McCollum Award Lecture, 1996: Protein-energy malnutrition in maintenance dialysis patients

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INTRODUCTION

I would like to express my deep appreciation to the American Society for Clinical Nutrition for the honor of the EV McCollum Award and the opportunity to present this lecture. Dr Elmer Verner McCollum was an outstanding biologist and nutritionist who had an enormous impact on the future course of the biological sciences. To receive an award associated with his name is indeed an honor.

In this paper I address a problem of major importance in nephrology: malnutrition in patients with chronic renal disease and renal failure. Patients with renal disease are prone to develop several types of malnutrition. These include deficiencies of certain minerals (eg, iron and possibly zinc and selenium) and vitamins (eg, vitamins B-6 and C, folic acid, and 1,25-dihydroxycholecalciferol [calcitriol]) and possibly impaired bioactivity of other essential nutrients (eg, carnitine) (1). However, because of the complexities of the subject matter and the clinical importance of the problem, I limit this discussion to the causes, effects, and potential methods of treating protein-energy malnutrition in patients with chronic renal failure, and, particularly, those individuals who are undergoing maintenance hemodialysis or chronic peritoneal dialysis.

THE PROBLEM OF PROTEIN-ENERGY MALNUTRITION IN PATIENTS WITH CHRONIC RENAL FAILURE

With possibly one exception, all of the about 30–40 surveys of the nutritional status of maintenance hemodialysis or peritoneal dialysis patients indicate that there is a high incidence of protein-energy malnutrition; the prevalence rate is about 16–54% in various reports (2–18). Results of two nutritional surveys that we conducted in maintenance dialysis patients are indicated in Table 1. We observed a similar prevalence of protein-energy malnutrition, about 40%, in both groups. About one-third of these patients had mild or moderate protein-energy malnutrition and about 6–8% had severe malnutrition.

Is protein-energy malnutrition bad for maintenance dialysis patients? Evidence clearly indicates that it is a powerful predictor for high morbidity and mortality. Such evidence for malnutrition as reduced visceral protein (eg, decreased predialysis serum albumin concentrations), reduced muscle protein mass (low predialysis serum creatinine concentrations), inadequate nutrient intake [low urea nitrogen appearance (UNA)], ie, net urea generation, an indicator of dietary protein intake], and decreased predialysis serum potassium, phosphorus, creatinine, and cholesterol concentrations are each associated with 12-mo odds ratios for increased mortality in maintenance hemodialysis patients (19–23). Low serum albumin and UNA also correlate with morbidity and mortality rates in chronic peritoneal dialysis patients (20, 23). In one large retrospective study, serum albumin concentrations were the strongest predictor of mortality, after age, in maintenance hemodialysis patients. In one report, the increased risk of mortality of patients with diabetes mellitus undergoing maintenance hemodialysis was eliminated after adjustment for their predialysis serum creatinine, albumin, and urea values (24). Also, the decreased mortality in African American as compared with white patients undergoing maintenance hemodialysis essentially disappears after adjustment is made for the higher predialysis serum creatinine concentrations of the African Americans (24). The relation of dietary energy intake, if any, with morbidity or mortality has not been examined carefully in maintenance dialysis patients because it is difficult and expensive to obtain accurate estimates of energy intake in large numbers of individuals. The findings that low serum cholesterol (21) and body mass index (EG Lowrie, personal communication, 1996) each correlate with odds ratios for mortality in maintenance hemodialysis patients suggest that energy intake is also a predictor of mortality.

Data showing these relations between nutritional status and morbidity or mortality were obtained from retrospective studies of cohorts of patients generally ranging in sample size from about 100 to 200 to about 20,000. These data were accessible because virtually all patients undergoing maintenance hemodialysis or chronic peritoneal dialysis in the United States routinely undergo many blood and serum chemistry measurements at monthly intervals. Large numbers of chronic dialysis facilities are often owned by a single employer, and laboratory measurements for the patients in these facilities are frequently performed in a central clinical laboratory. Moreover, deaths of patients who are treated in chronic dialysis units are accurately

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documented. Thus, it is relatively easy to assess the relation between nutritional status and mortality in large numbers of maintenance dialysis patients.

The foregoing findings do not prove that better nutritional intake or improved nutritional status will reduce mortality. Indeed, it is possible that comorbid conditions, including elevated inflammatory cytokines, may both reduce nutrient intake and cause protein-energy malnutrition and independently increase mortality. A recent report supporting this possibility indicates that if adjustments are made for comorbid conditions, the odds ratio for low serum albumin and mortality becomes substantially lower, although serum albumin still remains a significant risk factor for death (25). Moreover, the correlation between the protein nitrogen appearance and serum concentrations of albumin in dialysis patients is often poor (15, 20, 26). Serum concentrations of several acute phase proteins are increased in chronic hemodialysis patients (27). The finding that serum C-reactive protein concentrations correlate inversely (although poorly) with serum albumin in maintenance hemodialysis patients also suggests that comorbidity or inflammatory cytokines, at least, contribute to the relation between serum albumin and mortality (28, 29).

On the other hand, two retrospective studies suggest that improving nutritional status will reduce mortality (30, 31). Chertow et al (31) compared the odds ratio for mortality in 1679 malnourished maintenance hemodialysis patients who received intradialytic parenteral nutrition (ie, intravenous feeding only during dialysis treatments) with that in a matched group of 22,517 hemodialysis patients who did not receive parenteral nutrition. The data indicate that when the serum albumin concentration was ≤ 33 g/L, and particularly when the serum creatinine concentration was also ≤ 707 μmol/L (≤ 8.0 mg/dL), treatment with intradialytic parenteral nutrition was associated with a significantly lower odds ratio of mortality.

Capelli et al (30) examined the mortality rate in a nonrandomized study of 81 malnourished maintenance hemodialysis patients. Thirty-one patients did not receive intradialytic parenteral nutrition and served as control subjects, whereas 51 patients received intradialytic parenteral nutrition for a mean of 9 mo. The patients receiving intradialytic parenteral nutrition had a significantly greater survival rate. Prospective randomized controlled studies will be necessary to determine whether improved nutritional intake or nutritional status will decrease the mortality rate in maintenance dialysis patients.

### Table 1

<table>
<thead>
<tr>
<th>Protein-energy nutritional status of chronic dialysis patients</th>
<th>Maintenance hemodialysis (n = 36)</th>
<th>CAPD&lt;sup&gt;1,2&lt;/sup&gt; (n = 224)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No malnutrition</td>
<td>61</td>
<td>59</td>
</tr>
<tr>
<td>Mild-to-moderate malnutrition</td>
<td>33</td>
<td>33</td>
</tr>
<tr>
<td>Severe malnutrition</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>

<sup>1</sup> Continuous ambulatory peritoneal dialysis.

<sup>2</sup> Data obtained from reference 15.

### WHAT ARE THE CAUSES OF MALNUTRITION IN CHRONIC RENAL FAILURE?

Many potential causes of protein-energy malnutrition have been identified in patients with chronic renal failure:

1) Inadequate nutrient intake is probably the most important single cause of malnutrition (2, 3, 6, 9, 10, 12, 17, 18, 32, 33), and anorexia is the most important cause of reduced nutrient intake. Evidence indicates that anorexia may be induced by uremic toxins (34), underlying illnesses such as diabetes mellitus—which in its advanced stages alters gastric motility and emptying—and emotional disorders—particularly depression, which occur commonly in patients with advanced chronic renal failure. Chronic illnesses such as lupus erythematosus, emphysema, or congestive heart failure, and acute superimposed illnesses also may impair the patient's ability to eat. In my experience, such seemingly mundane problems as loss of dentures or inability to buy food can reduce nutrient intake. These latter factors frequently contribute to suboptimal nutrient intakes in maintenance dialysis patients because there is a high incidence of impoverishment among these individuals.

Recent evidence obtained from nonrandomized studies suggests that increasing the dose of dialysis will improve serum albumin, presumably by increasing appetite and nutrient intake (35). However, in all of these studies a substantial subset of patients still ingested low-protein diets. The dialysis dose above which nutrient intake will no longer increase as dialysis increases has not been defined. It is likely that the high prevalence of comorbidity in these patients will impair the ability of many individuals to develop a normal appetite regardless of their dialysis dose.

2) Patients with chronic renal failure frequently sustain superimposed acute or chronic illnesses that induce a hypercatabolic state and may also, as indicated above, reduce food intake (25, 36, 37).

3) Recent findings in maintenance dialysis patients indicate that part of the predictive value of serum albumin can be ascribed to comorbid conditions (25), that serum albumin does not always correlate with dietary protein intake (20), and that serum albumin correlates inversely with certain acute phase proteins, including C-reactive protein (28, 29). These observations raise the question as to whether both malnutrition and the direct relation between serum albumin and mortality reflect increased concentrations or actions of inflammatory and catabolic cytokines in uremia. Indeed, plasma concentrations or leukocyte production of interleukin 6 and tumor necrosis factor α are increased in advanced chronic renal failure (29, 38, 39). It is not known whether these increased concentrations are due to superimposed illness or are solely a direct result of the uremic condition per se.

The experience with different hemodialyzer membranes is pertinent in this regard. Some hemodialysis membranes stimulate a catabolic response. This is engendered at least in part by the release of interleukin from leukocytes, which activates the complement system. This, in turn, leads to the elaboration of catabolic cytokines, including tumor necrosis factor, and the activation of proteolytic enzymes released from polymorphonuclear leukocytes (38–42). Cuprophan, which is a commonly

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used dialyzer membrane, is considered to elicit such a catabolic response. More biocompatible dialyzer membranes are now available, although they are more expensive. Some experimental evidence suggests that patients who undergo maintenance hemodialysis with biocompatible membranes may attain more normal nutritional status than those who receive hemodialysis with more biocompatible dialyzer membranes (43).

4) The dialysis procedure itself removes nutrients, which may accentuate malnutrition. Depending on the permeability and clearance characteristics of the dialyzer membrane, on the blood and dialysate flow rates, on the duration of dialysis, and whether the patient is fasting or not, amino acid losses during a chronic hemodialysis treatment vary from about 6 to 12 g (44–48). Peptide losses average 2–3 g with low-permeability dialyzer membranes and are probably slightly greater with high-flux (large pore size), high-clearance hemodialyzers. About 15–25 g glucose are lost if a glucose-free dialysate is used; however, hemodialysate containing 5.6–11.1 mmol d-glucose monohydrate (dextrose)/L (100–200 mg/dL) is usually used, and a glucose gain or loss during hemodialysis is small if the patient is euglycemic—a glucose gain of roughly 10–12 g with hemodialysate containing 11.1 mmol d-glucose monohydrate/L (200 mg/dL). Generally, protein losses during hemodialysis are very small. An intriguing exception to this experience was noted recently (47, 49). Reused polysulfane dialyzers that are reprocessed many times with bleach and formaldehyde underwent an increase in porosity that was associated with large protein losses (± SD: 10.78 ± 7.87 g; range: 1.1–25.6 g) of albumin per hemodialysis with >24 dialyzer reuses (47). The manufacturing process for these polysulfane dialyzers is undergoing modification to prevent these dramatic increases in porosity.

Glucose is taken up by the patient during peritoneal dialysis because virtually all peritoneal dialysate solutions contain d-glucose monohydrate (1.5–4.25%). The quantity of glucose taken up by the patient is determined by the number of dialyses exchanges each day, the glucose concentration of each exchange, the dwell times of the exchanges, the permeability and clearance characteristics of the patient’s peritoneal membrane, and plasma glucose concentrations (50). In general, chronic peritoneal dialysis patients receive ~1255–2500 kJ (300–600 kcal) each day from the glucose absorbed from the hemodialysate (50). About 2–3.5 g amino acids/d are removed during continuous ambulatory peritoneal dialysis (CAPD) (51, 52).

In our experience, 8.8 ± 0.5 g (± SEM) total protein and 5.7 ± 0.4 g albumin are lost each day into peritoneal dialysate with CAPD (53). During acute peritonitis, a not rare complication of chronic peritoneal dialysis, protein losses increase. We observed the protein losses to increase to 15.1 ± 3.6 g/d with mild peritonitis (53), but losses may be much greater if peritonitis is severe. Protein losses fall rapidly with antibiotic therapy, but may remain elevated for many days to weeks after the peritoneal infection has been eradicated. There are losses of water-soluble vitamins and other bioactive compounds with both hemodialysis and peritoneal dialysis (2, 54, 55). An exception is vitamin B-12; because this vitamin is largely protein-bound in plasma, little is removed by dialysis treatment. Water-soluble vitamin losses are not great and are partly offset by the reduction in urinary vitamin excretion in patients with end-stage renal disease. These vitamin losses can be replenished easily from the diet. Individuals with poor nutritional intake or patients who avoid foods high in water or potassium content (eg, many fruits) may not replace the dialysate losses. Also, the metabolism or actions of some vitamins are altered in patients with chronic renal failure (56). These factors may lead to deficiencies of some water-soluble vitamins if vitamin supplements are not taken.

5) Patients with chronic renal failure may lose substantial amounts of blood as a result of gastrointestinal bleeding, which may be occult, frequent blood collections for laboratory measurements, and the sequestration of blood in the hemodialyzer (57, 58). Because blood is rich in protein, these blood losses may contribute to protein malnutrition. For example, an individual with a hemoglobin concentration of 120 g/L will lose about 16.5 g protein in each 100 mL blood removed.

6) It is possible but not established that the many endocrine disorders in renal failure may promote protein or energy malnutrition. There is resistance to the actions of insulin and insulin-like growth factor I (IGF-I) (59–61). Hyperglucagonemia and increased plasma parathyroid hormone concentrations may promote amino acid catabolism and glucoseogenesis (62, 63). Altered vitamin D metabolism may also promote malnutrition. Calcitriol deficiency, as well as hyperparathyroidism, has pervasive effects on calcium metabolism; vitamin D deficiency may cause a proximal myopathy; and 25-hydroxylcholecalciferol (calcitriol) stimulates skeletal muscle protein synthesis in vitro (64). Hence, it is not unlikely that calcitriol deficiency also causes protein wasting.

7) It is likely that the accumulation of toxic metabolic products in renal failure may engender malnutrition. There are probably hundreds of metabolic products that accumulate in plasma or tissues in renal failure; >120 such compounds have been identified (65, 66). Some of these compounds are bioactive (65, 66), and it is likely that some of them have catabolic or antiinflammatory actions. Some of the compounds that accumulate are acids. In animals with or without renal failure, acidemia enhances the decarboxylation of branched-chain amino acids and induces protein degradation. In humans, acidemia suppresses albumin synthesis, promotes negative nitrogen balance, and may induce protein catabolism (67, 68).

8) It is also possible that the loss of the metabolic processes within the failing kidney promotes protein-energy malnutrition. The kidney is one of the most metabolically active organs in the body (69). It synthesizes or degrades many biologically active compounds, including certain amino acids (eg, alanine and serine), peptides (eg, peptide hormones), glucose, and fatty acids. The disruption of some of these processes might alter nutritional status.

9) Finally, it is possible but not proven that exogenously derived toxins that are retained in renal failure may promote malnutrition. One such candidate might be aluminum, which accumulates in renal failure and can cause microcytic anemia, bone disease, encephalopathy, and debility (70, 71).

Many of the foregoing causes of protein-energy malnutrition are operative before patients develop end-stage renal disease
and commence maintenance dialysis therapy. Indeed, the prevalence of protein-energy malnutrition in patients beginning chronic dialysis treatment appears to be similar to the prevalence in patients who are well established on maintenance dialysis treatment. Moreover, we have found that in both children undergoing chronic peritoneal dialysis and adults undergoing maintenance hemodialysis, their nutritional status at the onset of dialysis treatment is a strong predictor of their nutritional status 1–2 y later (72). For example, among individuals who were commencing either self-care hemodialysis or intermittent chronic peritoneal dialysis at home, those who had a low relative body weight during the first 3 mo after commencing dialysis therapy had a low relative body weight 1–2 y later (Figure 1). In contrast, those patients who had a normal or high relative body weight at the onset of maintenance dialysis therapy had a body weight as high or higher 1–2 y later. Similar findings were observed in these same patients with regard to arm muscle diameter (Figure 2). If arm muscle diameter was reduced during the first 3 mo after commencing self-care hemodialysis or intermittent peritoneal dialysis at home, it was low 1–2 y later. On the other hand, those individuals who had a normal or large arm muscle diameter at the onset of maintenance dialysis therapy had a normal or large arm muscle diameter on reevaluation 1–2 y later.

In my experience, which does not constitute a prospective or systematic examination of this matter, nondialyzed patients with chronic renal failure appear to be at greatest risk for developing malnutrition between the time when the glomerular filtration rate (GFR) decreases to < 8–10 mL/min and especially when the GFR is < 5 mL/min and the time when the patient is well established on maintenance dialysis therapy (73).

The following factors probably conspire to induce a high risk for malnutrition at this time. Patients with GFRs < 8–10 mL/min, especially < 5 mL/min, are often frankly uremic and have advanced anorexia and often nausea and vomiting. They are frequently fasted for diagnostic procedures and also for vascular access or peritoneal catheter placement. While waiting for such surgery, their dialysis treatment may be delayed (even though temporary vascular accesses can usually be placed); they may become more uremic and anorexic because of these delays. Also, intercurrent catabolic illnesses often occur during this time.

Recently, we had the opportunity to examine the nutritional status of ∼1700 patients who were entering the baseline period of the Modification of Diet in Renal Disease (MDRD) Study (33). The data indicated that the patients' dietary protein and energy intakes and nutritional status began to decline when their GFR was about 25–38 mL min⁻¹ · 1.73 m⁻². These findings were obtained in a cross-sectional study comparing the patients' nutritional status with their GFR, measured as the [¹³¹]iodotoluamide clearance, by using the observations from each individual as a single data point. This decline was noted not only for protein and energy intakes, but also for serum transferrin, body weight, midarm muscle circumference, and percentage body fat. It should be emphasized that the patients were not malnourished—indeed, frank malnutrition was a criterion for exclusion from the study—but there was clearly a statistically significant trend toward worsening nutritional status as the GFR decreased.

A low energy intake was also observed in the patients who participated in both the pilot study and the main clinical trial of the MDRD Study, even though these patients met with a trained nephrology research dietitian once a month (32). This was observed in patients whose GFR at the onset of the study ranged from 25 to 55 mL min⁻¹ · 1.73 m⁻² as well as in those with a lower GFR, 13–24 mL min⁻¹ · 1.73 m⁻². These results may be particularly relevant because the patients in the MDRD Study were almost certainly a healthier subset of patients with chronic renal insufficiency because of the study's exclusionary criteria. On the other hand, patients with chronic renal disease who are carefully managed with low-nitrogen

![FIGURE 1](https://academic.oup.com/ajcn/article-abstract/65/5/1544/4655542/6555531)  
**FIGURE 1.** Direct relation between the relative body weight (RBW) obtained during the first 3 mo after the initiation of self-care hemodialysis or home intermittent peritoneal dialysis in nondiabetic patients and diabetic patients and their RBW 1–2 y later. RBW was calculated as the patient's weight × 100 divided by the median weight of normal individuals of the same age range, height, skeletal frame size, and sex, as determined from National Health and Nutrition Examination Survey data (8). Data from MJ Blumenkrantz, JD Kopple, and JW Coburn, unpublished observations, 1983.

![FIGURE 2](https://academic.oup.com/ajcn/article-abstract/65/5/1544/4655542/6555532)  
**FIGURE 2.** Direct correlation between the upper arm muscle diameter (AMD) obtained during the first 3 mo after initiation of self-care hemodialysis or home intermittent peritoneal dialysis in nondiabetic patients and diabetic patients and their upper AMD 1–2 y later. Data from MJ Blumenkrantz, JD Kopple, and JW Coburn, unpublished observations, 1983.
diets may retain normal serum albumin concentrations as they develop advanced or terminal renal failure (32, 33, 74). These results do not prove that low protein or energy intake is a common cause of the deterioration in nutritional status, but they are consistent with this possibility.

WHAT ARE THE DIETARY PROTEIN REQUIREMENTS OF CHRONIC DIALYSIS PATIENTS?

There are surprisingly few studies that address this question (75–81) and almost all of these studies were carried out by using hemodialyzers, schedules of hemodialysis or peritoneal dialysis therapy that are no longer used, or both. What data are available suggest that maintenance hemodialysis patients consuming diets providing ≲ 0.8 g · kg⁻¹ · d⁻¹ are often in negative nitrogen balance; patients consuming diets providing ≧ 1.25 g protein · kg⁻¹ · d⁻¹ are in neutral or positive nitrogen balance (76, 77). We examined the dietary requirements of six hemodialysis patients who underwent nitrogen-balance studies for 21 d in the clinical research center at Harbor–UCLA Medical Center while they ingested a diet providing, daily, 156 kJ (37 kcal)/kg body wt and 1.13 g protein/kg (Table 2) (82). These individuals had been participating in a metabolic balance study in which they ingested a constant protein intake but in which dietary energy intake varied every 3 wk, in random order, to about 105, 146, and 188 kJ (25, 35, and 45 kcal) · kg⁻¹ · d⁻¹. Mean (± SEM) nitrogen balance after equilibration, and adjusted for changes in body urea nitrogen, was +40.7 ± 30.0 mmol/d (+0.57 ± 0.42 g/d). If one adjusts for unmeasured nitrogen losses, which we estimated to be about 35.7–71.4 mmol/d (0.5–1.0 g/d), balance was neutral in these patients. Note that there was a rather large variance in nitrogen balances, and some patients were in negative nitrogen balance with this intake, at least for the 3-wk period of study.

We also examined dietary protein requirements in 13 studies that were conducted in eight patients undergoing CAPD who were fed low- or high-protein diets while they lived in a clinical research center under constant metabolic balance conditions (81). Patients were fed diets that provided an average daily protein intake of 0.98 or 1.44 g/kg. Total energy intake from both dietary intake and uptake of d-glucose from the peritoneal dialysate averaged 173 ± 8 (x ± SEM) and 176 ± 5 kJ (41.3 ± 1.9 and 42.1 ± 1.2 kcal) · kg⁻¹ · d⁻¹ with the low- and high-protein diets, respectively. The low- and high-protein diets were fed for about 16–35 d, and balance data were collected for 14–33 d. There was a curvilinear relation between dietary protein intake and nitrogen balance in the 13 studies (Figure 3). Nitrogen balance increased as protein intake rose until the protein intake was 1.09 g · kg⁻¹ · d⁻¹. At this intake, nitrogen balance was significantly positive. As dietary protein increased above this amount, there was no further increment in nitrogen balance. Most other studies in chronic peritoneal dialysis patients suggest that a rather similar quantity of dietary protein is necessary to maintain nitrogen balance (78–80).

On the basis of these findings and taking into account individual variability, the frequent occurrence of mild intercurrent illnesses that may raise protein requirements, and the high prevalence of protein malnutrition in these individuals, we recommend about 1.2 g protein · kg⁻¹ · d⁻¹ as a safe intake for maintenance hemodialysis patients and 1.2–1.3 g · kg⁻¹ · d⁻¹ for CAPD patients. We have also recommended, although without testing this question experimentally, that about 50% of this protein should be of high biological value.

How do these recommended intakes compare with the actual intakes of maintenance dialysis patients? The average dietary protein intakes of maintenance hemodialysis patients have been examined in several studies, including two clinical trials in which the results were remarkably similar (3, 6, 8, 9, 17, 18). These individuals ingest, on average, about 0.95–1.0 g protein · kg⁻¹ · d⁻¹. The reported dietary protein intakes of chronic peritoneal dialysis patients are similar (7, 17, 83, 84). Of greater concern are the dietary energy intakes of maintenance hemodialysis patients, which, in virtually all reports, average between 96 and 117 kJ (23 and 28 kcal) · kg⁻¹ · d⁻¹ (3, 6, 7, 9, 18).

Are these reduced energy intakes an adaptive response to a low rate of energy expenditure or are these low energy intakes maladaptive? We examined this question in a series of studies. In one study, energy expenditure was measured by indirect calorimetry in eight men undergoing continuous ambulatory peritoneal dialysis. Each circle represents the mean balance data observed in an individual patient fed a constant diet for 14–33 d in a clinical research unit. The curved line represents the calculated relation between nitrogen balance and protein intake. Reprinted with permission from Kidney International (81).

**TABLE 2**

<table>
<thead>
<tr>
<th>Nitrogen balance in six maintenance hemodialysis patients fed a diet providing 1.1 g protein · kg⁻¹ · d⁻¹ /</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Energy intake (kJ · kg⁻¹ · d⁻¹)</td>
<td>156 ± 8.8</td>
</tr>
<tr>
<td>(kcal · kg⁻¹ · d⁻¹)</td>
<td>37.3 ± 2.1</td>
</tr>
<tr>
<td>Protein intake (g · kg⁻¹ · d⁻¹)</td>
<td>1.13 ± 0.02</td>
</tr>
<tr>
<td>Duration of study (d)</td>
<td>21 ± 0</td>
</tr>
<tr>
<td>Nitrogen intake (mmol/d)</td>
<td>870.8 ± 37.8</td>
</tr>
<tr>
<td>(g/d)</td>
<td>12.2 ± 0.53</td>
</tr>
<tr>
<td>Nitrogen balance (mmol/d)</td>
<td>–72.8 to 149.2'</td>
</tr>
<tr>
<td>(g/d)</td>
<td>–1.02 to 2.09</td>
</tr>
</tbody>
</table>

/ Data reproduced from reference (82). x ± SEM. / Nitrogen balance after equilibration on the diet, adjusted for body urea nitrogen but not for unmeasured losses. / Range.
calorimetry in a group of normal subjects, patients with chronic advanced renal failure not in need of dialysis therapy, and patients who were undergoing maintenance hemodialysis (85). Energy expenditure was measured at bed rest after an overnight fast under basal conditions and while the patients were sitting quietly in a large easy chair (Figure 4). Energy expenditure under these conditions was not different between men and women in any of these three groups, nor was it different among the three groups. Similarly, energy expenditure was not different among the three groups during graded exercise on a stationary bicycle. The increase in energy expenditure after a standard mixed-nutrient meal was also similar in the three groups (Figure 5) (85). The finding that energy expenditure in patients with chronic renal failure was similar to that of normal individuals has also been reported by others (86).

We also examined the effects of different energy intakes on nitrogen balance and body composition in six nondialyzed men and women with chronic renal failure: mean (± SD) creatinine and urea clearances were 10.8 ± 3.5 and 4.7 ± 2.2 mL/min, respectively (87). Patients were studied in the clinical research center while they ingested a constant-protein diet that provided about 0.55–0.60 g protein · kg⁻¹ · d⁻¹ and were fed diets that provided 188, 146, 105, or 63 kcal (45, 35, 25, or 15 kcal) · kg⁻¹ · d⁻¹. Sixteen nitrogen-balance studies were conducted while the patients ingested these different energy diets; the mean (± SD) duration of study with each intake was 23.7 ± 5.7 d. The order in which the different energy diets were fed to an individual patient was determined randomly. Patients exercised daily on a stationary exercise bicycle.

Nitrogen balance, after equilibration and after adjustment for changes in body urea nitrogen and unmeasured losses, correlated directly with dietary energy intake. When the estimated unmeasured nitrogen losses of about 41.4 mmol/d (0.58 g/d) were adjusted for, nitrogen balance was negative in one of four patients fed 188 kcal (45 kcal) · kg⁻¹ · d⁻¹, in one of five patients fed 146 kcal (35 kcal) · kg⁻¹ · d⁻¹, in three of five patients fed 105 kcal (25 kcal) · kg⁻¹ · d⁻¹, and in both patients fed 63 kcal (15 kcal) · kg⁻¹ · d⁻¹ (Figure 6). UNA, UNA divided by nitrogen intake, and several plasma amino acid concentrations, measured after an overnight fast, each correlated inversely with dietary energy intake. These observations suggest that although some clinically stable nondialyzed patients with advanced chronic renal failure who are ingesting about 0.55–0.60 g protein · kg⁻¹ · d⁻¹ may maintain neutral or positive nitrogen balance with an energy intake < 126 kcal (30 kcal) · kg⁻¹ · d⁻¹, a dietary intake providing about 146 kcal (35 kcal) · kg⁻¹ · d⁻¹ is more likely to maintain neutral or positive nitrogen balance, maintain or increase body mass, and reduce net urea generation (87).

As indicated above, we also examined dietary energy requirements in four men and two women who were undergoing maintenance hemodialysis (82). Individuals lived in a clinical research center and were fed diets providing 188, 146, and 105 kcal (45, 35, and 25 kcal) · kg desirable body wt⁻¹ · d⁻¹. Each dietary energy intake was ingested for 21–23 d, and in each patient energy intakes were given in random order. With all diets, the protein intake was constant for each patient and averaged 1.13 ± 0.02 g · kg⁻¹ · d⁻¹ (x ± SEM). Each patient exercised daily on a stationary exercise bicycle.

Body weights rose with energy intakes of 188 and 146 kcal (45 and 35 kcal) · kg⁻¹ · d⁻¹ (P < 0.05) and fell with an intake of 105 kcal (25 kcal) · kg⁻¹ · d⁻¹ (P < 0.05) (Figure 7). Nitrogen balance, after equilibration with the diets and adjusted for

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**FIGURE 4.** Direct correlation between resting and sitting energy expenditure in normal subjects, nondialyzed patients with chronic renal failure, and patients undergoing maintenance hemodialysis in men (●) and women (○). Reprinted with permission from *Kidney International* (85). To convert kilocalories to kilojoules, multiply by 4.184.

**FIGURE 5.** Mean (± SEM) energy expenditure after a standard test diet in normal subjects (●; n = 12), nondialized patients with chronic renal failure (●; n = 8), and patients undergoing hemodialysis, (●; n = 13). The energy expenditure in the morning before and after the meal and the increment in energy expenditure after the meal were not significantly different among the three groups. Reprinted with permission from *Kidney International* (85). To convert kilocalories to kilojoules, multiply by 4.184.
Changes in body urea nitrogen and estimated unmeasured losses, was neutral with the diet providing 188 and 146 kJ (45 and 35 kcal) \cdot \text{kg}^{-1} \cdot \text{d}^{-1} and negative with the diet providing 105 kJ (25 kcal) \cdot \text{kg}^{-1} \cdot \text{d}^{-1}. Nitrogen balance was neutral or positive in all six patients fed 188 kJ (45 kcal) \cdot \text{kg}^{-1} \cdot \text{d}^{-1}, in four of the six patients fed 146 kJ (35 kcal) \cdot \text{kg}^{-1} \cdot \text{d}^{-1}, and in none of the six patients fed 105 kJ (25 kcal) \cdot \text{kg}^{-1} \cdot \text{d}^{-1} (Figure 8). Nitrogen balance and changes in body weight, midarm muscle circumference and area, and percentage body fat each correlated directly with energy intake. Interestingly and in contrast with the findings in the chronic renal failure patients, plasma concentrations of many amino acids, obtained after an overnight fast, were directly correlated with energy intake. The energy intake, estimated from regression equations, that would be necessary to maintain neutral nitrogen balance was 161 kJ (38.5 kcal) \cdot \text{kg} \text{desirable body wt}^{-1} \cdot \text{d}^{-1}; to maintain an unchanging midarm muscle circumference and muscle area the estimated energy intake was 143 and 138 kJ (34.1 and 33.0 kcal) \cdot \text{kg}^{-1} \cdot \text{d}^{-1}, respectively. To maintain an unchanging body weight or percentage body fat, the projected energy intake was 136 and 134 kJ (32.4 and 32.0 kcal) \cdot \text{kg}^{-1} \cdot \text{d}^{-1}.

The results of these studies, which it is emphasized were carried out in only six maintenance hemodialysis patients, suggest that maintenance hemodialysis patients may require about 159 kJ (38 kcal) \cdot \text{kg}^{-1} \cdot \text{d}^{-1} to maintain nitrogen balance when they ingest an average of 1.13 g protein \cdot \text{kg}^{-1} \cdot \text{d}^{-1}. Somewhat lower energy intakes—about 134–142 kJ (32–34 kcal) \cdot \text{kg}^{-1} \cdot \text{d}^{-1}—were necessary to maintain body weight, muscle mass, and muscle fat.

Thus, the low dietary energy intakes of nondiazyed patients with chronic renal failure and patients undergoing maintenance hemodialysis are not adaptive. Rather, they are maladaptive and inadequate for the patients’ energy needs. The finding of a high incidence of protein and energy malnutrition, as described above, is consistent with the thesis that the dietary intake of patients with chronic renal failure is often inadequate. The observation that the average dietary protein intake of maintenance dialysis patients is not markedly different from what is recommended suggests that the greater nutrient deficiency is for energy intake.

**ARE THESE EXPERIMENTALLY DETERMINED ENERGY REQUIREMENTS EXCESSIVELY HIGH?**

The data obtained from normal individuals that are reflected in the dietary energy needs (not the recommended dietary allowances) proposed by the Food and Nutrition Board, National Research Council, National Academy of Sciences, are instructive in this regard. Their recommended dietary energy intakes for normal, nonpregnant, nonlactating men and women who engage in light to moderate physical activity are (in...
evaluation. When feasible, the patient and his or her family unit (ie, spouse, friends, parents, or children) should be involved in the counseling sessions. If assessment of nutritional status indicates that nutrient intake is too low, a search for causes is instituted. As indicated above, causes may vary from associated physical illnesses or emotional disorders to such seemingly mundane factors as loss of dentures or inability to purchase or prepare food because of poverty or physical or mental debility. Dietary counseling to correct reduced or unhealthy nutrient intakes is performed by a nutritionist, and, ideally, by one who is trained and experienced in renal dietetics. If dietary counseling is unsuccessful, food supplements may be tried. Some supplements are designed for the specific nutritional needs of dialysis patients (89).

Dialysis patients who do not respond adequately to dietary counseling can often be induced to increase their protein and energy intakes by ingesting commercial food supplements (90–92). These supplements are usually liquid preparations and are well-tolerated by a subset of dialysis patients who appear able to ingest supplements for many weeks or months. It is ironic that there is a disproportionately high prevalence of impoverished individuals in the chronic dialysis patient population, and most reimbursement agencies, including Medicare, will not reimburse the costs of food supplements. Hence, many malnourished maintenance dialysis patients who might benefit from food supplements do not take them because of this reluctance or inability to pay the purchase price. We hope that if the health delivery program for maintenance dialysis patients converts to a capitated system, oral food supplements will be included as part of the provisions covered by the capitation rate.

Tube feeding is an alternate approach for providing nutrition to malnourished, anorexic maintenance dialysis patients. There are almost no published reports concerning its use in adult dialysis patients, but several series of cases of infants and children undergoing chronic dialysis who received tube feeding have been reported (93–95). The data were collected without the use of control subjects. Nonetheless, the results are clearly encouraging, with the children displaying an increased growth rate as compared with their pretube-feeding status. Catch-up growth was often inadequate, as it has been with most treatments with the exception of short-term (eg, 1 y) growth hormone treatment (see below). Research is needed to define optimal methods for delivering nutrients and preferred nutritional formulations for tube-feeding adults undergoing chronic dialysis.

Intradialytic parenteral nutrition offers the advantages of providing intensive parenteral nutrient therapy with use of concentrated hypertonic solutions three times weekly during hemodialysis treatments without the need for establishing a central venous line. The nutrients are infused into the drip chamber for the venous blood line at the distal end of the dialyzer. Very few of the infused fuels are removed by the dialysis procedure; only about 10% of the infused amino acids are lost into the dialysate (46).

There have been ≥16 studies that have examined the potential benefits of intradialytic parenteral nutrition in maintenance hemodialysis patients (5, 30, 31, 96–108). Perhaps of particular interest are the nonrandomized study of Capelli et al (30) and the retrospective case-mix study of Chertow et al (31), which suggest that intradialytic parenteral nutrition may reduce

\[ y = 0.067x - 2.08 \]
\[ r = 0.62 \]
\[ P < 0.01 \]

**FIGURE 8.** Direct correlation between dietary energy intake and nitrogen balance, after equilibration on each diet, in six patients undergoing maintenance hemodialysis while they lived in a clinical research center. Circles indicate values from an individual patient; open circles indicate the two female patients. Thin lines connect data from the same individual; heavy lines indicate the least-squares regression line. Reprinted with permission from *Kidney International* (82). To convert kilocalories to kilojoules, multiply by 4.184.

**WHAT CAN BE DONE TO PREVENT OR TREAT PROTEIN-ENERGY MALNUTRITION IN MAINTENANCE DIALYSIS PATIENTS?**

Strategies for the prevention or treatment of protein-energy malnutrition include 1) more standard therapy: dietary counseling, a possible increase in the dialysis dose, food supplements, enteral feeding, intradialytic parenteral nutrition, and total parenteral nutrition; and 2) more experimental therapy: amino acids in dialysate (peritoneal dialysis and hemodialysis), appetite stimulants (eg, megestrol acetate), and growth factors (growth hormone, IGF-1, and anabolic steroids).

For almost all of these maneuvers there is clinical experience and often prospective clinical studies or retrospective analyses providing evidence of the effectiveness of treatment. Unfortunately, there are virtually no randomized, prospective, well-controlled large-scale trials indicating that nutritional therapy will prevent or improve nutritional status, reduce morbidity or mortality, or improve quality of life.

The first approach to the management of chronic dialysis patients with protein-energy malnutrition is to obtain a medical history and conduct a physical examination and psychosocial

\[ \text{kJ} \cdot \text{kg}^{-1} \cdot \text{d}^{-1} \], respectively, as follows: ages 19–24 y, 167 (40 kcal) and 159 (38 kcal); 25–50 y, 155 (37 kcal) and 151 (36 kcal); and ≥51 y, 126 (30 kcal) and 126 (30 kcal) (88).
mortality rates in malnourished maintenance hemodialysis patients (see above). Although most of these trials reported some benefit of this therapy, there were major problems with the interpretation of the data. Most of the studies did not have randomized control groups. In several studies, patients were either given amino acids with little or no nonnitrogenous fuel substrates or they were given fuel substrates without amino acids, but not both. In some studies it was not clear whether all patients had protein-energy malnutrition. Dietary intake of foods was usually not controlled or monitored. Small numbers of patients were evaluated, this was especially true for the randomized, prospective controlled trials. Almost invariably, the outcome data were not adjusted for the comorbid conditions of the patients in the study, and in those few cases in which they were adjusted, it was not done adequately. In most studies, the outcome measures were nutritional indexes; only rarely were the arguably more important outcomes of morbidity, quality of life, or mortality examined. Comparisons of intradialytic parenteral nutrition with such less expensive treatments as food supplements or tube feeding were not done.

Government reimbursement agencies have made it very difficult to qualify malnourished maintenance hemodialysis patients for reimbursement for intradialytic parenteral nutrition. As a result, the possibility of conducting a well-designed, large-scale randomized controlled clinical trial to test the potential benefits of intradialytic parenteral nutrition is small, at least for the near future.

Several experimental studies have examined the possibility of providing nutrients to the patient by hemodialysis or peritoneal dialysis (48, 109–112). This routinely occurs for several nutrients because patients take up calcium, sometimes other minerals, and bicarbonate or acetate with each hemodialysis or peritoneal dialysis treatment. Also, as indicated above, peritoneal dialysis virtually always provides glucose to the patient. Indeed, it is generally accepted that a major cause for the greater body fat mass and for the propensity for elevated serum lipid concentrations in patients undergoing chronic peritoneal dialysis as compared with those individuals receiving maintenance hemodialysis is the greater glucose concentration and uptake from peritoneal dialysate than from hemodialysate (30).

There is more research experience with the provision of amino acids in peritoneal dialysate than in hemodialysate. When 1.1% amino acids are substituted for glucose in peritoneal dialysate, about 80% of the amino acids are absorbed over a 4-h period (111, 112). Several clinical trials, usually without randomized control groups and often not well controlled, suggest that such dialysate, used once or twice daily, may improve the nutritional status of chronic peritoneal dialysis patients (112). One study of 19 malnourished patients undergoing CAPD examined the nutritional response to this treatment under carefully controlled conditions (113). Most patients had been ingesting low amounts of dietary protein before the study. They lived in clinical research centers for 35 d while they underwent nitrogen-balance studies. During this study the patients ingested a constant dietary protein and energy intake and followed a constant CAPD regimen, except that from the 16th through the 35th d, a dialysate containing a 1.1% mixture of essential and nonessential amino acids was substituted each day for one or two of the standard glucose-containing dialysates. The total intake of dietary protein plus dialysate amino acids was between 1.1 and 1.3 g · kg body wt⁻¹ · d⁻¹. The results of this study indicated that after subjects began the exchanges with the dialysate that contained the amino acids, nitrogen balance changed from neutral to strongly positive, total-body protein anabolism—determined from [¹⁴C]glycine turnover studies and calculated from the difference between protein synthesis and degradation—increased and there was a rise in serum transferrin and total protein concentrations and several postabsorptive plasma essential and nonessential amino acids (113). Serum albumin did not change. Patients developed a mild metabolic hyperchloremic and anion gap acidosis that, in the future, should be readily controlled by changing the electrolyte composition of the dialysate solution.

A prospective clinical trial was subsequently conducted in which 105 malnourished patients undergoing chronic peritoneal dialysis were randomly assigned to receive for 3 mo either one or two of the dialysate exchanges with 1.1% amino acids, instead of dextrose, or all of the dialysate exchanges with standard dextrose solutions (114). There was no significant difference in the response of nutritional indexes between the two groups, but this may reflect the inclusion of some patients in the study who were not hypalbuminemic and in whom dietary protein intake was not very low. When an analysis of the subset of patients who were in the lowest tertile for baseline serum albumin concentrations was conducted, the patients prescribed the dialysate containing 1.1% amino acids had a significant increase in serum albumin and prealbumin concentrations, whereas those assigned to receive exclusively the standard dialysate containing D-glucose had no change. In the patients in the highest tertile for baseline albumin, midarm muscle circumference rose only in the patients receiving the dialysate containing amino acids.

Several studies have examined the uptake of amino acids from hemodialysate (48, 109). Chazot et al (48) evaluated six clinically stable male maintenance hemodialysis patients in the postabsorptive state while they underwent three typical hemodialyses. During one hemodialysis, a standard hemodialysate was used that contained no amino acids; during the other two hemodialyses, the standard hemodialysate was supplemented with amino acids in concentrations that were one or three times the typical postabsorptive plasma amino acid concentrations of normal adults. The patients lost 9.3 ± 2.7 g amino acids when they were dialyzed with no amino acids in the dialysate, and plasma total amino acid concentrations decreased by 52% by the end of the dialysis procedure. During the hemodialysis performed with dialysate containing one times the postabsorptive plasma amino acid concentrations, there was no net exchange of total amino acids from dialysate (1.5 ± 3.6 g), and plasma total amino acids did not change. With hemodialysis providing three times the postabsorptive concentrations of amino acids in the dialysate, there was a net amino acid uptake of 39.1 ± 14.8 g and plasma total amino acids increased by 50%. These studies show that substantial amounts of amino acids can be taken up from hemodialysate during a standard hemodialysis procedure. More research is required to show whether this treatment, possibly with other nutrients added, will improve the nutritional status or clinical outcome of malnourished dialysis patients. It also is necessary to show that providing nourishment to patients through a dialyzer has advantages over less-expensive techniques, such as food supplements. I suspect that for selected patients who will not ingest food supplements, this treatment may be beneficial.
The use of appetite stimulants, particularly megestrol acetate, is also under investigation. This progestational agent improves appetite and food intake in malnourished patients with carcinomatosis or acquired immunodeficiency syndrome (115, 116). Many individuals gain edema-free weight when taking this medicine, but it is not clear whether only body fat mass rises or whether other nonaqueous corporeal constituents increase as well. Clinical trials are currently ongoing to examine whether megestrol acetate will increase appetite and food intake and improve nutritional status in malnourished anorexic patients with chronic renal failure.

Anabolic steroids have been used to enhance protein anabolism in patients with acute renal failure and patients undergoing chronic peritoneal dialysis (117, 118). The anabolic effects of these agents appear to abate with chronic use. Moreover, there are several adverse effects associated with anabolic steroids. In addition, in the preerythropoietin era, large doses of these medicines were given chronically to maintenance dialysis patients to raise their hematocrits. There was the clinical impression—which, to my knowledge, was never confirmed with systematic studies—that the patients receiving large doses of anabolic steroids were not better nourished than those who did not receive these medicines. These observations, taken together, have dissuaded nephrologists from using anabolic steroids for the chronic treatment of protein-energy malnutrition.

Finally, several studies have examined the potential benefits of recombinant human growth hormone (rhGH) or recombinant human IGF-I (rhIGF-I) to improve the nutritional status of malnourished patients undergoing maintenance hemodialysis or peritoneal dialysis. Many excellent reviews discuss the physiology and metabolic and clinical effects of these growth factors in health or disease (119-121). In the practice of nephrology, rhGH is used to promote catch-up growth as well as normal growth in children who have chronic renal disease and are not receiving dialysis, who are undergoing maintenance dialysis therapy, or who are renal transplant recipients (122-124). rhGH is effective at stimulating growth in most of these children. However, some children are rather refractory to treatment, and in some the effects of rhGH on growth tend to diminish after about 1 yr of treatment.

The use of rhGH and rhIGF-I to enhance anabolism in adults with chronic renal failure is experimental. The rationale for the use of these growth factors is that many malnourished chronic renal failure patients will not eat adequately even after counseling or provision of food supplements. Moreover, even when adequate nutrition is provided, the metabolic status of the patient, perhaps engendered by their comorbid conditions, may impair the patient’s ability to utilize the nutrients for anabolic processes. In individuals without renal disease who have acute illness or catabolic stress, rhGH can reduce the catabolic response and preserve protein mass; when these latter patients receive nutritional support, rhGH may even induce positive nitrogen balance and protein turnover (125-127). In experimental animals, rhGH may enhance immune function (128).

Some patients who are severely stressed may be unresponsive to rhGH (129, 130). In these latter studies, those patients who did not show an anabolic response to rhGH also displayed little or no rise in serum IGF-I. Thus, it appears that sepsis or severe catabolic stress as well as severe malnutrition may blunt the response of serum IGF-I to rhGH and thereby nullify the anabolic effects of rhGH (131).

Several short-term studies have been carried out in which maintenance hemodialysis patients were treated with rhGH. Ziegler et al. (132) treated five such patients with rhGH for 2 wk and observed a decrease in UNA and in predialysis serum urea, phosphorus, and parathyroid hormone concentrations (132). Schulman et al. (105) treated seven malnourished maintenance hemodialysis patients with intradialytic parenteral nutrition for 12 wk. During the last 6 wk of treatment, patients also received rhGH injections. Serum transferrin concentrations increased during treatment with intradialytic parenteral nutrition. When rhGH treatment was added, the protein equivalency of total nitrogen appearance decreased from 0.81 ± 0.04 (SEM) to 0.67 ± 0.03 g·kg⁻¹·d⁻¹, suggesting a more positive nitrogen balance, and the serum albumin rose significantly.

We evaluated whether rhGH injections may improve nutritional status in malnourished maintenance hemodialysis patients (133). Maintenance hemodialysis patients who were malnourished, as evidenced by low serum albumin or body weight, lived in the Harbor-UCLA Clinical Research Center for ≤ 35 d. During this time, patients were maintained on their usual hemodialysis regimen and on a constant protein and energy intake that was similar to their prehospital diet. After completing a baseline period to allow for equilibration, patients were given daily subcutaneous injections of rhGH, 0.05 mg/kg body wt. Six patients (three men and three women) aged 41-67 y (mean: 59 y) were studied for 14 or 21 baseline days and about 17 d of rhGH injections. Patients 3 and 4 developed acute illnesses during the study. The patients’ responses to rhGH were divided into two types. Patients 1, 2, 5, and 6 became anabolic, often dramatically so, whereas patients 3 and 4, who were acutely ill during the study, showed a less dramatic anabolic response to rhGH. Predialysis serum urea nitrogen fell markedly in patients 1, 2, 5, and 6 and less so in patients 3 and 4. Nitrogen balance increased in all six patients who received rhGH, but the increase was substantially greater in patients 1, 2, 5, and 6. All patients manifested an increase in serum growth hormone after commencing rhGH injections. Serum IGF-I concentrations increased substantially in patients 1, 2, 5, and 6, whereas in patients 3 and 4 serum IGF-I was low before rhGH treatment and rose only slightly with rhGH injections.

It may be relevant that the patients who had the greatest improvement in nitrogen balance, fall in predialysis serum urea nitrogen, and increase in serum IGF-I also had the highest nitrogen intake in addition to no acute catabolic stress. These findings are similar to the previous observed lack of anabolism or rise in serum IGF-I in response to growth hormone injections in some patients or animals with marked malnutrition or severe catabolic stress (129-131). The present study in malnourished or acutely stressed maintenance hemodialysis patients, in association with the previous observations of the failure of rhGH to promote protein anabolism in severely stressed, nonuremic patients, provides a rationale for using rhIGF-I rather than rhGH to treat severe malnutrition—particularly when protein and energy intakes are low—or hypercatabolic stress in patients with renal failure. Such an approach could circumvent the impairment in rhGH-induced IGF-I synthesis or release that may occur under these conditions.

As a result of these observations, we have begun to examine malnourished maintenance dialysis patients treated with rhIGF-I. Six malnourished CAPD patients were treated in the
Harbor–UCLA Clinical Research Center for 35 d by using a protocol similar to that used in the rhGH studies (134). The patients maintained their usual CAPD treatment regimen and constant protein and energy intakes, which were similar to those of their prehospital diet. From days 16 to 35, the patients received injections of 100 μg rhIGF-I/kg body wt every 12 h. Nitrogen balance, which was essentially neutral during the 15-d baseline period, became abruptly and substantially positive when rhIGF-I injections began. The positive nitrogen balance was sustained throughout the 20 d of rhIGF-I injec-
tions. The findings raise the possibility that rhIGF-I may have a role to play in the treatment of protein-energy malnutrition. Clearly, more research is required to show that this chronic treatment with rhIGF-I is safe and effective in these patients.

A key dilemma faced by researchers and clinicians concerning the maintenance of good protein-energy nutrition or the treatment of malnutrition is a lack of a clear definition of the goals of nutritional management. Is the goal merely to maintain normal or supranormal elements of body composition with increased total body protein; increased fat, elevated glycogen mass, or all three components; increased protein in selective tissues such as skeletal muscle or liver; increased total body enzyme mass; or increased amounts of other specific proteins? If so, which body proteins should we strive to increase? Should good nutritional management focus on maintaining or improving biological functions? Should we focus on enhancement of immunologic surveillance or response, increased host resistance, or enhanced capacity to heal tissues? Should the goal be more clinically oriented such as the enhancement of the individ-
al’s sense of energy, vigor, well-being, quality of life, or level of rehabilitation? Should the goal emphasize the appropriate balance of cytokines in tissues (eg, tumor necrosis factor and interleukin 2 or interleukin 6 concentrations) or the plasma concentrations of the cytokines or counterregulatory hor-
mones? And apropos the relation between nutritional and clinical responses, what should the target for blood pressure and control of uremia be? Indeed, there is growing evidence that many amino acids, lipids, vitamins, and other nutrients may function as pharmacologic agents. It is my perception that the clinical role for the nutritional management of chronic renal failure patients is still in its infancy. The possibility that better nutrition of these individuals may improve physiology and metabolism, enhance health, and prolong life appears to be real.

SUMMARY

There is a high prevalence of protein-energy malnutrition in patients with chronic renal failure who are undergoing mainte-
nance dialysis therapy. The high prevalence of malnutrition is a potentially serious problem because indexes of protein-
energy malnutrition are powerful predictors of mortality in maintenance dialysis patients. Although the data do not prove that improving nutritional intake will reduce mortality, nonran-
domized studies suggest that provision of additional amino acids and energy to such patients is associated with reduced mortality. There are many causes for protein-energy malnutri-
tion in maintenance dialysis patients. Among the three most important factors are the nutritional status of the patient before commencing dialysis therapy, inadequate protein and energy intakes after they become dialysis patients, and acute and chronic illnesses. Improving the nutrient intake of maintenance dialysis patients is a challenging task because most chronic renal failure patients with malnutrition are anorectic, and dietary counseling has had limited success at increasing their nutrient intake. Other methods for improving nutritional status in adults, infants, and children with chronic renal failure that have been tried with varying degrees of success include increasing the dose of dialysis and the use of food supplements and tube feeding. Less well-proven techniques for the treat-
ment of protein-energy malnutrition include intradialytic par-
enteral nutrition. The use of appetite stimulants and such growth factors as rhGH and rhIGF-I are still in the experimen-
tal stage.

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