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NUTRITIONAL MANAGEMENT OF MAINTENANCE DIALYSIS PATIENTS: Why Aren't We Doing Better?

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■ **Abstract** About 40% of patients undergoing maintenance dialysis suffer from varying degrees of protein-energy malnutrition. This is a problem of substantial importance because many measures of nutritional status correlate with the risk of morbidity and mortality. There are many causes of protein-energy malnutrition in maintenance dialysis patients. Evidence indicates that nutritional decline begins even when the reduction in glomerular filtration rate is modest, and it is likely that the observed decrease in dietary protein and energy intake plays an important role. The nutrient intake of patients receiving maintenance dialysis also is often inadequate, and several lines of evidence suggest that toxins that accumulate with renal failure suppress appetite and contribute to nutritional decline once patients are on maintenance dialysis. Recent epidemiologic studies have suggested that both increased serum levels of leptin and inflammation may reduce nutrient intake and contribute to the development of protein-energy malnutrition. It is likely that associated illnesses, which are highly prevalent, contribute to malnutrition in maintenance dialysis patients. Recent data from the United States Renal Data System registry suggest that in the United States, the mortality rate of dialysis patients is improving. However, it remains high. We offer suggestions for predialysis and dialysis care of these patients that can result in improvement in their nutritional status. Whether this improvement will result in a decrease in patient morbidity and mortality is unknown.

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INTRODUCTION

In the United States, over the past decade the number of patients undergoing maintenance dialysis (MD) has increased progressively (231). The vast majority of these patients are treated by in-center maintenance hemodialysis (MHD), while about 15% receive chronic peritoneal dialysis (CPD). Even though there has been a progressive decline in the annual mortality rate of these patients, it remains inordinately high: The adjusted first-year mortality rate for MD patients who commenced dialysis in 1997 was 18.4 per 100 patient years (231). The high prevalence of protein-energy malnutrition (PEM) and its association with poor patient outcome was recognized almost two decades ago and has been reaffirmed in numerous studies since then. Although PEM is most widely recognized and studied, it should be pointed out that many MD patients may have deficiencies of vitamins and minerals, and malnutrition of these nutrients may have adverse clinical ramifications as well. In this review, we focus on some of the key factors that contribute to PEM in MD patients and suggest some reasons why we are not doing better at preventing or treating this disorder.

Prevalence of Protein-Energy Malnutrition in Maintenance Dialysis Patients

Numerous surveys of MD patients in the United States and elsewhere have demonstrated a high prevalence of PEM. The estimates of prevalence vary, but the average is about 40% (4, 35, 76a, 91, 128, 139, 163, 174, 177, 185, 190, 237, 246). The majority of these patients have mild to moderate malnutrition, with about 6%–8% having severe malnutrition. At first glance, it may appear that the prevalence rates of various measures of PEM have remained unchanged over the past two decades. However, the patients on dialysis today are, on average, older and sicker (e.g. from diabetes mellitus, vascular disease) than they were even 5 years ago (231), which may explain the finding that the prevalence of PEM remains high.

Relationship Between Malnutrition and Patient Morbidity and Mortality

In MHD patients, nutritional parameters that have been independently correlated with increased mortality and morbidity include low visceral protein concentrations (e.g. low predialysis serum albumin) (7, 34, 38, 39, 57, 88, 90, 117, 128, 132, 172,

227), reduced muscle protein mass (indicated by low predialysis serum creatinine concentrations) (7, 30, 39, 128), decreased nutrient intake (low urea nitrogen appearance rates—i.e. net urea generation, an indicator of dietary protein intake) (1, 43, 178), low predialysis serum cholesterol concentrations (7, 43, 57, 128), and low total body nitrogen (5, 185). Furthermore, in direct contrast to findings in the general population, body size is inversely correlated with patient outcome in MHD patients (43, 48, 113, 117, 240). Similarly, in CPD patients, low serum albumin levels (6, 7, 20, 28, 42, 74, 140, 192, 208, 220), reduced urea nitrogen appearances (52, 143, 220), decreased edema-free/fat-free mass (33, 143), low serum creatinine (6, 7) and creatinine appearance rates (182), poorer overall protein and energy nutritional status as assessed by subjective global assessment (33, 143), or decreased total body nitrogen content (52, 185) also are associated with high morbidity and mortality. Hence, understanding the mechanisms that lead to malnutrition and how they contribute to the excess morbidity and mortality are critical for improving the outcomes for these patients.

ETIOLOGY OF PROTEIN-ENERGY MALNUTRITION IN MAINTENANCE DIALYSIS PATIENTS

MD patients constitute a highly heterogeneous group of individuals, and the etiology of PEM in these patients is likely to be multifactorial. The proposed causes are summarized in Table 1. It is likely that in a given patient, varying combinations of these causes result in PEM, and the relative contributions of some or all of these factors vary widely between patients. A detailed analysis of each of these etiologies is beyond the scope of this discussion, and a brief overview of the key factors is presented in the following sections before discussion of the key question: Why are we not doing better?

FACTORS LIMITING IMPROVEMENT IN NUTRITIONAL STATUS

Nutrition in the Predialysis Phase of Chronic Renal Failure

Evidence of nutritional decline begins long before patients with progressive chronic renal failure (CRF) develop end-stage renal disease. Several single- and multicenter studies from various parts of the world have demonstrated the presence of PEM in a significant proportion of patients with decreased renal function (i.e. predialysis patients) or in those who have just commenced MD therapy (28, 153, 176, 210, 218, 242). Between 1995 and 1997, over 60% of all incident MD patients in the United States were classified as hypoalbuminemic (168). During the screening (baseline) phase of the Modification of Diet in Renal Disease (MDRD) Study, a cross-sectional assessment of 1785 clinically stable patients

TABLE 1 Causes of protein-energy malnutrition in patients with end-stage renal disease

Low nutrient intake
Inadequate solute clearances
Impaired gastric emptying
Increased leptin levels
Comorbidity
Intraperitoneal instillation of dialysate
Comorbidity
Inflammation
Endocrine disorders of uremia
Resistance to insulin
Resistance to insulin-like growth factor-1 and growth hormone
Hyperparathyroidism
Hyperglucagonemia
Nutrient losses during dialysis
Blood loss
Occult gastrointestinal bleeding
Venipuncture
Sequestration in hemodialyzer
Metabolic acidosis

with moderate to advanced CRF [mean $\pm$ standard deviation glomerular filtration rate (GFR): 39.8 $\pm$ 21.1 ml/min/1.73 m^2] demonstrated a high prevalence of measures of nutritional decline (153). It must be pointed out that the vast majority of patients studied were not malnourished. Of the patients, 11%–16% had a dietary protein intake (DPI) of $<$0.75 g/kg/day, 10% had a body weight $<$90% of standard, 19% had a serum albumin of $<$3.8 g/dl, 30% had a serum transferrin level of $<$250 mg/dl, and 9% had a serum cholesterol of $<$160 mg/dl; the mean of these and other nutritional parameters declined as the GFR decreased (153). Moreover, there was a direct association between various anthropometric and serum markers of nutritional status with GFR in this and one other study (84, 153). Because the MDRD Study screened only clinically stable patients, it is likely that the magnitude of undernutrition among patients with moderate to advanced CRF is significantly higher than was determined during the baseline phase for this study. These findings are of particular importance because nutritional parameters at the time of initiation of dialysis are strong predictors of subsequent patient outcome (12, 33, 34, 90, 143, 192, 227), and the predictive value persists for at least 5 years (117).

The causes for this nutritional decline is probably multifactorial; the decrease in protein and energy intake plays a particularly important role. Several cross-sectional studies have demonstrated a progressive decline in DPI with decreasing

GFR (110, 148, 153, 186); this observation has been confirmed in longitudinal studies as well (84, 197). The mean dietary energy intake in the baseline phase of the MDRD Study was ~29 kcal/kg/day, a value substantially lower than that recommended for healthy adults (216) and for those with CRF (161); these abnormally low energy intakes were evident even for patients with a GFR > 50 ml/min/1.73 m^2 (153). Because DPI and various nutritional markers covary with GFR and energy intakes are abnormally low even at modest declines in GFR, it has been postulated that low nutrient intake contributes to the nutritional decline observed during the predialysis phase. Until recently, this hypothesis remained untested. In a recent analysis of the baseline phase of the MDRD study, the association of GFR with several of the anthropometric and biochemical and nutritional parameters was either attenuated or eliminated after controlling for protein and energy intakes (153). These epidemiological studies suggest that a low nutrient intake may indeed contribute to the nutritional decline in CRF patients. Because the reduction in dietary energy intake—as opposed to the apparent energy needs—is greater than the inadequacy of dietary protein intake, it is likely that inadequate energy intake is the more important contributor to the development of PEM in these patients. Indeed, in short-term studies in nondialyzed CRF patients, an increase in energy intake resulted in an improvement in various nutritional parameters (111).

Thus, there is strong evidence that the nutritional decline begins early in CRF, and a key strategy for preventing PEM or improving the nutritional status of patients as they approach MD therapy requires intervention regarding nutritional intake long before they present for dialysis. However, almost one third of CRF patients in the United States are referred to a nephrologist <1 month prior to commencing MD and almost one half have never seen a dietitian (228). Only about one third of all incident patients starting MD have seen a dietitian on two or more occasions (228). Hence, the vast majority of the incident MD patients receive suboptimal nutritional care prior to initiation of dialysis. The causes for this problem are beyond the scope of this discussion, but this remains a serious problem that requires attention.

Low Nutrient Intake in Maintenance Dialysis Patients

The relationships between nutritional status and dietary nutrient intake in MD has largely been studied using measurements of dietary protein intake (DPI) derived from urea kinetic modeling. In clinically stable MD patients, the rate of urea nitrogen appearance (UNA) in the dialysate and urine is assumed to closely reflect the DPI and is called the protein equivalent of nitrogen appearance (PNA). Whereas in MHD patients the PNA is derived from sophisticated computer modeling, in CPD patients the PNA is estimated by direct measurement of urea nitrogen in dialysate and urine. This PNA, in grams per day, may then be normalized to a standardized body weight (nPNA), which, in turn, is derived from equations based on age, gender, actual body weight, and height. However, it has been argued that this normalization may be misleading because malnourished patients with reduced

edema-free/fat-free masses may appear to have an adequate or high protein intake even though the intake is low in relation to their requirements (67). This may be the principal reason why several investigators have been unable to demonstrate any relationship between nPNA and various measures of nutritional status (65, 99, 244) or patient outcome (21). In two recent studies, normalizing PNA to a desirable body weight or to an edema-free/fat-free mass yielded significant correlations with measures of nutritional status whereas normalizing to actual body weight did not (105, 188), leading some investigators to suggest that PNA should be normalized to edema-free/fat-free mass (29). Thus, data indicate that low nutrient intake is a major determinant of the nutritional status of MD patients, and a critical assessment of the method for normalizing PNA is necessary before concluding otherwise. Convenient, reliable, and inexpensive methods for assessing the energy intake in a large number of MD patients would also be of great value for examining this matter.

Protein and Energy Requirements in Maintenance Dialysis Patients

The ideal study design to determine the protein and energy requirements for MD patients would be to conduct a prospective, controlled trial using patients who are randomized to receive different levels of energy and protein intake and to study the impact on nutritional status, morbidity, and mortality. However, it is unlikely that such a trial will be conducted in the near future in the United States, and hence, we are obliged to depend on such surrogate measures as metabolic balance studies to determine the requirements. The rigorous methodology used in these studies permits an accurate estimation of protein and energy requirements, and therefore, they usually involve small numbers of patients studied at clinical research centers. It is unclear what denominator should be used to normalize the energy and protein requirements of these patients. Rather than current body weight, it has been suggested that standard body weight, based upon patient age, gender, height, and frame size, derived from the Second National Health and Nutrition Evaluation Survey should be used to calculate the dietary requirements. The body composition of MD patients, particularly those receiving CPD, is significantly different than in healthy adults, and some investigators have suggested that desirable body weight should be computed from edema-free/fat-free body mass, which in turn could be determined from dialysate and urine creatinine appearance (232). Even though these arguments have merit, we should await outcome-based studies before making any fundamental changes to our approach in dealing with this issue.

Energy Requirements for Maintenance Hemodialysis Patients To maintain neutral energy balance, energy intake should equal energy expenditure. Several studies have demonstrated that the energy expenditure in MHD patients is identical to that of healthy adults under a variety of conditions (Table 2) (155, 201, 217); only one study demonstrated a higher resting energy expenditure by 7.3% (86). The effect of hemodialysis (HD) procedures remains uncertain because the two

TABLE 2 Energy requirements of maintenance hemodialysis patients

Energy Expenditure	Requirement (reference)
Lying	Normal (155, 201, 217); 7.3% increase (86)
Sitting	Normal (155)
Postprandial	Normal (155)
Exercise	Normal (155)
Hemodialysis	Same as resting (170); 20% greater than resting (86)
Nutrition Parameter[a]	**Energy Intake[a] (kcal/kg of desirable body weight)**
Body weight (kg)	32.4
Nitrogen balance (g/day)	31.1
Nitrogen balance minus unmeasured losses (g/day)	38.5
Midarm circumference (cm)	34.1
Midarm muscle area (cm^2)	33
Body fat (%)	32

[a]From Reference 206.

studies that addressed this issue came to conflicting conclusions (86, 170). In the study by Ikizler et al, which demonstrated a 20% increase in energy expenditure during HD (86), patients had eaten shortly before the onset of the dialysis procedure. This increase in energy expenditure may actually reflect the specific dynamic action of food.

Studies of nitrogen balances and a variety of anthropometric parameters have been used to determine the energy intake necessary to maintain a stable nutritional status in MHD patients consuming an average of 1.13 g of protein/kg/day (Table 2) (206). These analyses suggest such that such an energy intake should be between 31.1–38.5 kcal/kg/day (Table 2).

Based upon these studies, the National Kidney Foundation-Kidney Dialysis Outcome Quality Initiative (NKF-KDOQI) suggests a dietary energy intake of 35 kcal/kg/day for MHD patients younger than 65 years of age and an intake between 30–35 kcal/kg/day for patients older than 65 years of age (161). There are no studies available to determine energy requirements in elderly MHD patients.

Energy Requirements for Chronic Peritoneal Dialysis Patients Energy intake of patients on peritoneal dialysis (PD) represents a sum of dietary intake and absorption of glucose from the dialysate. At least three published studies have addressed the issue of energy requirements in CPD patients (15, 70, 232). The

resting energy expenditure of CPD patients is similar to that of healthy, normal adults (70). Metabolic balance studies of patients on chronic ambulatory peritoneal dialysis (CAPD) eating their usual diets showed a strong correlation between total energy intake and nitrogen balance, irrespective of the duration for which the patients were on dialysis (15). Based upon these studies, the NKF-KDOQI suggests a dietary energy intake of 35 kcal/kg/day for CPD patients younger than 65 years of age and an intake between 30–35 kcal/kg/day for patients older than 65 years of age (161). In a recent study, Uribarri et al demonstrated stable total body weight, edema-free/fat-free mass, and anthropometric parameters in 49 CPD patients on a total energy intake of ∼29 kcal/kg/day and a DPI of ∼1 g/kg/day over a 6-month period (232). However, the CPD patients were relatively obese for their height, and when adjusted for the patients' overweight condition, energy intake rose to recommended levels.

Protein Requirements for Maintenance Hemodialysis Patients Most healthy adults and nondialyzed patients with CRF are able to maintain neutral nitrogen balance while eating a diet containing about 0.60 g of protein/kg/day as long as adequate energy is provided and most of the proteins are of high biological value. However, the dietary protein requirements of MHD patients are increased above these values by an amount that is greater than can be accounted for by the obligatory amino acid and protein losses. To our knowledge, there are six published studies that have evaluated nitrogen balance in MHD patients (Table 3) (25, 54, 112, 121, 189, 206). In addition, several observational studies demonstrated a relationship between DPI and morbidity and mortality (1, 43, 66, 178) that others were unable to reproduce (158, 159). Based upon currently available data, the NKF-KDOQI on nutrition in CRF (161) suggests that a DPI of 1.2 g/kg/day is necessary to ensure neutral or positive nitrogen balance in most clinically stable MHD patients; at least 50% of the DPI should be of high biological value.

Protein Requirements for Chronic Peritoneal Dialysis Patients To our knowledge, three nitrogen balance studies have been conducted using CPD patients (Table 4) (15, 23, 56). These studies indicate that a DPI of 1.2 g/kg/day or greater is almost always associated with neutral or positive nitrogen balance. Moreover, several studies have shown a relationship between DPI, as determined by the normalized protein equivalent of total nitrogen appearance, the serum albumin and total body protein balance (15, 23, 56), and mortality (28). Based on currently available data, the NKF-KDOQI recommended a DPI of 1.2–1.3 g/kg/day for clinically stable CPD patients (161). There are no studies available for patients receiving automated peritoneal dialysis (APD). However, there is no reason to believe that their requirements will be materially different from those undergoing CAPD. Hence, the recommendations should be applicable to patients undergoing APD as well.

TABLE 3 Dietary protein requirements, as determined by nitrogen balance, in maintenance hemodialysis patients[a]

Author (reference)	No.	Age Range	Diabetics	Study Duration (days)	Dialysis Regimen (times/week)	Energy Intake (kcal/kg/day)	Protein Intake (g/kg/day)	Mean N-Balance (g/day)
Ginn et al (54)	4	17–22	None	7–32	2	50–55	0.4–1.48 HBV	Neutral/+ at ≥0.75 g/kg HBV protein
							0.14–0.95 LBV	Negative at 0.95 LBV protein
Kopple et al (112)	3		None	21–28	2	35–45	0.75 (0.63 HBV)	Neutral
							1.25 (0.88 HBV)	Neutral
Borah et al (25)	5	35–65	None	7	3	20.5–30.9	0.5 (37% HBV)	−1.98
							1.4 (77% HBV)	+0.95
Lim et al (121)[b]	6	20–59	None	9	3	29.5 ± 1.5	0.87 ± 0.06	0.37 ± 1.0
Slomowitz et al (206)	6	24–64	None	21–23	3	37.3 ± 2.1	1.13 ± 0.2	0.57 ± 0.42 (0/+ 4/6) (neutral/positive in 4 of 6 patients)
Rao et al (189)[c]	15	18–55	None	7	3	33 ± 6.5	0.61 ± 0.1	0.17
						32.8 ± 6.7	1.06 ± 0.18	4.03

[a]N-balance was not adjusted for unmeasured losses through the skin, hair, and nail growth, sweat, and flatus. HBV, high biological value; LBV, low biological value.

[b]Energy intake was not constant from patient to patient.

[c]All nitrogen output was estimated and not measured directly.

TABLE 4 Dietary protein requirements, as determined by nitrogen balance, in chronic peritoneal dialysis patients[a]

Author	No.	Age Range	Diabetics	Study Duration (days)	Dialysis Regimen	Protein Intake (g/kg/day)	Total Energy Intake (kcal/kg/day)	N-Balance (g/day)
Giordano et al (56)	8	25–73	None	14	CAPD	1.2	39.6–44.9	0/+ in 7/8
Blumenkrantz et al (23)	8	27–59	None	14–33	CAPD	0.98 ± 0.03 1.44 ± 0.02	41.3 ± 1.9 42.1 ± 1.2	+0.35 ± 0.83 +2.94 ± 0.54
Bergstrom et al (15)	12	27–62	None	6–11	CAPD	0.76–2.09	28–50	+correlation with DPI
	9	27–62	None	6–11	CAPD	0.64–1.69	25–51	No correlation with DPI

[a]CAPD, Chronic ambulatory peritoneal dialysis; DPI, dietary protein intake.

Spontaneous Protein and Energy Intake in Maintenance Dialysis Patients

Some of the studies that have examined the spontaneous dietary energy and protein intake in MD patients are summarized in Table 5. As is evident, the mean intakes of both energy and protein in MD patients are substantially lower than their reported nutritional needs; the decrement in the energy intake is greater than the decrement in protein intake. There is evidence that energy intake is more important than protein intake in determining the nutritional status of MD patients. An insufficient energy intake, even in the face of adequate protein intake, can result in a negative nitrogen balance in CRF patients (111, 198, 206). In the nitrogen balance studies by Bergstrom et al using CPD patients (15), dietary energy intake correlated significantly with nitrogen balance in all studies, whereas the DPI correlated with nitrogen balance only among patients who had recently started dialysis. Finally, in studies by Pollock et al, using both MHD and CPD patients, total body protein as measured by neutron activation analysis correlated with estimated energy intake rather than protein intake (185).

Causes of Anorexia in Maintenance Dialysis Patients

There are probably several causes for anorexia in MD patients. In this section, we present an overview of some of the key factors suspected to play a role. More recently, the potential contribution of inflammation to PEM in MD patients has been investigated; the potential role of comorbidity in inducing anorexia is discussed below, as is the role of inflammation in suppressing appetite.

Inadequate Solute Clearances Anorexia is a cardinal uremic manifestation in patients with progressive CRF that tends to improve over several days or weeks after initiation of MD. Based upon these observations, it has been proposed that uremic toxins exist that accumulate during the progressive decline of renal function and that they are removed, to varying degrees, by dialysis. This hypothesis was initially tested in cross-sectional studies: The dose of dialysis was expressed

TABLE 5 Spontaneous dietary protein and energy intake in maintenance dialysis patients[a]

Author (reference)	Dietary Energy Intake	Dietary and Peritoneal Energy Intake	Dietary Protein Intake
MHD			
Blumenkrantz et al (22)	29		1.01
Schonfeld et al (202)	23.6		0.95
Wolfson et al (241)	26.4		1
Stewart et al (214)	24.9		1.02
Lorenzo et al (126)	26.8		1.02
HEMO Study (221)	22.8		0.94
CAPD			
Baeyer et al (8)	23	30	0.83
Heide et al (73)		29–33	1.0–1.4
Guarnieri et al (62)	23.9		1.03
Schilling et al (199)	24		0.98
Pollock et al (184)	24		0.98

[a]MHD, Maintenance hemodialysis; CAPD, chronic automated peritoneal dialysis.

as Kt/V, an index of urea removal, and nPNA, an index of DPI derived from UNA appearance. These analyses demonstrated a significant relationship between measures of small solute removal (Kt/V) and DPI (nPNA) in both MHD and CPD patients (14, 15, 58, 124, 130, 167). This led to the assumption that there are small-molecular-weight uremic toxins that are responsible for anorexia in CRF patients. It was soon pointed out that part of this relationship was secondary to mathematical coupling (68, 226), as both indices are derived from the terms utilized to calculate the rate of UNA and are normalized to the volume of distribution of urea. However, several investigators have demonstrated a relationship between the dose of urea removal and DPI, calculated from dietary records and interviews (15, 68), and hence, this relationship may be statistically significant, even when the dose of urea and creatinine removal is not normalized to body size (15, 167).

Three lines of evidence suggest that an increase in solute clearances will lead to an increase in DPI. First, initiation of dialysis in uremic CRF patients usually results in an increase in DPI; this effect has been demonstrated for both MHD (146, 179, 186) and CPD patients (143, 186). Second, several longitudinal studies over the past few years lend support to the notion that an increase in solute clearances may result in a rise in dietary intake of nutrients. At least one randomized, controlled trial demonstrated that an increase in the dose of dialysis for MHD patients with a DPI < 1.0 g/kg/day resulted in an increase in DPI over the 3-month follow-up period (123). A more recent, uncontrolled study came to the same conclusion (142). A more definitive answer to this question for MHD patients is likely to be available once the ongoing HD adequacy study (HEMO), funded by the National Institutes of Health, is completed. At least three uncontrolled studies have

shown that in CPD patients, there is an increase in DPI with a rise in small solute clearances (41, 55, 135). More recently, a prospective, randomized trial confirmed the beneficial effect of an increase in dialytic clearances on the DPI in CPD patients (133). The only study unable to demonstrate a relationship between an increase in dialysis volumes and DPI in CPD patients was unable to achieve any increase in total clearances, which were below the currently acceptable minimum standards for adequacy of PD (69). Third, uncontrolled observations of small numbers of patients have shown that a new approach to dialysis therapy, daily treatment with nocturnal HD, which results in substantial increases in solute clearances, results in significant increases in DPI (145, 171, 183). To our knowledge, no published study has evaluated the influence of increased clearances on total energy intake for either MHD or CPD patients.

Significant progress has been made in elucidating the nature of uremic toxins that result in anorexia in uremic patients. Early observations suggested that for the same level of small solute clearances by dialysis, CPD patients had a higher DPI than did MHD patients dialyzed with low-flux membranes (14). In MHD patients hemodialyzed with high-flux membranes, the DPI for a given level of small solute clearance was demonstrated to be higher than in patients dialyzed with low-flux membranes (124). Because high-flux hemodialyzer membranes remove more molecules of a higher molecular weight, and because PD seems to remove more of the larger molecules than does HD, it was inferred that this improvement in DPI may be related to the removal, by dialysis, of substances of larger molecular weight, the so-called middle molecules. Recent experimental data suggest that middle molecule fractions, in the 1- to 5-kDa range, isolated from both the dialyzer ultrafiltrate of plasma and from normal urine inhibit food intake in rats in a dose-dependent manner (3). It is likely that these middle molecule fractions act in the splanchnic region and/or brain to inhibit food intake and that the effect is specific for ingestive behavior (138). However, a recent study was unable to demonstrate an increase in DPI when the middle molecule clearances were presumably increased by transferring MHD patients from a low-flux to a high-flux dialyzer (141). The HEMO study may provide additional information as to whether HD with high-flux characteristics (i.e. with a greater propensity to remove larger middle molecules) will increase DPI, dietary energy intake, and nutritional status.

Delayed Gastric Emptying Gastroparesis is a well-known complication of diabetes mellitus and probably contributes to the low nutrient intake in this subgroup of patients. Gastroparesis may also occur not uncommonly in nondiabetic MD patients. Several studies have shown an impairment in gastric motility in MHD and CPD patients using both radionuclide studies (19, 60, 96) and electric gastrography (106, 119). In a recently published study using electric gastrography, over 50% of MHD and CPD patients demonstrated abnormal gastric emptying (119). However, it should be pointed out that not all investigators have demonstrated abnormalities in gastric emptying in MD patients (207, 243). Nevertheless, it is possible that occult gastroparesis contributes to the pathogenesis of PEM in some nondiabetic

MD patients; administration of erythromycin to hypoalbuminemic nondiabetic MHD patients with occult gastroparesis results in improvement in gastric emptying accompanied by an increase in serum albumin (193). The etiology of this gastroparesis remains unclear, although it has been postulated that derangements in the endocrine system of the gut may play a pathogenic role. In CPD patients, instillation of dialysate into the peritoneal cavity may contribute to abnormal gastric electrical activity (119) as well as to the prolongation in gastric emptying time (102).

Increased Serum Leptin Levels Leptin is a polypeptide that is encoded by the *ob* gene. In rodents, leptin acts on the hypothalamus to regulate food intake and energy expenditure (27, 64, 180) and, hence, plays a key role in regulating body weight. The role of leptin in regulating body weight in humans is less clear. Several investigators have demonstrated elevated serum leptin levels in MD patients (75, 80, 93, 150, 165, 169, 204, 213, 247). Hence, elevated leptin levels may play a role in determining the nutritional status of MD patients. Several cross-sectional studies have shown an inverse correlation between serum leptin levels and DPI (93, 247). Others have been unable to demonstrate a relationship between recent weight change or other nutritional measures and serum leptin levels (150). However, three recent longitudinal studies have demonstrated that increased serum leptin levels are associated with weight loss in MHD (169) and CPD patients (75, 213).

The etiology of hyperleptinemia in MD patients is likely to be multifactorial. Leptin is metabolized, at least in part, in the kidney and, hence, accumulates in progressive renal failure (151, 204). Moreover, insulin stimulates leptin synthesis (109, 136), and the hyperinsulinemia associated with CRF may contribute to hyperleptinemia. Finally, activation of the acute-phase response (APR) may result in increased leptin levels; a recent study using CPD patients demonstrated a significant direct correlation between C-reactive protein and serum leptin levels in CPD patients (213).

Intraperitoneal Instillation of Dialysate Clinical experience suggests that CPD patients are more likely to report early satiety or feelings of fullness. A study of the eating behavior of CPD patients indicates that compared with MHD patients, they have a lower food intake (82), which is associated with a constant feeling of fullness, a lower ranking of palatability of food, and a lower eating drive than in the predialysis state (83). An impairment in gastric emptying, as discussed above, may contribute to this abnormality. At least two other probable explanations have been offered to explain the suppression of appetite in CPD patients.

The abdominal distention produced either by intraperitoneal instillation of large volumes of dialysate or large ultrafiltration induced by the PD solutions, which are hyperosmolar, may have a direct inhibitory effect on appetite, independent of the absorption of nutrients, as has been demonstrated in a rabbit model of PD (9). If this hypothesis is true, the suppression of appetite should be uniform for all kinds of nutrients. In a PD model designed to study the ingestive behavior of rats,

instillation of glucose-based dialysate resulted in a dose-dependent suppression of carbohydrate intake only, whereas the instillation of an amino acid-based dialysate resulted in a dose-dependent suppression of both carbohydrate and protein intake (137). This suggests that the inhibition of appetite caused by PD solutions is specific for various nutritional constituents of the diet and is not simply an effect of hyperosmolality or large filling volumes. This observation is highly relevant because the PD solutions available commercially use glucose as an osmotic agent, and up to 70% of instilled glucose is absorbed, accounting for 20%–30% of the total energy intake in CPD patients (59).

Impact of Comorbidity on Nutritional Status

In the United States, MD patients have a high incidence and prevalence of comorbidity (231). Over 50% of the patients who commence MD are over the age of 65 years and almost half are diabetic (231). There is a high prevalence of cardiovascular disease at the time of initiating MD—almost a third have a history of congestive heart failure and almost a quarter have a history of ischemic heart disease (231). Almost 50% of new patients have three or more comorbid conditions when they initiate MD (231). Moreover, this high prevalence of comorbidity is generally acknowledged to be an underestimate of the true burden; a more rigorous review of a sample of the national cohort demonstrated a significantly higher prevalence of associated diseases than are reported in the national registry (230). Each year, 10%–15% of prevalent MD patients are diagnosed with atherosclerotic heart disease, congestive heart failure, peripheral vascular disease, and/or cerebrovascular disease (231). In 1998 in the United States, the average number of hospital admissions was 1.5 times per MD patient, with each spending an average of 13–15 days per year in the hospital (231). There is also a high incidence of complications resulting from dialysis vascular accesses or peritoneal catheters used in MD and CPD patients (i.e. infectious complications, vascular access thromboses), which may not require hospitalization but which add to the disease burden of these individuals. These comorbidities are responsible for a substantial proportion of the medicines prescribed on an average day. During 1996–1997, the median number of medications consumed per day by MD patients ranged from 8 to 10 (229); in addition, 26%–30% were prescribed proton pump inhibitors and 13% an agent that promotes gastrointestinal motility (229).

It is likely that the associated comorbidities, intercurrent illnesses, and medications consumed by MD patients contribute not only to the high prevalence of PEM but also to the association between malnutrition and high mortality in MD patients. The presence of comorbid illnesses has been shown to increase the mortality risk in MHD and CPD patients (101, 215). Older age, the presence of diabetes mellitus, and the presence of cardiac disease are each associated with an increased risk of death for MD patients (231) as well as with a worse nutritional status (20, 118, 188). It truly is the question of what came first, the chicken or the egg. On the one hand, in some epidemiological analyses that adjust for the presence

of comorbid illnesses, such measures of PEM as serum albumin lose their value as predictors of mortality for MD patients (101). On the other hand, the excess risk of death associated with diabetes mellitus is eliminated when the analyses are adjusted for predialysis serum albumin, creatinine, and urea (129).

Associated illnesses may both increase morbidity and mortality and cause malnutrition in ways in which the malnutrition makes little or no contribution to the elevated mortality. Alternatively, a comorbid illness might cause an increase in morbidity and mortality in part by lowering nutrient intake or by impairing intestinal absorption of nutrients. Associated illnesses may also result in the activation of the APR; some studies have reported that elevated serum levels of acute-phase proteins are restricted to older MD patients (188), who in turn are likely to have greater comorbidities. Finally, inadequate nutrient intake due to anorexia, e.g. caused by chronic uremia, may predispose to many illnesses, thereby increasing morbidity and mortality.

Inflammation

Over the past 5 years, several studies have suggested a role for inflammation both in CRF patients not on dialysis and in MD patients.

Markers of Inflammation and Renal Failure

Tissue injury, inflammation, or infection initiates an acute-phase response (APR). The first step results in the activation of monocytes and/or macrophages, which, in turn, release the two major cytokines that are the proximate initiators of the APR: interleukin (IL)-1 (45) and tumor necrosis factor alpha (TNF-α) (17). Both of these cytokines stimulate the release of IL-6, which amplifies this APR. These cytokines, in turn, stimulate or inhibit the synthesis of a variety of proteins in the liver, the so-called acute-phase proteins (APPs): namely, C-reactive protein (CRP), serum amyloid A (SAA), C3 component of complement, α-acid glycoprotein, fibrinogen, haptoglobin, and α-chymotrypsin (156, 209). The hepatic synthesis of the visceral proteins, albumin (10, 157), prealbumin (11, 53), and transferrin, which are traditionally considered markers of nutritional status, are reciprocally inhibited by these cytokines. The short-term activation of the APR is considered to be a key protective mechanism; however, its activation in a wide variety of chronic illnesses in humans is potentially maladaptive.

Activation of each of these levels of the APR has been documented in CRF and MD patients. Elevated levels of IL-1 (18, 44, 77, 125, 181), TNF-α (32, 44, 77, 181), IL-6 (24, 31, 78, 95), and hepatocyte growth factor (134) have been demonstrated in the predialysis blood of MHD patients or the steady state blood of CPD patients (44, 120, 181). However, not all investigators have been able to demonstrate an elevated concentration of these cytokines (40, 187). The differences might, in part, be related to the relative short half-life of these cytokines and the transient, rather than continuous, nature of the inflammatory response in some patients (98). The serum concentrations of several positive APPs [CRP

(47, 65, 71, 85, 89, 100, 144, 173, 188, 224, 244, 248), SAA (100, 244, 248), and fibrinogen (108, 188, 223, 234)] have also been elevated in variable proportions of MD patients. The most frequently studied serum APP, CRP, is reported to be elevated in 22%–53% of MHD patients in cross-sectional studies. In summary, there is overwhelming evidence that the APR is activated in a significant proportion of MD patients.

Acute-Phase Response and Malnutrition

Studies of cachexia associated with cancer and chronic infections have shed light on the relationship between the markers of the APR and malnutrition. It appears that much of the adverse nutritional impact of the APR is mediated by the cytokines, primarily IL-6. The cytokine cascade outlined above has been implicated in anorexia as well as in the depletion of somatic proteins by both a catabolic and an antianabolic effect and in depletion of visceral proteins by an antianabolic effect. Anorexia and, hence, inadequate dietary protein and energy intake are likely to exacerbate this depletion of protein stores.

Cytokines, especially TNF-α, may suppress appetite (104). It is also likely that this anorectic effect is modulated by prostaglandins because antiinflammatory agents blunt the anorectic effects of cytokines (46). Also, these cytokines induce muscle catabolism with release of amino acids and inhibition of muscle protein synthesis (13, 154, 238). Specifically, intravenous administration of TNF-α in animals results in an increased breakdown of skeletal muscle (49). Transgenic mice with elevated levels of IL-6 have a muscle-wasting syndrome with up-regulation of ubiquitin-proteasome–mediated proteolysis, an effect abolished by the administration of IL-6 receptor antibody (225). Furthermore, there is a close association between proinflammatory cytokines and an increase in resting energy expenditure in cachectic individuals with rheumatoid arthritis (195).

The APR also engenders hypoalbuminemia by decreasing the rate of albumin synthesis (157). In vitro treatment of hepatocytes with IL-1 rapidly inhibits albumin synthesis (10); it is now known that this inhibition occurs at the transcriptional level (10). Hypocholesterolemia, another manifestation of PEM, may also be linked to the APR. Serum cholesterol concentrations tend to decrease during an APR (for example, after an acute myocardial infarction or with an infection) and increases after the APR has abated (196). A reduction of serum cholesterol has been observed during IL-2 infusions (239).

Acute-Phase Response and PEM in MD Patients

Over the past 5 years, a compelling case has been made that APR contributes to the manifestations of PEM in MD patients, particularly with respect to hypoalbuminemia. Serum CRP has been used by many investigators as a marker for the APR; a highly significant negative correlation between serum albumin and serum CRP has been consistently demonstrated in MHD (98, 100, 173, 188) and CPD (65, 244) patients. Similar correlations have been demonstrated between serum albumin and both SAA (100, 244) and IL-6 (95). The correlation

coefficient values for these relationships have generally been between 0.25 and 0.55 (65, 98, 100, 173, 188, 244, 248) and, hence, suggest that in addition to inflammation, other causes play a role in inducing hypoalbuminemia in these patients. Kinetic analyses have shown diminished albumin turnover rates in six hypoalbuminemic MHD patients (99). The serum levels of positive APPs, α2-macroglobulin and ferritin, were significantly greater in these patients compared with six individuals with normal serum albumin levels. By multiple regression analyses, the rate of albumin synthesis was negatively correlated with α2-macroglobulin (99); this argues for a role of APR in reducing the rate of albumin synthesis and inducing hypoalbuminemia (99). Although there are no studies correlating serum cholesterol and APPs, a negative correlation has been demonstrated between the serum cholesterol level and IL-6 levels (24).

Several studies have analyzed the relationship between measures of both the somatic protein pool and body mass with markers of the APR in MHD patients. In a study of 45 MHD patients, Kaizu et al demonstrated that IL-6 levels correlated negatively with both midarm muscle area and body weight change over 3 years (95). In the study by Qureshi et al, two thirds of MHD patients with moderate to severe malnutrition as defined by subjective global assessment had a high CRP level compared with 29% with mild malnutrition and 17% with normal nutritional status (188). The exact mechanisms by which inflammation affects the nutritional status of MD patients remain elusive. One study examined the relationship between DPI and serum CRP and SAA levels in MHD patients and was unable to demonstrate a correlation (100). This study, however, did not exclude a role for inflammation in inducing PEM in MD patients because the nutritional effects of the APR may be manifested by a decline in energy or protein intake. Furthermore, failure to demonstrate a correlation between the APR and DPI may be a result of a blunting of the APR in patients with low DPI and malnutrition, as has been observed in animal models of PEM (92). In a study using CPD patients, the serum levels of TNF-α were higher in patients with anorexia and were particularly high in patients with gastrointestinal symptoms (2). On the other hand, it is not known whether an increase in APP in serum of CRF or MD patients is associated with a hypercatabolic state, as no investigator has systematically studied this question.

In summary, the above evidence suggests a role for inflammation in the pathogenesis of some of the manifestations of PEM in MD patients. However, it is highly unlikely to be the sole cause because only about 50% of CRF patients with malnutrition show evidence for elevated APPs (210). Although one explanation for this may be the transient nature of the APR (98), another equally likely explanation is that PEM in MD patients is, indeed, multifactorial. Moreover, as indicated previously, PEM, by reducing host resistance, may predispose to comorbid conditions associated with inflammation. Thus, it is possible not only that inflammation contributes to PEM, but that PEM predisposes to inflammation. The PEM-inducing effects of inflammation also appear to be due to induction of anorexia. Thus, if the nutrient intake of MD patients were maintained, the adverse effects of inflammation on nutritional status might be markedly ameliorated. Finally, it should be recognized that in CRF and MD patients, the role of inflammation as cause of PEM,

morbidity, and mortality is so far based on epidemiological data. There are virtually no randomized, prospective, interventional studies of CRF or MD patients that have examined whether reduction in inflammatory status (*a*) decreases the incidence, prevalence, or severity of PEM or (*b*) decreases morbidity or mortality.

The Relationship Between Inflammation and Increased Dietary Protein Requirements in Maintenance Dialysis Patients

A clinically stable MD patient does not have a marked increase in urea nitrogen appearance compared with normal individuals ingesting similar diets providing 1.1–1.4 g of protein/kg/day. However, it has been suggested that an MD patient has, in general, a decreased ability to conserve body proteins when protein intake is reduced below the recommended levels. Indeed, the recommended dietary protein allowances for MD patients are higher (1.2–1.3 g/kg/day) than for normal, nonpregnant, nonlactating adults (161). This increase exceeds the increment in the daily protein intake that is necessary to offset the losses into the dialysate of proteins, peptides, and free amino acids (122). The finding that many MD patients may be unable to decrease their net protein degradation to maintain protein balance when the dietary intake falls below 1.0–1.2 g/kg/day suggests that MD patients may have an inability to conserve protein normally.

Sources of Inflammation Related to the Dialysis Procedure

To maximize interventions aimed at reducing inflammation in dialysis patients, an understanding of what engenders the APR is imperative. A wide variety of mechanisms have been proposed and are summarized in Table 6.

Bioincompatible Membranes A dialysis membrane that results in activation of the complement cascade is considered to be bioincompatible. Evidence that complement activation induces the APR is conflicting. Several investigators have demonstrated that HD with bioincompatible membranes, as opposed to biocompatible membranes, results in activation of APR (32, 149). Other investigators have either been unable to demonstrate elevated levels of cytokines following HD (40, 95, 187) or have demonstrated an equal activation of the APR with both kinds of membranes (79). Still others have demonstrated that contact with bioincompatible membranes results in an increase in IL-1β and TNF-α mRNA transcription in mononuclear cells exiting from the dialyzer, without actual elevation in the serum concentrations of these cytokines (200). It is probable that these primed mononuclear cells require a second stimulus in order to translate the enhanced gene expression to an increase in the synthesis and release of these cytokines. Elegant experimental studies demonstrate that complement-activating membranes induce net protein catabolism (63). In a randomized control trial, the use of biocompatible membranes was associated with several manifestations of better nutritional status: namely, higher serum levels of albumin and insulin-like growth factor-1 as well as greater weight gain (179). In another study, transferring hypoalbuminemic MHD

TABLE 6 Proposed sources of inflammation in end-stage renal disease

Related to the dialysis procedure
Hemodialysis
Dialyzer
Bioincompatible membranes
Processing of dialyzers for reuse
Dialysate
Endotoxins
Vascular access
Prosthetic arteriovenous grafts
Percutaneous catheters
Peritoneal dialysis
Dialysate
Plasticizers
Glucose degradation product
Access
Peritoneal dialysis catheters
Related to chronic renal failure per se
Uremic toxicity (oxidant and carbonyl stress)
Volume overload
Growth hormone resistance
Altered intestinal bacterial flora
Chronic subclinical infection

patients from a bioincompatible to a biocompatible membrane resulted in a small but significant increase in serum albumin (219). Overall, the evidence suggests that the use of bioincompatible membranes may have an adverse nutritional impact, possibly via the activation of the APR. However, recent studies demonstrating an increased prevalence of an activated APR were conducted using patients who had been dialyzed with biocompatible membranes (24, 98, 100, 248). Furthermore, in 1997, less than 20% of US dialysis units were still using bioincompatible membranes, further reducing the clinical importance of these membranes as a cause of inflammation (231). Hence, it is reasonable to conclude that although bioincompatible membranes may induce the APR, they are unlikely to be the predominant cause for the high incidence of inflammation in MD patients.

Dialysate The dialysate that is used during the HD procedure is nonsterile and may contain small amounts of endotoxin. Endotoxin has been implicated as a cause of the APR in MHD patients (116). One in vitro study found no difference in the measures of inflammation when ultrapure dialysate was compared with nonsterile dialysate when the endotoxin concentrations were in the range usually found in dialysate (222). Kaysen et al failed to demonstrate an increase in IL-1β, SAA, or monocyte mRNAs encoding IL-1α, IL-1β, IL-2, or TNF-α when

pre- and postdialysis blood samples were compared (100). Nonetheless, the data from some in vivo studies are more consistent with the thesis that impure dialysate can elicit an inflammatory response (114). Therefore, whereas the use of nonsterile dialysate remains suspect, the issue remains unresolved.

With respect to the potential role of the sterile dialysate used in PD, strong evidence exists that PD solutions induce a low-grade inflammatory reaction within the peritoneal cavity (26). However, to our knowledge, no study has examined the role of peritoneal dialysate in inducing a systemic APR.

Dialysis Vascular Access Several studies have demonstrated that in MHD patients, serum albumin levels are the greatest in those with native arteriovenous fistulae, are significantly lower in those who have prosthetic arteriovenous grafts, and are the lowest in those with transcutaneous venous catheters (100, 118). Although it is tempting to speculate that these differences in serum albumin are due to variations in the activation of the APR, the only study that has addressed this issue was unable to demonstrate a relationship between the elevation of serum CRP or SAA with the type of vascular access (100). It is likely that the relationship between the type of vascular access and nutritional status is confounded by comorbidity. For example, elderly or more chronically ill patients are more likely to have a prosthetic arteriovenous graft or transcutaneous catheter. Similarly, prosthetic arteriovenous grafts, and particularly the transcutaneous catheter, are more likely to induce comorbid events than are native arteriovenous fistulae.

Sources of Inflammation Related to Chronic Renal Failure per se

Two lines of evidence strongly suggest that activation of the APR in patients with end-stage renal disease (ESRD) is independent of the dialysis procedure. First, elevated serum levels of cytokines (61, 78, 160, 181) as well as APPs (210, 211) have been consistently demonstrated in nondialyzed patients with near–end-stage renal failure. Second, recent data suggest that the elevation of APPs in patients with ESRD is intermittent and spans a period of several dialysis treatments (98), a finding that is less consistent with a dialysis-related cause of inflammation. Several hypotheses for dialysis-independent causes of inflammation have been postulated.

Uremia-Dependent Processes There is compelling evidence from CRF and MD patients for an increased oxidative stress (increased levels of oxidants and decreased levels of antioxidants leading to oxidation of carbohydrates and lipids) (127) and carbonyl stress (inadequate detoxification or inactivation of reactive carbonyl compounds derived from both carbohydrates and lipids by oxidative and nonoxidative reactions) (152). It is probable that oxidative and carbonyl stress may stimulate the vascular endothelium and activate the APR (81, 94).

Volume Overload Chronic congestive heart failure is associated with elevated levels of proinflammatory cytokines; this is probably caused by such factors as

low tissue perfusion, hypoxia, liver congestion, and bowel wall edema. It has been suggested that proinflammatory cytokines play a pivotal role in the loss of edema-free/fat-free body mass and the development of the hypoalbuminemia of cardiac cachexia (51). Recent evidence suggests that volume overload may predispose to the transfer of endotoxin across the bowel wall and the induction of an APR (164). It has not been shown whether volume overload, which occurs commonly in MD patients, will cause the same response in these individuals.

Altered Hormonal Milieu Uremia is characterized by resistance to the anabolic effects of growth hormone and insulin-like growth factor-I (50). In a highly provocative study of adult patients without renal failure but with growth hormone deficiency, treatment with recombinant growth hormone resulted in a significant decline in the levels of CRP (203). This may suggest that a functional deficiency of growth hormone, and/or insulin-like growth factor-1 may be a cause of the APR in CRF and MD patients. However, this hypotheses remains untested.

Sources of Inflammation Related to Comorbidity

The role of comorbidity, superimposed illnesses, and medication usage was discussed above. These illnesses may engender an inflammatory response and might be an important cause of the elevated serum levels of cytokines and APPs in CRF patients.

Is Inflammation the Link Between Malnutrition and Cardiovascular Mortality?

To date, five studies have demonstrated the relationship between elevated serum CRP concentrations and the risk of death for MHD patients (16, 89, 173, 245, 248). In all except one study (173), serum CRP was a more powerful predictor of death than was albumin. Similar relationships have been demonstrated for CPD patients (166). Furthermore, elevated serum levels of other APPs [hepatocyte growth factor (134), hyaluronan (212)] and cytokines [IL-6 (24, 103)] are associated with an increased risk of death for CRF and MD patients. Moreover, both in predialysis patients as well as in those undergoing MD, there are significant correlations between markers of inflammation and carotid atherosclerosis (134, 210). Thus, it is likely that inflammation indeed may be the link between malnutrition and cardiovascular mortality.

It is now widely accepted that atherosclerosis is an inflammatory disease (194). During the early stages of atherosclerosis, the initial endothelial dysfunction initiates an APR, which further promotes atherosclerosis, thus creating a vicious cycle. It is possible that the elevated levels of cytokines and APPs in patients with ESRD may just be a marker, rather than the cause, of the vascular process. Indeed, in a recent study using predialysis patients, the atherosclerotic burden assessed via carotid duplex ultrasonography correlated significantly with the serum CRP (210).

On the other hand, there is a large body of evidence that the APR may potentiate atherosclerosis.

Two pro-atherogenic substances, lipoprotein(a) [Lp(a)] and fibrinogen, are positive APPs, and their serum levels are elevated in patients with an activated APR. Elevated concentrations of Lp(a) have been demonstrated in MD patients (115). In normal subjects, the genetically inherited polymorphism in the size of apo(a) explains a large part of the variability in plasma Lp(a) concentrations (233), and there is evidence that this apo(a) size polymorphism is an important determinant of serum Lp(a) concentrations in patients with renal failure (211). However, these data fail to explain all the variability in plasma Lp(a) concentrations in MD patients. Plasma Lp(a) concentrations are reported to be higher in malnourished predialysis patients (211). There are two likely explanations for this association. First, IL-6 responsive motifs have been identified in the 5′ flanking regulatory region on chromosome 6 of the gene for apo(a), which is a component of Lp(a) (235), and Lp(a) has been shown to have the characteristics of an acute-phase reactant (131). Several studies have now demonstrated a close relationship between plasma Lp(a) in MHD patients and markers of inflammation (97, 188, 211, 248). Second, in CPD patients, elevated serum Lp(a) levels correlate with peritoneal albumin losses (76, 236), raising the possibility that it is the hypoalbuminemia that stimulates the hepatic synthesis of Lp(a). With respect to fibrinogen, elevated serum levels of this protein are consistently demonstrated in MHD patients (107, 108, 188, 223, 234), and it is widely accepted as an APP.

The APR may not only raise the serum concentrations of proatherogenic proteins, but also reduce the protective effect of high-density lipoprotein (HDL) cholesterol. Unmodified HDL contains enzymes (PAF acetyl hydrolase and paroxanase) that destroy oxidized low-density lipoprotein, an atherogenic molecule. Apo A-1 normally comprises half of all the proteins in HDL. During the APR, SAA replaces apo A-1 on the HDL (37), and ceruloplasmin binds to HDL (162). Whereas the former process inhibits the protective activity of the HDL enzymes and reduces its ability to prevent the infiltration of monocytes into fatty streaks (162), the latter process promotes the oxidized LDL-induced stimulation of macrophage chemotactic protein-1 in the arterial wall (162). Hence, the net effect of these changes is to convert HDL from an anti- to a proatherogenic compound. There is evidence for reduced activity of paroxanase in uremic patients (175); however, the relationship between the markers of inflammation and this reduced activity have not been tested.

Hence, it is highly likely that the activated APR in MD patients contributes to the accelerated atherosclerosis and the high cardiovascular mortality seen in these patients.

WHY ARE WE APPARENTLY NOT DOING BETTER?

There is strong evidence that in the United States, the outcome for MD patients has been progressively improving. Between 1988 and 1997, death rates for all incident MD patients in the United States have fallen 38.5% (231). This has occurred even

TABLE 7 Why are we not doing better?

Patient-related factors
Increasing age
Increasing comorbidities
Health care system–related factors
Predialysis care
Delayed referral to nephrologist
Suboptimal nutritional assessment and management
Inadequate reimbursement for dietitian services
Delayed initiation of maintenance dialysis
Dialysis care
Inadequate dose of dialysis
Inadequate reimbursement for oral, enteral, or intravenous nutritional supplements
Short duration of hemodialysis treatments
Inadequate time spent by nephrologists with patients
Expanding frontiers of our knowledge
Uremic factors that suppress appetite
Causes and potential role of hyperleptinemia
Causes and potential role of inflammation

though the dialysis population has become older and has a greater proportion of individuals with diabetes mellitus and the prevalence of other comorbidities appears to be increasing (231). The time trend of the nutritional status of the US dialysis population is, however, difficult to ascertain because no systematic studies have addressed this issue. Yet, there is a sense that the prevalence rates of malnutrition have largely remained unchanged. However, as indicated above, the patient pool today is remarkably different from that of two decades ago. Hence, the unchanged prevalence rate may, in fact, reflect an improvement in the nutritional management. Moreover, MD patients with PEM are more likely to die, and the mortality rate of MD patients has fallen; these considerations also suggest that the true prevalence of PEM in MD patients may have decreased. Nonetheless, there is much room for improvement. We have summarized in Table 7 some possible causes of PEM in MD patients that, in our opinion, deserve special attention. In the following paragraphs, we present our recommendations, which may be valuable in improving the nutritional management of MD patients.

As discussed earlier, nutritional decline begins even when there is only a moderate reduction in GFR. Because prevention is usually better than cure, nutritional care should begin when patients have mild to moderate CRF. The severity of renal failure is often underestimated if one relies on measurement of serum creatinine alone (205). The creatinine clearance can be easily estimated by formulae that incorporate a patient's age, gender, body weight, and serum creatinine (36), an easy bed-side tool. The decline in energy intake in patients with progressive CRF is evident even when the GFR exceeds 50 ml/min/1.73 m^2 (153), a level of renal

function that usually is associated with a serum creatinine in the range of 1.5–2.5 mg/dl, and the patient at that stage may be cared for by nonnephrologists. We recommend that patients with this degree of renal failure be referred to a nephrologist and managed in a multidisciplinary manner that includes the service of a dietitian. Nutritional assessment and management should be included as part of the evaluation of CRF patients. In patients with advanced CRF, if nutritional management is unable to improve the dietary protein and energy intakes to safe levels, timely initiation of MD should be considered (147, 161).

The past few years have seen an increase in the delivered dose of dialysis in the United States, and the proportions of patients who meet the adequacy standards for dialysis clearances of small solutes has progressively increased. There still remains room for improvement: In the United States, 20% of adult MHD patients between October and December 1998 (72) and 44% of adult CPD patients in 1999 (191) were underdialyzed according to current standards. The debate over the optimal length of HD treatments remains unresolved, but experience with nocturnal dialysis (145, 171, 183) and long, diurnal dialysis (87) suggests that a longer length of HD may improve patient morbidity or mortality. Recent studies also suggest that the frequency of physician visits and the total amount of time the physicians spend with MD patients is directly related to patient survival. Hence, increasing the physician time per patient may result in improved outcomes. Finally, of the techniques available for nutritional support (oral food supplements, tube feeding, intradialytic parenteral nutrition, total parenteral nutrition, intraperitoneal nutrition), there are government and third-party–payer barriers, including, arguably, unreasonable requirements for reimbursement. Prevention of PEM, thus, in MD patients with inadequate dietary energy and protein intakes remains elusive.

Aggressive treatment of associated illnesses, particularly cardiac illnesses, is also likely to pay rich dividends. The role of antioxidants to lower the oxidant stress in uremia remains untested but holds promise. In conclusion, we need to make progress on all fronts in order to improve the nutritional management of these patients.

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