg of ideal body weight per day; (*b*) a very-low-protein diet (VLPD) containing ~0.3 g of predominantly vegetable protein per kg per day supplemented with a mixture of EAA; or (*c*) a VLPD diet supplemented with a mixture of EAA and the nitrogen-free analogues of amino acids (ketoacids). Since restricting dietary protein also limits the intake of phosphates, sulfates, acid, etc, any benefit cannot be attributed solely to protein restriction (13). If urinary protein losses exceeds 3 g/day, it is advisable to provide an additional gram of dietary protein for each gram of proteinuria.

Kopple & Coburn demonstrated that the mean protein requirement of normal subjects (~0.6 g of protein/kg per day) also maintained neutral nitrogen balance in CRF patients (29). Moreover, CRF does not interrupt critical compensatory responses invoked in response to dietary protein restriction (i.e. suppression of amino acid oxidation and postprandial inhibition of protein degradation) (22). With the more restrictive VLPD regimen supplemented with either EAA or ketoacids, nitrogen balance also remains neutral and the adaptive metabolic are sustained during long-term therapy (1, 42, 45, 64). Importantly, serum albumin and transferrin are also maintained during long-term therapy (45, 64, 68).

MONITORING DIETARY ADEQUACY AND COMPLIANCE

Successful dietary therapy requires periodic assessment of the patient's nutritional status and compliance with the dietary prescription. Fortunately, a simple method is available for estimating the protein intake of CRF patients (39). First,

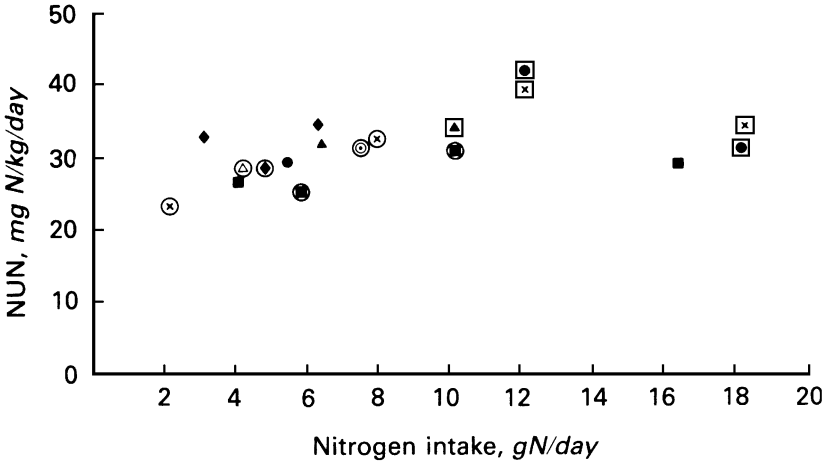

Figure 1 Calculated values of non-urea nitrogen (NUN) in normal subjects (*closed triangles*, *circles*, and *squares*), in patients with chronic renal failure (CRF) treated with low-protein diets (*open circles with cross*, *open triangle*, *solid diamond*, and *solid diamond*), in CRF patients treated by dialysis (*open square with solid triangle* and *open circle with solid square*), or in CRF patients treated by continuous ambulatory peritoneal dialysis (*open square with solid circle* and *open square with cross*). The results indicate that despite large differences in renal function and nitrogen intake, NUN excretion is relatively constant. The average value was 0.031 g of N/kg per day, identical to that reported in CRF patients consuming an unrestricted diet or a very-low-protein diet supplemented with ketoacids. [Reprinted with permission (39)].

it should be appreciated that waste nitrogen derived from degraded protein is excreted principally as urea, and the urea nitrogen appearance rate (i.e. urea excretion plus accumulation) closely parallels protein intake. In contrast, non-urea nitrogen excretion (i.e. nitrogen in urinary creatinine, uric acid, ammonia, etc, as well as in feces) does not vary significantly with protein intake and averages 0.031 g of nitrogen per kg of body weight per day (39) (Figure 1). If one assumes that the patient is in neutral nitrogen balance (B_N), then nitrogen intake (I_N) will equal urea nitrogen appearance (U) plus non-urea nitrogen (NUN) excretion (i.e. if $B_N = 0$, then $I_N = U + NUN$). If the patient is in steady state (and, hence, serum urea nitrogen is unchanging), then urea nitrogen appearance (U) will equal the 24-h urinary urea nitrogen excretion (UUN). In the example provided in Table 1, the prescribed and estimated protein intake are similar, so we conclude that the patient is compliant with the protein prescription. If the estimated intake is less than what is prescribed, the patient should be instructed to increase his or her protein intake to the goal. If the estimated intake exceeds that which is prescribed by more than 25% (i.e. precision of the method), there

Table 1 Estimating dietary protein intake from the 24-h urinary urea nitrogen excretion of a 45-year-old women seen one month following instruction in a diet providing 0.6 g of protein/kg per day (i.e. 36 g of protein)[a]

Weight: 60 kg; UUN = 3.9 g/day; NUN = 0.031 g of N × 60 kg = 1.9 g of N/day
If $B_N = 0$, then I_N = UUN + NUN
= 3.9 + 1.9 = 5.8 g of N
= 5.8 g of N × 6.25 g of protein/g of N
= 36.3 g of protein/day

[a]UUN, 24-h urinary urea nitrogen excretion (grams of N/day); NUN, non-urea nitrogen (grams of N/day); B_N, nitrogen balance (grams of N/day); I_N, nitrogen intake (grams of N/day).

are two possible explanations: (*a*) A catabolic stimulus (e.g. metabolic acidosis) has stimulated the degradation of body protein stores and increased waste nitrogen production; or (*b*) the patient is noncompliant with the diet. If no clinical abnormality is found, the patient is referred to the dietician for assistance in achieving dietary compliance.

The importance of an adequate energy intake cannot be overemphasized, and patients should be prescribed ~35 kcal/kg per day (30). In contrast to protein intake, which can be estimated reliably from the 24-h urinary urea excretion (39), dietary diaries and diet recall are the only available methods for assessing energy intake in the outpatient setting. Although their limitations are well recognized (9), as a compromise between accuracy and compliance, we have utilized three-day food diaries to monitor energy intake. Nutritional status is monitored by serial measurements of anthropometrics, serum albumin, and transferrin. The assistance of a skilled dietician is beneficial in assisting with the monitoring of patients prescribed low-protein diets.

In summary, when prescribing low-protein diets it is important to monitor dietary adequacy and compliance. Once patients are comfortable with the dietary regimen, we typically see individuals as outpatients every three months while (*a*) estimating protein intake from the 24-h UUN excretion plus an estimate of NUN losses as 0.031 g of N/kg per day; (*b*) estimating caloric intake from three-day food diaries; (*c*) monitoring serum albumin, transferrin, and anthropometrics; and (*d*) using these indices to provide patient feedback.

PROTEIN RESTRICTION AND PROGRESSION OF RENAL INSUFFICIENCY

Conventional Low-Protein Diets and Progression

One of the earliest trials examining the effects of a low-protein diet on the progression of CRF was reported by Maschio et al (41). They compared three

groups of patients. Groups I and II had initial Scr values of 1.6–2.7 and 2.9–5.4 mg/dl, respectively. Both groups were prescribed a diet containing 0.6 g of predominantly high-quality protein per kg, 40-kcal energy intake per kg, ~650 mg of phosphorus, and 1.0–1.5 g of calcium daily. Group III (initial Scr, 1.6–4.7 mg/dl) consumed an unrestricted diet and served as the control group. Progression was assessed by evaluating changes in Scr. Notably, the loss of renal function in groups I and II was far slower than in group III. Dietary compliance was not rigorously evaluated.

In 1989, these same researchers reported results from 390 patients treated with a low-protein diet for 54 $\pm$ 28 months (54). They found that 57% of the patients had stable Scr values, 11% had slower deterioration (defined as a decrease in the decline of Scr^{-1} at a rate exceeding -0.02 but less than -0.04 dl/mg per month), while 32% had more rapid loss of kidney function (>-0.04 dl/mg per month). Individuals who began the low-protein diet early had a more favorable course, and patients with interstitial nephritis fared better than those with chronic glomerulonephritis or polycystic kidney disease. The initial Scr, level of proteinuria, and blood pressure were independent risk factors associated with an increase in Scr. Importantly, indices of protein nutrition including weight, other anthropometric measurements, and serum proteins were maintained, although following five years of dietary therapy the serum albumin, serum transferrin, and protein concentration in muscle biopsies from a subgroup of eight patients decreased significantly, despite stable anthropometric measurements (54).

Rosman and coworkers reported the results of a prospective, randomized trial involving 149 patients followed for at least 18 months (average of 24 months) after being assigned to either a low-protein or a control diet (61). The degree of protein restriction varied: Patients with Ccr between 30–60 ml/min were assigned to 0.6 g of protein/kg per day, while those with Ccr between 10–30 ml/min were prescribed 0.4 g of protein/kg per day. Based on urea excretion, the difference in protein intake between the protein-restricted and control subjects averaged 18 g/day. Based on changes in Scr^{-1}, the authors concluded that a protein-restricted diet reduced the rate of progression by three- to fivefold. There were no adverse changes in nutritional status, but from the values of urea excretion it can be calculated (39) that the actual dietary protein intake was higher than was prescribed.

After four years, this group reported follow-up results in 153 of the 248 patients initially entering the study (60). The benefit of a low-protein diet persisted in terms of slowing the loss of renal function, but mainly in patients with more advanced renal insufficiency or with glomerulonephritis. The diet had a more beneficial effect in men; the response to the diet was minimal in women. It was concluded that any slowing of progression in patients with

polycystic kidney disease was related entirely to successful blood pressure control and not to the diet. In patients with other types of disease, blood pressure control was not correlated with preservation of renal function.

Regarding nutritional status, both body weight and serum proteins were stable over 36 months of dietary therapy even though the prescribed diet provided less than the minimum daily protein requirement (29, 38). However, the actual protein intake (estimated from body weight and urea excretion) was closer to 0.7 g of protein/kg of body weight per day (39).

Ihle et al conducted an 18-month prospective, randomized trial of the influence of a low-protein diet on changes in GFR (24). The low-protein diet group was prescribed 0.4 g of protein/kg per day while the control group consumed an isocaloric diet providing at least 0.75 g of protein/kg per day. Progression was measured from changes in GFR calculated from the plasma disappearance of ^{51}Cr-EDTA, and dietary compliance and nutritional adequacy were monitored every three months. Of the 72 patients who were enrolled into the trial, 8 were excluded from the analysis: 3 withdrew voluntarily, and 5 were excluded for noncompliance with their diet or medications. Thus, the analysis was restricted to the 64 individuals who were compliant with therapy. End-stage renal disease developed in 9 of 33 patients (27%) who were given an unrestricted diet compared with only 2 of 31 (6%) who were compliant with the protein-restricted diet ($P < 0.05$). The mean GFR decreased in the control group from 15 to 6 ml/min (60% reduction; $P < 0.01$) whereas it fell from 14 to 12 ml/min in the low-protein diet group (13% reduction; nonsignificant probability) (Figure 2). The average protein intake calculated from urea excretion was ~0.7 g/kg per day in the low-protein diet group (Figure 2). Over the 18 months of observation, serum albumin and anthropometric measurements remained stable, whereas a modest albeit significant decrease in weight, serum transferrin, and total lymphocyte count occurred during the first six to nine months and then stabilized. These authors concluded that dietary protein restriction slows the rate of progression of renal failure and delays the time to onset of end-stage renal failure.

In contrast to these reports indicating that dietary protein restriction slows progression, Williams and associates did not demonstrate a benefit in their clinical trial (70). Some 95 CRF patients were randomly assigned either to a diet containing 0.6 g of protein/kg per day and 800 mg of phosphorus or to a diet providing more than 0.8 g of protein/kg per day and 1 g of phosphorus/day (a minimal restriction of phosphorus); a third group was assigned to at least 0.8 g of protein/kg per day with no phosphorus restriction (control group). Following randomization, patients were followed for 19 $\pm$ 3 months, and changes in Ccr were measured (70). Protein intake estimated from urea excretion (39) was significantly lower in the low-protein group (0.71 $\pm$ 0.02 g/kg per day, mean $\pm$ standard error; $P < 0.001$) compared with the low-phosphorus (0.92 $\pm$ 0.03)

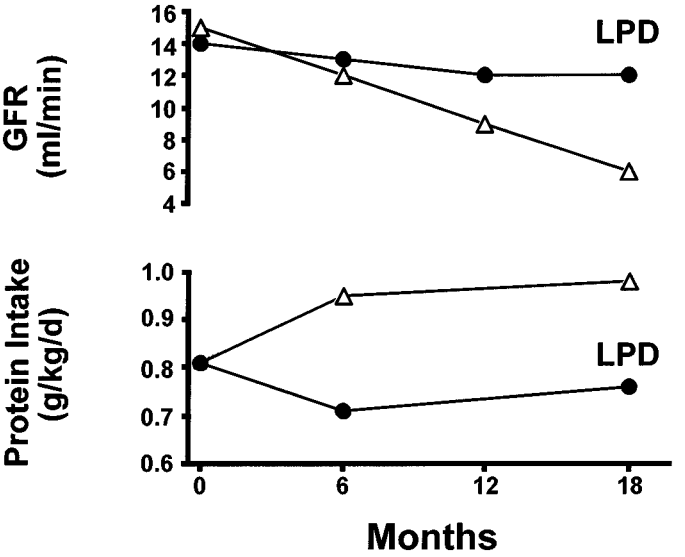

Figure 2 Changes in glomerular filtration rate (GFR) measured from the plasma clearance of iothalamate in patients with chronic renal failure prescribed a protein-restricted or unrestricted diet. The calculated level of dietary protein based on urea excretion (39) is also shown. The low-protein regimen significantly reduced the decline in GFR ($P < 0.01$). Modified from Ihle et al (24).

and control groups (0.95 ± 0.04). After randomization, the rate of decline in Ccr in the low-protein and low-phosphorus groups slowed by 2.2 ml/min per 1.73 m^2 per year whereas it increased by 1.0 ml/min per 1.73 m^2 per year in the control group (nonsignificant probability). Although assignment to the low-protein diet was not associated with a slower loss of Ccr, it should be appreciated that the control patients consumed less than the usual protein intake in the United Kingdom (i.e. 1.2 g/kg per day), which may have limited the studies power to detect a benefit of protein restriction. Changes in body weight, mid-arm muscle circumference, serum transferrin, albumin, and immunoglobulins did not differ between groups, so assignment to a protein-restricted diet did not adversely affect nutritional status.

Results from the Northern Italian multi-center trial were reported by Locatelli et al (35). In this trial, 456 patients were assigned either a low-protein diet providing 0.6 g/kg per day ($n = 226$) or a control diet containing 1.0 g/kg per day ($n = 230$). Patients were stratified into three groups, according to the severity of their renal insufficiency, and progression was evaluated by analyzing the time-to-dialysis and/or the doubling of Scr (renal survival). There was a

trend for improved renal survival in patients prescribed the low-protein diet (27 vs 42 end points in the control group; $P < 0.06$). In contrast, no difference was seen in the rate of decline in renal function between patients consuming the control and patients consuming the low-protein diets. Assuming that patients weighed 70 kg on average, based on urea excretion values (39) the protein intake was ~0.9 vs ~0.78 g of protein/kg per day in subjects assigned to the control and low-protein diets, respectively. Thus, there was a minimal difference (i.e. about 9.5 g of protein/day) between the low-protein and the control diets, and compliance was poor. It should also be appreciated that rates of renal progression were very slow in both the low-protein diet and the control groups and that based on their initial sample size estimates the study lacked sufficient power. Regarding nutritional status, only weights were recorded, and they did not change significantly.

Diabetic Nephropathy and Dietary Protein Restriction

Diabetes mellitus is the most common cause of end-stage renal disease in the United States, and the number of patients with diabetic nephropathy continues to rise. Therefore, evidence that a low-protein diet can slow the rate of progression of diabetic nephropathy would be of benefit.

Walker et al examined the course of renal function in 19 patients with type I insulin-dependent diabetes mellitus (IDDM) and persistent proteinuria while they consumed an unrestricted diet (1.13 g of protein/kg per day) (65). When the patients were switched to a diet providing 0.67 g of protein/kg per day, these investigators found that the loss of GFR and the rise in albuminuria slowed significantly (GFR from 0.61 to 0.14 ml/min per month). This slowing of progression was significant even after adjustment for differences in blood pressure, energy intake, and glycosylated hemoglobin levels.

Raal and colleagues compared diets containing 0.8 or $\geq$1.6 g of protein/kg per day in a six-month study of 32 type I IDDM patients with proteinuria and GFR values of 50–66 ml/min per 1.73 m^2 (59). Patients prescribed the low-protein diet exhibited no decline in GFR, while their proteinuria significantly decreased. In contrast, patients consuming the high-protein diet group lost GFR at an average rate of 1.3 ml/min per 1.73 m^2, and the degree of proteinuria increased. These differences could not be attributed to blood pressure or glycemic control. Thus, the low-protein diet appeared to exert a beneficial effect in this short-term study.

Zeller et al confirmed these benefits in a randomized, prospective, controlled trial involving 35 patients with type I IDDM with clinically evident nephropathy (GFR = 48 ml/min; proteinuria, 3.7 g/day) consuming a diet providing at least 1.0 (control group; $n = 15$) or 0.6 g of protein/kg per day (low-protein diet; $n = 20$) (71). Patients were followed for at least 12 months (average,

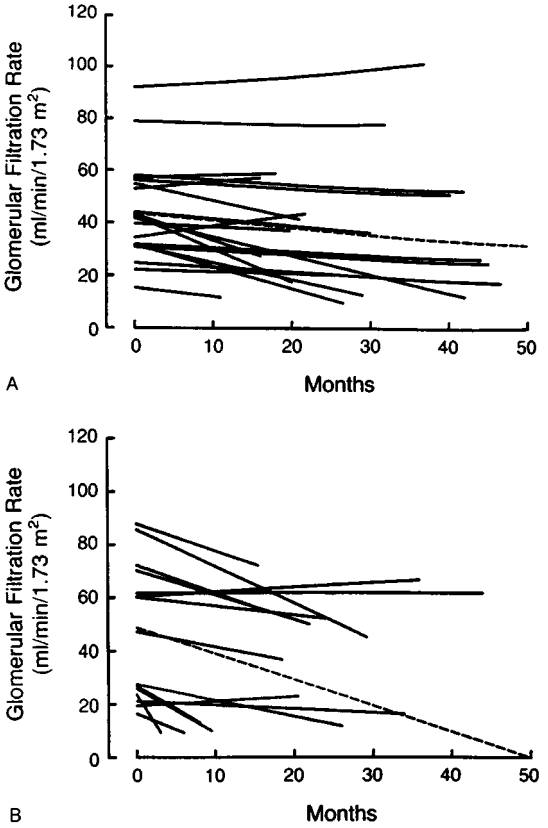

Figure 3 The change in glomerular filtration rate over time in 20 patients with diabetic nephropathy following a low-protein, low-phosphorus diet (*A*) and in 15 patients following a diet unrestricted in protein and phosphorus (*B*). The dashed line in each panel is the mean change in glomerular filtration rate over time for each group ($P = 0.02$ between groups). Reprinted with permission (71).

35 months), and rates of progression were assessed from the renal clearance of [^{125}I]iothalamate (GFR). Blood pressure was well controlled and the degree of glycemic control was comparable in both groups. Dietary protein intake was 1.08 ± 0.10 g of protein/kg per day (mean $\pm$ standard error) in the control group as compared with 0.72 ± 0.06 g of protein/kg per day in the low-protein diet (i.e. 111% of goal; $P < 0.001$), when the two patients whose intakes persistently exceeded 0.8 g of protein/kg per day were excluded. The rate of decline in GFR was fourfold slower in the patients consuming the low-protein diet (12.1 vs 3.1 ml/yr respectively; $P < 0.02$) (Figure 3). The beneficial effect

of the low-protein diet could not be attributed to better glycemic control or more frequent visits to the clinic. Although the mean arterial blood pressure was ~3 mm Hg lower in the low-protein diet group ($P < 0.05$), the authors concluded that it was highly unlikely that this small difference could explain the marked differences in the rates of progression between dietary groups. Importantly, there was no decrease in weight, mid-arm circumference, or serum albumin, indicating that this degree of protein restriction did not have adverse nutritional consequences over the three years of the study.

Supplemented Low-Protein Diets and Progression

Evidence that more restrictive diets (0.3 g of protein/kg per day) supplemented with a mixture of EAA slow progression is tenuous. Alvestrand & Bergstrom studied 17 patients with well-defined rates of decrease in Scr^{-1} despite treatment with a conventional low-protein diet (2). The EAA-based regimen slowed the decline in Scr^{-1} in 14 patients, but subsequent data by the same group was less positive and they concluded that any slowing of progression depended on the control of hypertension (8). However, the difference in protein intake was small (0.65 vs 0.86 g/kg per day).

The effects on progression of the same VLPD supplemented with a mixture of the nitrogen-free analogues of EAA (i.e. ketoacids) have been studied more extensively. Barsotti and coworkers found a linear loss of Ccr in 31 CRF patients treated with a diet containing 0.5 g of protein/kg per day (5). The loss of Ccr was interrupted in 11 of 12 patients after they were switched to a regimen containing about 0.2 g of protein/kg per day plus a supplement of the calcium salts of ketoacids. These results were confirmed in a larger group of patients; the loss of Ccr was halted in 27 compliant patients (6). Ketoacid salts of basic amino acids (i.e. ornithine and lysine) were given as a supplement to this low-protein diet to 17 patients with well-defined rates of progression (as assessed by changes in Scr^{-1}) (49). Ten patients had a significantly slower rise in Scr during long-term therapy (average, 20 months). Walser et al compared an EAA-based to a ketoacid-based regimen in 12 patients with advanced CRF using a cross-over study design (i.e. ketoacid then EAA and vice versa) (69). The ketoacid regimen appeared to slow progression to a greater degree than the EAA regimen, and there was no weight loss or decrease in serum albumin with either dietary regimen. Although the number of patients is small, it is important to emphasize that progression was blunted even in patients with advanced CRF.

The Modification of Diet in Renal Disease Study

The largest study to test the influence of low-protein diets on progression of renal failure was the National Institutes of Health sponsored Modification of Diet in Renal Disease Trial (MDRD study) (28). This multi-center, randomized,

prospective trial was designed to evaluate the impact of two levels of blood pressure [usual mean arterial pressure (MAP) = 107 mm Hg (~140/90) vs low MAP = 92 mm Hg (~125/75)] and two levels of protein intake on the rate of progression of renal failure (insulin-requiring diabetics were excluded). In study A, 585 patients with GFRs between 25–55 ml/min were randomly assigned either to their usual or to a low-protein diet (1.3 vs 0.58 g of protein/kg per day). In study B, 255 patients with GFRs between 13–24 ml/min were randomly assigned either to a low- or to a very-low-protein diet (0.58 vs 0.28 g of protein/kg per day); the very-low-protein diet was supplemented with a ketoacid–amino acid mixture and provided a protein intake similar to the low-protein diet. Thus, in study B both groups of patients were treated with a low-protein diet (i.e. there was no control diet).

Protein intake assessed from the 24-h urea excretion (39) and GFR was measured every four months from the renal clearance of [^{125}I]iothalamate. The mean follow-up was 2.2 years. Compliance with the prescribed protein intake was quite good [study A: 1.11 ± 0.19 vs 0.73 ± 0.15 g of protein/kg per day; study B: 0.69 ± 0.12 vs 0.46 ± 0.15 g of protein/kg per day (mean ± standard deviation at two-years follow-up)]. During the first four months following randomization, renal function declined more rapidly in study A patients assigned to the low-protein and low blood pressure groups ($P = 0.004$ and 0.01, respectively) (Figure 4). Thereafter, the rate of decline in GFR was 28% less in the low protein ($P = 0.009$) and 29% less in the low blood pressure group

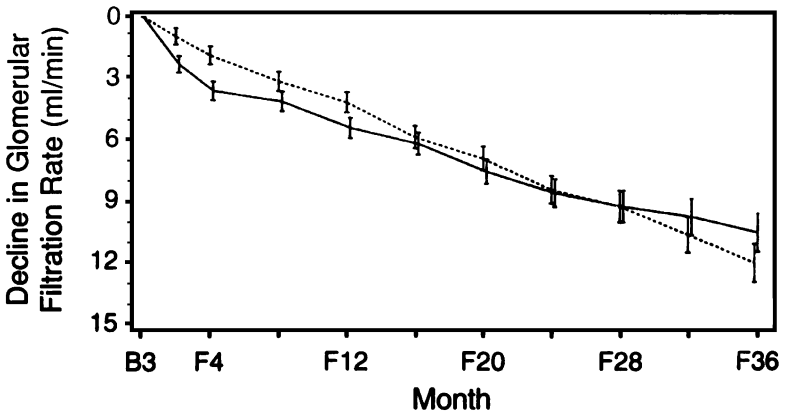

Figure 4 Changes in glomerular filtration rate in patients with moderately severe renal insufficiency (study A) extrapolated to three years (mean follow-up, 2.2 years) in the Modification of Diet in Renal Disease study (28). Note the initial, more rapid decline in patients assigned to the low-protein diet (*solid line*) followed by a slower decline in glomerular filtration rate.

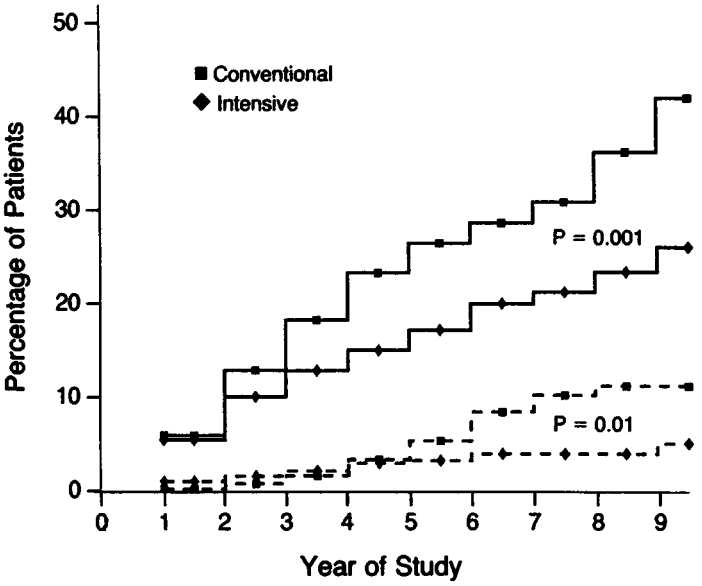

Figure 5 For comparison, the cumulative incidence of urinary albumin excretion greater than 300 mg/day (*dashed lines*) and greater than 40 mg per 24 h (*solid lines*) in diabetic patients receiving standard insulin therapy or intensive insulin therapy to control blood glucose in the Diabetes Control and Complications Trial (Adapted from Reference 15a. Copyright 1993. Massachusetts Medical Society. All rights reserved.) Note that the benefit of intensive insulin therapy was not detectable until after three to four years of therapy.

($P = 0.006$). When analyzed from randomization and regardless of compliance (i.e. intention-to-treat analysis), the projected decline in GFR at 3 years did not differ significantly between diet or blood pressure groups (Figure 4). In study B, the rate of decline in GFR was 19% slower in the very-low-protein as compared to the low-protein group ($P = 0.065$), and the cumulative incidence of end-stage renal disease or death did not differ between the diet groups. No beneficial effect of low as compared to usual blood pressure control was demonstrated in either study A or B, with the exception that the rate of progression was significantly slower in patients with proteinuria (>1 g/day) assigned to the low blood pressure group.

The authors concluded that in patients with moderately severe renal failure (study A), the slower decline in renal function that began four months following the institution of a low-protein diet suggested a small benefit of this dietary intervention (Figure 4). Among patient with more severe renal insufficiency (study B), a very-low-protein diet did not significantly slow the progression of renal disease when compared with a low-protein diet.

The interpretation of MDRD study conclusions are complicated by several factors, some of which were unanticipated at the time the study was designed. First, evidence of progression was not a requirement for enrollment, and approximately 15% of the study A control group had no evidence of loss of GFR. Conversely, there was a disproportionate number of patients (∼20%) with polycystic kidney disease, and these patients do not appear to benefit from protein restriction or aggressive treatment of hypertension, therefore potentially obscuring the impact of the nutritional intervention on the loss of GFR in other renal diseases. Second, the sample size requirements were based on the assumption that GFR would decline ∼6 ml/min per yr in patients eating an unrestricted diet and maintaining their usual blood pressure goals. In fact, overall rates of progression were ∼30% slower than expected, dampening the power to detect a benefit of the interventions. Third, the more rapid initial decline in renal function in study A patients assigned to the low-protein and low blood pressure groups was unexpected (presumably a hemodynamic effect). The intention-to-treat analysis, therefore, obscures a potential benefit of the interventions on the overall rate of decline in GFR. This is further exacerbated by the short study duration (2.2 years), as it is possible that with longer follow-up a statistically significant slowing of progression would have been demonstrated. For example, during the initial two years of follow-up, strict glycemic control in the Diabetes Control and Complications Trial appeared to exacerbate diabetic retinopathy, and the benefits of this intervention were not apparent until after three to four years of therapy (Figure 5) (15a). Likewise, the benefits of a supplement of fish oils on slowing the loss of renal function in patients with immunoglobulin A nephropathy could not be demonstrated before three years (16). Finally, since there was no control diet group in study B, the results do not support or refute the benefit of dietary protein restriction in patients with advanced renal insufficiency. In fact, when the results were analyzed according to the protein intake actually consumed, a benefit of dietary protein restriction was demonstrated (32). A reduction of 0.2 g/kg per day in protein intake was associated with a 29% slower rate of loss of GFR and a 41% prolongation in the time to dialysis ($P < 0.01$); however, there was no independent influence of the ketoacid regimen.

Meta-Analyses of Low-Protein Diets in Chronic Renal Insufficiency

Why do the conclusions differ among these studies? One possibility is that dietary protein restriction does not slow progression. Alternatively, the hypothesis was not tested since the protein intake between the experimental and control groups in several of these studies did not differ substantially. Finally, it is possible that the number of patients enrolled was insufficient to detect a benefit of protein restriction. To address these possibilities would require another

expensive study. An alternative approach has been to perform meta-analyses of the effectiveness of low-protein diets on the progression of CRF. This technique is based on combining results from several studies and is valid as long as the outcome being examined in each trial is similar.

Fouque et al performed a meta-analysis of six clinical trials, including 890 randomly assigned patients who were followed for at least one year (studies of diabetic patients were excluded) (20). An intention-to-treat analysis was used, and the outcome measure was the odds ratio for the initiation of dialysis or death (i.e. renal death). They concluded that five of the six trials showed a reduction in the number of renal deaths (61 for low-protein diet groups vs 95 for control groups) and calculated an odds ratio for renal death of 0.54 in patients prescribed a low-protein diet ($P < 0.002$), corresponding to a 46% decrease in the likelihood of kidney failure. They concluded that these results strongly supported the effectiveness of a low-protein diet in delaying the onset of end-stage renal failure.

Pedrini et al (56) also performed a meta-analysis of the course of renal failure in 1413 patients participating in five studies of patients with non-diabetic renal disease (24, 28, 35, 60, 70) and five studies including 108 patients with type I IDDM (4, 12, 17, 65, 71). An intention-to-treat analysis was also used, and the results of the MDRD study were included. In non-diabetic patients, the low-protein diet was associated with a 33% reduction in the risk of renal failure or death ($P < 0.007$). For diabetic patients, a low-protein diet reduced the risk of further kidney damage (a decrease in Ccr or GFR) or increasing proteinuria by 46% ($P < 0.001$). The beneficial effect of a low-protein diet could not be explained by differences in blood pressure or glycemic control. Moreover, angiotensin-converting enzyme inhibitors were used in only 9 of 108 diabetic patients, so any benefits were independent of this drug. Interestingly, these authors estimated that a study would need to enroll at least 1000 patients to detect a 33% reduction in the risk of renal failure or death. Neither the MDRD study or any other clinical trial has included this many patients.

In principal, a low-protein diet could reduce the risk of renal failure either by slowing the progression of renal disease or by ameliorating uremic symptoms. Based on the secondary analyses of the MDRD study indicating a strong correlation between achieved protein intake and both the rate of decline in GFR and the incidence of renal failure or death in patients with advanced renal disease (32), it seems probable that both mechanisms contribute to the beneficial effect of a low-protein diet.

CONCLUSIONS

As we have attempted to emphasize in this review, it has not been proven that dietary manipulation slows progression in unselected patients in spite

of many provocative observations from small numbers of patients. Randomized trials enrolling relatively large numbers of nondiabetic patients when analyzed according to diet assignment (rather than achieved intake) have not consistently demonstrated that the dietary protein restriction slows progression. In contrast, two meta-analyses have demonstrated a 33–46% reduction in the risk of renal failure, supporting evidence of the effectiveness of a low-protein diet in delaying the onset of end-stage renal failure in patients with nondiabetic renal disease (32, 56). Although based on results from studies that used smaller numbers of patients, evidence that dietary protein restriction can slow the loss of renal function and/or worsening of proteinuria (a predictor of progressive renal failure) in patients with type I IDDM appears more secure.

Our approach to the treatment of patients with CRF is to focus initially on blood pressure control, aiming for $<$125/75 mm Hg in patients with proteinuria exceeding 1 g/day (57). Angiotensin converting enzyme inhibitors should be considered first-line therapy since the rate of progression renal disease with these agents is $\sim$50% slower in both diabetic and nondiabetic patients, despite comparable blood pressure control (33, 40). For diabetic patients we also encourage intensive insulin therapy, since strict glycemic control slows the development of diabetic complications, including nephropathy (15a). In motivated patients with progressive renal failure who have not responded to treatment of hypertension, we initiate dietary protein restriction. From a practical point of view, compliance with low-protein diets can be assessed reliably with available methods, and these dietary regimens do not cause malnutrition if patients are monitored for nutritional adequacy (38, 39).

Finally, it should be recognized that the argument that a spontaneous decrease in dietary intake in patients with progressive CRF who consume unrestricted diets is justification to avoid low-protein diets (23, 25) is unfounded. In fact, the evidence suggests just the opposite. Namely, low-protein diets maintain nutritional status while limiting uremic symptoms (45, 64, 68). Moreover, their use in the predialysis period does not worsen and may improve patient survival following initiation of dialysis (14).

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