Dietary Protein Restriction in Chronic Renal Failure: Nutritional Efficacy, Compliance, and Progression of Renal Insufficiency

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ABSTRACT
Two findings prompted investigators to examine the effects of dietary manipulation on progression of chronic renal failure: dietary protein restriction is an effective method of ameliorating uremic symptoms and the course of renal insufficiency in an individual patient is predictable. Results from studies of patients and animals with chronic renal failure suggested that a low-protein, phosphorus-restricted diet could slow the rate of loss of renal function. In evaluating these studies, three questions should be considered. First, is the diet nutritionally adequate? Second, has dietary compliance been monitored and achieved? Third, is there evidence that restricting the diet will change the rate of loss of renal function? The scientific basis for each of these questions is addressed in this review.

Key Words: Uremia, nitrogen balance, dietary compliance, progression of renal failure

The economic impact of end-stage renal failure (ESRD) on the federal budget has been well described (1). ESRD also has a major impact on the social activities and lifestyle of the patients. For both reasons, a safe regimen that can interrupt the pattern of progressive chronic renal failure (CRF) could have a major impact on the treatment of CRF patients. Although not yet proven, reports suggest that implementation of a protein-restricted diet can change the prognosis of patients with progressive renal failure. These reports underscore the difficulties in clinical investigation: patients must participate with monthly visits for 1 or more years; a consistent change in the diet must be maintained; and the rate and pattern of changes in renal function must be analyzed. Some of these reports have been criticized for study design (including the lack of randomization), the use of data obtained retrospectively, inadequate attention to compliance, and/or the use of serum creatinine or creatinine clearance to estimate changes in residual renal function. For these reasons, conclusions regarding the efficacy of dietary protein and/or phosphorus restriction on progression in humans must be considered tentative. Results from ongoing, multicenter trials should provide more definitive evidence.

In this review, three questions to consider when evaluating reports of the effects of low-protein diets (LPD) on progression of CRF will be emphasized. First, is the new diet nutritionally adequate? Second, has compliance been monitored? Third, what published evidence supports the efficacy of restricting the diet in changing the course of renal insufficiency?

NUTRITIONAL ADEQUACY OF LPD

Three types of low-protein dietary regimens have been used in attempts to slow the progression of CRF: (1) a conventional LPD containing 0.6 g of protein/kg ideal body wt/day of primarily high-quality protein; (2) 0.3 g of protein/kg/day of predominantly vegetable proteins supplemented with a mixture of essential amino acids (EAA); or (3) the predominantly vegetable protein diet supplemented with a mixture of EAA and the nitrogen-free analogs of amino acids, called ketoacids.

LPD were initially used in CRF patients to relieve uremic symptoms associated with excessive accumulation of nitrogenous waste products. To suppress formation of waste products, the diets supplied less than the minimum daily protein requirement for normal adults and resulted in a period of negative nitrogen balance (B) lasting many weeks. It was reported...
that, ultimately, the patients achieved neutral $B_n$ (2,3), and it was proposed that CRF patients were capable of developing or activating a metabolic pathway that used the nitrogen in urea to synthesize amino acids. This would accomplish two goals: it would limit nitrogen waste product formation, and it would increase the supply of amino acids for protein synthesis.

Subsequent reports showed that urea is not important in meeting the nitrogen requirements of CRF patients (4–6). In fact, the minimum daily protein requirement of normal subjects, about 0.6 g of protein/kg ideal body wt/day (7), is also required by CRF patients (8). In fact, the neutral $B_n$ is possible only if the following conditions are met: (1) a high proportion of the protein (>60%) must be of high biological value, i.e., proteins containing a high proportion of EAA; (2) caloric intake must be adequate (9); and (3) a daily supplement of B and C vitamins must be taken (10,11). Obviously, active participation of a skilled dietitian is critical to ensure that the regimen is nutritionally sufficient and that the food preferences of a patient are included when recipes are planned. Evidence indicates that compliance can be achieved, i.e., nitrogen intake can be reduced substantially during long-term therapy (12–14).

$B_n$ IN UREMIA

If protein and caloric requirements are met and there is no catabolic stimulus, $B_n$ should become neutral within days of starting the diet. This occurs because metabolic responses are activated to return $B_n$ to zero during the initial period of negative $B_n$. This response is termed adaptation and includes a reduction in both amino acid oxidation and protein degradation; changes in protein synthesis appear to be less important (15). If the adaptation responses do not occur or are inadequate and $B_n$ remains negative, the process is called “accommodation” (16).

Many attempts have been made to identify the factors causing protein wasting in patients with advanced CRF (17). To date, the only factor shown to impair protein metabolism in renal failure is metabolic acidosis. May and associates provided the first demonstration that metabolic acidosis is catabolic. During an investigation of the source of glutamine used by normal rats to excrete excess acid (18), it was found that metabolic acidosis stimulated protein degradation in muscle. Glucocorticoids appeared to play a critical role in this process. It was also found that branched-chain amino acid catabolism is increased sharply in muscle of rats with metabolic acidosis (19). The mechanism for increased amino acid catabolism was linked to stimulation of the activity of the rate-limiting enzyme, branched-chain amino acid dehydrogenase. Recent data confirm that metabolic acidosis stimulates protein and amino acid breakdown in vitro (20) and that adrenalectomy blocks the increase in whole body catabolism (May et al. unpublished results). However, the role of glucocorticoids may be more complicated. England and Mitch (21) found that the addition of glucocorticoids to serum-supplemented media caused no additional increase in the proteolysis stimulated by intracellular acidification of cultured myocytes.

How do these results pertain to uremia? In rats with CRF, even a mild degree of metabolic acidosis (serum bicarbonate, <21 mM) causes accelerated catabolism of protein and branched-chain amino acids in muscle (22,23). In fact, both catabolic processes were shown to be fully corrected by adding NaHCO3 to the diet to “normalize” serum bicarbonate. Because glucocorticoid production was not suppressed by the addition of NaHCO3, there must be a key role for acidosis.

Acidosis also causes catabolism in CRF patients. Providing supplements of NaHCO3 decreases urea production and improves the $B_n$ of CRF patients (24), and Bergstrom and coworkers find that the valine concentration in muscle is linearly related to the plasma bicarbonate concentration in dialysis patients (25). Note that successful adaptation to a LPD requires suppression of amino acid oxidation and protein degradation—precisely those metabolic processes stimulated by metabolic acidosis. Taken together, these results suggest that untreated metabolic acidosis in CRF would increase the dietary protein requirement and counteract the adaptive responses to a LPD.

The metabolic responses of CRF patients to a LPD have received scant attention. Goodship and coworkers compared the metabolic responses of normal subjects and CRF patients (average serum creatinine, 5 mg/dl) to two levels of dietary protein: 1 and 0.6 g of protein/kg/day (26). They used the technique of infusing $^{13}$C-labeled amino acids and measuring expired $^{13}$CO2 and steady-state enrichment of the plasma amino acid with the labeled amino acid (16). $B_n$ was also measured. The results led to two important conclusions. First, it was found that the metabolic responses of CRF patients and normal subjects to the LPD were indistinguishable. Both groups exhibited a sharp reduction in amino acid oxidation and protein degradation; protein synthesis changed minimally with the LPD. However, none of the CRF patients had metabolic acidosis, which could counteract the adaptive responses to a LPD, so it is possible that more severely uraemic or acidotic patients might respond differently than the subjects studied by Goodship et al. (26). The second conclusion was that both normal subjects and CRF patients were in negative $B_n$, at least during the initial 7 days after beginning the LPD (Figure 1). The negative $B_n$ could not be adequately explained by a low energy intake or by failure to account for changes in the urea pool.
(this component of Bn was measured). Interestingly, negative Bn was not observed just after instituting a more restrictive regimen containing about 0.3 g/day of protein plus a supplement of ketoacids (27).

ASSESSMENT OF DIETARY COMPLIANCE

Successful therapy with a restricted diet requires a simple, accurate means of assessing dietary compliance. An effective method involves the measurement of the urea nitrogen appearance rate.

It has been known for many years that a change in urinary nitrogen excretion is the primary metabolic response to a change in dietary protein. In fact, the major component of urine nitrogen to vary with protein intake is urea (28-30). This is true because amino acids not used for protein synthesis are degraded and the nitrogen is used almost entirely for urea synthesis. It should be emphasized that the rate of urea production exceeds the steady-state rate of urea excretion in both normal and uremic subjects. This occurs because of the extrarenal clearance of urea, which is attributable to urea degradation by ureases of gastrointestinal bacteria (5,31). As noted earlier, there is no advantage of this process to CRF patients because the nitrogen is recycled to urea (32).

To measure net urea production in CRF and a low urea clearance, the rate of urea accumulation must be calculated. This is necessary because an increase or decrease in dietary protein can increase or decrease the size of the urea pool. In normal subjects, this refinement is generally unnecessary because urea is excreted so rapidly: the half-life is only about 7 h, so a change in the blood urea level after an increase or decrease in protein intake is 90% complete within 24 h. Fortunately, it is possible to measure changes in the size of the urea pool in CRF patients because the concentration of urea is equal throughout body water and water represents 60% of body weight in nonedematous patients (28,33). Hence, changes in the urea nitrogen pool can be calculated by multiplying 60% of body weight (in kilograms) by the serum urea nitrogen concentration (SUN) in grams per liter. After calculating changes in the size of the urea pool, the net production of urea, termed the urea appearance rate (UNA), can be calculated as the sum of urinary urea nitrogen excretion plus accumulation (positive or negative) of urea nitrogen; if SUN and weight are stable, UNA equals the excretion rate.

The nonurea nitrogen excretion rate, NUN, includes nitrogen excreted in feces and in uric acid, creatinine, and unmeasured nitrogenous products contained in urine. Maroni and coworkers found that NUN does not vary significantly with changes in nitrogen intake (Figure 2) and averages 0.031 g of nitrogen/kg/day (28). However, in patients receiving parenteral nutrition, fecal nitrogen is virtually absent and urea contributes a more variable fraction of urinary nitrogen (34). Consequently, the value, 0.031 g of nitrogen/kg/day is not a reliable estimate of NUN in such patients.

To assess dietary compliance of patients treated with a LPD, protein intake is converted to nitrogen by multiplying by 0.16 because protein is 16% of nitrogen (Table 1). If Bn is assumed to be zero, nitrogen intake will be equal to the sum of UNA plus 0.031 g of nitrogen/kg/day (28). As described above, to calculate urea appearance, body weight, SUN and the 24-h urine urea nitrogen content are needed (if SUN and weight are stable, urea appearance equals urinary urea nitrogen). If the difference between prescribed intake and calculated total waste nitrogen excretion exceeds 20%, then reasons for noncompliance or impaired Bn should be investigated (35). Other methods of assessing protein intake, including de-
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![Graph](image)

**Figure 2.** Calculated values of total NUN in normal subjects (closed triangles, circles, and squares) and in patients with CRF being treated with nutritional therapy (solid diamond, open circles with cross, open triangle, and solid diamond), by hemodialysis (open circle with solid square, open square with solid triangle), or continuous ambulatory peritoneal dialysis (open square with cross, open square with solid circle). The average value found by Maroni et al. (28) was 0.031 g of nitrogen/kg/day.

**Table 1.** Relationships among protein intake, B_n, and steady-state BUN

<table>
<thead>
<tr>
<th>Intake</th>
<th>B_n</th>
<th>B_n = ( 12.8 - (10.3 + 0.31 \times 70) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>50 g/d</td>
<td>12.8</td>
<td>12.8 - (10.3 + 0.31 × 70)</td>
</tr>
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</table>

If \( B_n \) is assumed to be zero, then intake can be estimated:

\[ B_n = \ln - \text{UNA} - \text{NUN} \]

\[ B_n = \ln + (0.31 \times \text{nigrogen/kg/day} \times \text{weight}) \]

If a 70 kg patient has a urea clearance of 6 mL/min, then the steady-state BUN is estimated as:

\[ \text{steady-state BUN} = \frac{12.8 - 0.031 \times \text{nigrogen/kg/day}}{C_{\text{urea}}} \times 100 \]

*Abbreviations and units: B_n, g of nitrogen/day; \( \ln \), nitrogen intake (g of nitrogen/day); UNA, g of nitrogen/day; BUN, mg/dL; \( C_{\text{urea}} \), urea clearance (L/day).

Dietary histories, etc., have been exhaustively reviewed by Bingham (36). Interview methods are less accurate, and the errors increase in repeatedly examined patients because they learn the appropriate responses to questions about dietary habits. To properly assess the influence of the diet on progression of renal failure, repeated evaluation of compliance is necessary and this is possible (Table 1).

**UREA GENERATION AND THE PROTEIN CATABOLIC RATE**

The relationships between urea and nonurea nitrogen metabolism are emphasized because of their practical usefulness (Table 1). It is also necessary to understand these concepts to clarify some confusing terms. The relationship between urea appearance and \( B_n \) has led to two new terms, urea generation and the protein catabolic rate, abbreviated PCR (37,38). Because urea synthesis in dialysis patients or nondialysis patients is determined by the amount of nitrogen released from the degradation of amino acids, it follows that urea generation in dialysis patients is the same as net urea production or urea appearance in nondialysis patients. Because both values are calculated from the same variables, both values parallel nitrogen intake closely.

A more confusing term is the PCR. PCR is simply the protein equivalent of the UNA plus 1.7 g of nitrogen/day to represent nonurea nitrogen. Because urea appearance (or generation) is the major component of nitrogen excretion varying with protein intake, it follows that PCR must approximate protein intake closely in patients who are in nearly neutral \( B_n \). However, the term PCR suggests that protein catabolism is being measured. Clearly, PCR does not measure protein catabolism because the daily turnover of protein in humans is far greater than protein intake (and, hence, PCR). Results of isotope dilution studies place the rate both of protein synthesis and of degradation at 45 to 55 g of nitrogen/day each (39). This is roughly equivalent to the protein in 1 to 1.5 kg of muscle. Although the principle of conservation of mass dictates that the difference between “whole body” protein synthesis and degradation must equal waste nitrogen production \( \times 6.25 \), the implication that PCR yields insight into or is a measure of whole body protein catabolism is erroneous.

There are limitations to these calculations to evaluate nitrogen metabolism. First, there is the problem of an incomplete urine collection, which limits the precision of the calculated intake. The only way to reduce this error is to collect urine for 3 or more days and obtain an average value. Second, there is the problem of proteinuria. The value of 0.031 g of nitrogen/kg/day for nonurea nitrogen excretion was derived from patients with less than 5 g/day of proteinuria. If proteinuria exceeds 5 g/day, the extra nitrogen lost must be added to the NUN value when assessing nitrogen balance or protein intake. This is especially important because of the evidence that proteinuria impairs protein metabolism. Kaysen and associates (40) have shown that proteinuria in nephrotic rats was associated with a decrease in body nitrogen content whereas increasing dietary protein led to worsening of proteinuria. In humans, the same group reported that reducing dietary protein to 0.8 g/kg body wt/day from 1.6 g/kg/day resulted in less proteinuria without compromising albumin homeostasis (41). Other investigators have not found such an effect (42). Regardless, the impact of a LPD on body protein stores is less clear, especially during long-term therapy.
DIETARY PROTEIN RESTRICTION AND PROGRESSION OF RENAL INSUFFICIENCY

Among the earliest studies of progression of CRF in patients treated with a conventional LPD was the report of Maschio et al. (43). They compared three groups of patients; Groups I and II differed in their initial serum creatinine values (1.5 to 2.7 and 2.9 to 5.4 mg/dL, respectively), and both were prescribed a diet containing 0.6 g/kg of predominantly high-quality protein, 40 kcal/kg energy intake, about 650 mg/day of phosphorus, and 1.0 to 1.5 g of calcium daily. Group III (initial serum creatinine, 1.6 to 4.7 mg/dL) had no dietary manipulation and served as a control group. Progression was assessed by changes in serum creatinine. The loss of renal function in Groups I and II was far slower than that in Group III. Dietary compliance was not rigorously evaluated.

The Verona group has periodically updated their experience (44). In 1989, they reported on 390 patients treated with a LPD for 54 ± 28 months: 57% of the patients had stable serum creatinine values, 11% had slower deterioration (defined as a decrease in 1/serum creatinine greater than −0.02 but less than −0.04 mL/mg/month), and 32% had rapid deterioration (greater than −0.04 mL/mg/month). Individuals with milder renal disease seemed to have a more favorable course, and patients with interstitial nephritis fared better than did those with chronic glomerulonephritis or polycystic kidney disease. Initial serum creatinine, proteinuria on presentation, and systolic and diastolic blood pressures were determined to be independent prognostic factors. No adverse effects of dietary therapy were noted, and indices of protein nutrition were well maintained (43). However, after an additional 5 yr of dietary restriction, there was significant loss of muscle protein and a decrease in serum albumin and transferrin concentrations (despite stable anthropometrics) in a subgroup of eight patients, suggesting that nutritional status tends to worsen after 5 yr or more (45). Unfortunately, the energy intake of these eight patients was lower (26 to 29 kcal/kg/day) than prescribed so it is not clear that dietary protein restriction alone causes protein wasting.

In another study of the influence of dietary protein restriction, Rosman and coworkers reported the results of their prospective randomized trial involving 149 patients monitored for at least 18 months (average, 24 months) after assignment to a LPD or a control diet (46). The prescription depended on the degree of renal insufficiency: 0.6 or 0.4 g of high-quality protein/kg/day for patients with creatinine clearances between 30 to 60 mL/min and 10 to 30 mL/min, respectively. After analyzing changes in serum creatinine and creatinine clearances, they concluded that the LPD slowed the loss of renal function; patients under 40 yr of age progressed more rapidly than did older subjects. The authors noted no adverse influence of protein restriction on nutritional status. Urea excretion values suggested differences in intake among the groups, but intake must have been higher than prescribed.

Recently, Rosman and coworkers have reported a 4-yr follow-up of 153 of the 248 patients initially entering the study (47). Although a significant benefit of dietary protein restriction was still noted, it was most apparent in the group with more advanced renal insufficiency. In both the control and LPD groups, there was a more rapid loss of creatinine clearance in men but the protein-restricted diet still seemed to slow the rate of loss of creatinine clearance. Evidence for a beneficial response in women with renal disease was minimal. From the data presented, slowing of progression was evident only in patients with glomerulonephritis. Differences in rates of progression in patients with polycystic kidney disease appeared to be related entirely to blood pressure control. In the other diagnostic groups, blood pressure was not correlated with the preservation of renal function.

An important aspect of this study was evidence concerning the effects of the LPD on body weight and serum proteins. Both indices of nutrition were stable over 36 months of dietary therapy, suggesting that the regimen preserved nutritional status. However, by using data provided in the article and the relationships described by Maroni et al. (28), it can be estimated that the average intake was about 0.7 g of protein/kg body wt/day and, hence, above the presumed minimum daily protein requirement. Because the prescribed intake of 0.4 g of protein/kg/day for patients with more advanced disease would be well below the minimum daily requirement, this part of the regimen cannot be recommended (7,8).

Results from a more recent randomized trial of the influence of a LPD on changes in renal function was published by workers from Australia. Ihle et al. conducted a prospective, randomized trial of a diet containing 0.4 g of protein/kg/day compared with an unrestricted protein intake in 64 subjects who were monitored for 18 months (13). Changes in GFR were determined from measurements of the plasma disappearance of [51Cr]EDTA. The groups were initially well matched for blood pressure and serum creatinine (range, 4.0 to 11.0 mg/dL), serum calcium, and phosphorus concentrations. End-stage renal failure developed in 9 of 33 patients (27%) who followed the unrestricted diets compared with only 2 of 31 (6%) who were felt to be compliant with the protein-restricted diet (P < 0.05). The GFR decreased on average from about 15 to 6 mL/min in patients without dietary restriction but did not change significantly in the protein-restricted group (e.g., the average change was from about 14 to 12 mL/min). Because the out-
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The response of patients with diabetic nephropathy is of interest for two reasons: first, a substantial proportion of patients with insulin-dependent diabetes develop renal failure, and this is a major cause of ESRD (1). Second, the metabolic abnormalities associated with diabetes could greatly complicate the design of the diet. One factor that seems to accelerate the proteinuria and, possibly, the rate of loss of GFR in patients with diabetic nephropathy is hypertension. The reason for interest in proteinuria is that most investigators believe that the presence of microalbuminuria indicates a high risk for the development of clinical diabetic nephropathy. Besides influencing the degree of albuminuria, there are a few instances in which effective antihypertensive therapy is reported to slow the decline in renal function in diabetic patients (48).

Dietary protein restriction has also been reported to have a beneficial effect in patients with diabetic nephropathy. For example, short-term protein restriction reduces protein losses in diabetic patients with microalbuminuria (14,49). There are only a few reports of the influence of dietary manipulation on changes in GFR. A report from Guy's Hospital in London detailed the course of 19 insulin-dependent diabetic patients with persistent proteinuria. When their diet was changed from an unrestricted diet (average, 1.13 g of protein/kg/day) to a diet averaging 0.67 g of protein/kg/day, there was a significant reduction in the rate of decline in GFR (from 0.61 to 0.14 mL/min/month) (49). Slowing of progression was significant even after adjustments were made for differences in blood pressure, energy intake, and glycosylated hemoglobin level. Albumin excretion and its fractional clearance also fell with the LPD.

In the United States, as well, diabetic patients appear to respond to a LPD. For example, the influence of a diet containing 0.6 g of protein/kg/day was compared with a regimen that did not restrict dietary protein (14). Besides the dietary manipulation, patients in the two groups were treated similarly over a period of 1.5 to 2 yr. Changes in renal function were evaluated by measuring serum creatinine as well as the renal clearances of creatinine and $^{[38]}$thesize; albuminuria was also measured. The results from this report provide several interesting conclusions. First, the group prescribed the LPD ate an average of about 0.7 g of protein/kg/day and did not develop malnutrition over the 1.5 to 2 yr of study. Thus, the investigators achieved reasonable compliance with the protein-restricted diet in spite of the metabolic abnormalities of diabetes. Second, the average declines in GFR and creatinine clearance were significantly slowed by the protein-restricted diet (Figure 4). It should be emphasized that some of the patients eating the unrestricted diet did not exhibit progressive loss of GFR during the study. Obviously, a spontaneous cessation of progression is a major issue in documenting whether the diet influences the progression of CRF. Third, the apparent beneficial effect of the dietary regimen could not be attributed to differences in blood pressure or glycemic control or to the frequency of examinations, making it most likely that dietary restriction was the major factor.

The evidence for a positive effect of a more restricted diet supplemented with a mixture of EAA is more tenuous. Alvestrand and coworkers reported that this regimen was effective in slowing the decline in the reciprocal of serum creatinine concentration...
Figure 4. Changes in GFR measured as the renal clearance of lathalamate in diabetic patients prescribed a protein-restricted diet or an unrestricted diet. Figure drawn from the results of Zeiller et al. (14).

in 17 patients with well-defined rates of progression in spite of a conventional LPD [50]. Only three patients had no slowing of progression with the EAA-based regimen. An interim evaluation of the results from an ongoing prospective, randomized trial by the Stockholm group has cast doubt on whether the EAA-supplemented dietary regimen does slow progression of CRF. Instead, they have raised the possibility that improved blood pressure control and more frequent evaluations slowed progression (51). In their view, any slowing of progression appeared to be most closely related to a small (2 mm Hg), but significant, reduction in diastolic blood pressure. The regimen also tended to improve proteinuria, but firm conclusions cannot be made because of the preliminary nature of the report. Of the 57 patients initially enrolled, 10 (24%) did not progress during the baseline period while eating an “unrestricted” diet. Of the 23 patients with progressive loss of function during the baseline period, 11 were randomized to the protein-restricted regimen and 12 were assigned to the unrestricted diet. Unfortunately, only five of the former and nine of the latter patients satisfied the requirements of dietary compliance, availability of GFR, and observation for more than 200 days. The average difference in protein intake was small (0.65 versus 0.86 g/kg/day) and, although significant, was not striking. Thus, a regimen based on EAA can control uremic symptoms but any benefit on progression is uncertain. Regarding a comparison with other regimens, there are little data. Walser and colleagues evaluated 12 patients with moderately severe CRF and a progressive decline in creatinine clearance, despite having received a diet containing 0.3 g of protein/kg/day plus an EAA supplement (52). After changing to a ketoacid supplement, all six patients whose serum creatinine exceeded 7.5 mg/dL continued to progress, but six of seven patients with serum creatinine values between 6.0 and 7.4 mg/dL at crossover had stable values of isotopically measured GFR during the 1- to 2-yr follow-up; one subject who was noncompliant progressed to dialysis. Few conclusions can be drawn from the study of such a small number of subjects.

The effects of a ketoacid-based regimen on progression also has been studied. Barsotti and coworkers studied the rate of loss of creatinine clearance in 31 patients treated with a diet containing 0.5 g of protein/kg/day [53]. They observed that the decline in clearance was linear in patients with different types of disease. The pattern was interrupted in 11 of 12 patients who were switched to a regimen containing about 0.2 g of protein/kg/day plus supplements of calcium salts of ketoacids. Similar results were reported in an examination of 48 patients (54). Twenty-seven of these patients were considered compliant, and, on average, their change in creatinine clearance was reversed from −0.65 to +0.15 mL/min/month (P < 0.005). Besides calcium salts, basic amino acid salts of ketoacids given as a supplement to a LPD appear to slow the loss of renal function. Among 17 patients with well-defined rates of progression as assessed by changes in the reciprocal of serum creatinine concentration, 10 (or 59%) had a significantly slower rise in serum creatinine during long-term therapy (average, 20 months) [12]. The effect was seen exclusively in patients who had not reached a stage of advanced renal failure (serum creatinine, above 8 mg/dL). As noted earlier, Walser and colleagues tested whether ketoacids influence the rate of loss of GFR in patients receiving an EAA-based regimen [52]. Four of five patients had significant slowing of progression. In another report from this group, the ketoacid regimen appeared to slow the loss of GFR more than an EAA-based regimen on a conventional LPD regimen [55]. However, the number of patients studied was small and the differences were not significant statistically.

As this review emphasizes, it has not been proven that dietary manipulation will slow progression in spite of many provocative observations. One or more of the prospective, randomized multicenter trials now in progress may answer this question. Hopefully, information in this brief review will be useful for readers examining reports evaluating the effects of dietary manipulation on patients with CRF.

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