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Relative Contributions of Nutrition and Inflammation to Clinical Outcome in Dialysis Patients

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● Protein-energy malnutrition (PEM) is a common phenomenon in maintenance dialysis (MD) patients and a risk factor for poor quality of life and increased morbidity and mortality, including cardiovascular death, in these individuals. The association between undernutrition and adverse outcome in MD patients, which stands in contrast to that seen in the general population, has been referred to as *reverse epidemiology*. Measures of food intake, body composition tools, nutritional scoring systems, and laboratory values are used to assess the degree of severity of PEM, but no uniform approach is available for rating the overall severity of PEM. Epidemiologic studies suggest that inflammation is a missing link between PEM and poor clinical outcome in MD patients, and the existence of a *malnutrition inflammation complex syndrome* is suggested in these patients. Inflammation may be due to subclinical and clinically apparent illnesses. Some investigators suggest that PEM may predispose to illness and inflammation. There is a paucity of information concerning the effect of nutritional therapy on morbidity and mortality in MD patients. Interventional studies of the effect of nutritional support on outcome often are difficult to interpret because of small sample sizes, short duration of study, and other limitations. Large-scale, randomized, clinical trials of the effects of nutritional intake, nutritional status, and inflammation on clinical outcome are needed to define better the relationships between these factors in MD patients.

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INDEX WORDS: Dialysis; nutrition; inflammation; protein-energy malnutrition; food intake; nutritional support; morbidity; mortality.

PATIENTS UNDERGOING maintenance dialysis (MD) experience lower quality of life, significantly greater morbidity, higher hospitalization rates, and higher mortality compared with the general population.¹⁻³ Numerous reports indicate that there is a high rate of protein-energy malnutrition (PEM), ranging from 18% to 75%, in MD patients.^{4,5} In contrast to the general population, in which overnutrition is associated with increased risk of cardiovascular disease, decreased nutritional measures, such as a low body mass index or weight-for-height⁶ or a reduced serum cholesterol concentration (<150 mg/dL),⁷ appear to be correlated strongly with increased morbidity and mortality including higher risk of cardiovascular death in MD patients. This paradoxical observation has been referred to as *reverse epidemiology* in the end-stage renal disease (ESRD) population and has been observed with regard to the impact of blood pressure on mortality in MD patients and in other conditions associated with chronic illnesses or debility.^{8,9}

MD patients also have a high occurrence rate of inflammatory processes.^{10,11} There appears to be a strong association between PEM and inflammation in MD patients, and in these individuals, PEM and inflammation are associated with increased morbidity and mortality, including risk of cardiovascular death.¹¹⁻¹³ The nature of the relationships between PEM and inflammation

and the relative contributions of these two entities to clinical outcome have not been elucidated clearly.¹⁰⁻¹³ These considerations are important because the annual mortality rate among MD patients is unacceptably high (ie, approximately 20%) despite many improvements in dialysis treatment,¹ and PEM and inflammation are strong risk factors for mortality.¹⁰⁻¹³

PROTEIN-ENERGY MALNUTRITION

Many studies have found significant correlations between measures of PEM and such clinical outcomes as increased rate of hospitalization, mortality, and worsened quality of life in MD patients.^{2,4,5} Indicators of PEM in MD patients include decreased dietary protein and energy intake; reduced serum albumin, prealbumin, transferrin, cholesterol, creatinine, and insulin-

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like growth factor-1 concentrations; decreased total body nitrogen and total body potassium; decreased weight-for-height and body mass index; and reduced midarm muscle mass and skinfold thicknesses (Table 1).^{4,8} Many other tools for assessment of the nutritional status of dialysis patients are available, ranging from the well-known subjective global assessment (SGA) of nutritional status¹⁴ to more elaborate techniques such as dual-energy x-ray absorptiometry.⁴

Although the foregoing measures of nutritional status have practical value, each of these methods has limitations. Serum albumin, transferrin, and prealbumin are negative acute-phase reactants and may reflect inflammation.¹⁰ The SGA also may be a marker of the degree of

sickness in MD patients.¹⁴ During acute catabolic states, the urea nitrogen appearance may increase transiently independent of food intake.¹⁵

NUTRIENT INTAKE

A low normalized protein equivalent of total nitrogen appearance (nPNA), also known as *normalized protein catabolic rate*, is believed to reflect the daily protein intake and is among the monthly reported laboratory measures in many dialysis centers.¹⁶ The nPNA, which may be confounded because of its mathematical coupling with Kt/V, has been shown in some but not all studies to be a predictor of hospitalization and mortality in MD patients.^{4,17} We have shown that among MD patients who have a reportedly adequate Kt/V (>1.20), the nPNA maintains a strong association with dialysis outcome.¹⁸ In this latter study, 122 MD patients with a delivered Kt/V greater than 1.20 at the start of the study were followed for 12 months. The nPNA ranged from 0.5 to 2.15 g/kg/d (mean $\pm$ SD, 1.13 ± 0.29 g/kg/d). Using multivariate analysis, there was no statistically significant correlation between Kt/V and nPNA ($r = 0.09$); serum albumin and nPNA were the only variables with significant correlations with mortality and three measures of hospitalization (H): total days of H (H1), total number of H (H2), and time to first H (H3). The case-mix adjusted correlations for serum albumin and nPNA versus total days and frequency of hospitalization were $rH1 = -0.19$ and $rH2 = -0.26$ ($P < 0.05$). Cox analysis based on H3 and time to death resulted in statistically significant odds ratios for each SD decrement for serum albumin and nPNA. The relative risk of first hospitalization for each 0.3 decrease in nPNA was 1.43 (95% confidence interval, 1.06 to 1.93; $P = 0.02$), and the relative risk of death was 3.29 (95% confidence interval, 1.57 to 6.91; $P = 0.002$).¹⁸

In another study using food frequency questionnaires, we showed that MD patients consumed significantly lower amounts of potassium, vitamin C, dietary fibers, and some carotenoids,¹⁹ a finding similar to previous reports.²⁰ It is possible that prescribed restrictions in potassium in MD patients lead to reduced fruit and vegetable intake. This modification of dietary habits leaves meat and fats as the main source of calories, which may contribute to atherosclerosis

Table 1. Assessment Tools That Have Been Used to Evaluate Protein-Energy Malnutrition or Inflammation in Maintenance Dialysis Patients

Nutritional intake	
Direct:	diet recalls and diaries, food frequency questionnaires
Indirect:	based on urea nitrogen appearance: nPNA (nPCR)
Body compositions	
Weight-based measures:	BMI, weight-for-height
Other anthropometries:	caliper (skinfold and extremity muscle mass)
Energy-beam based methods:	DEXA, BIA, NIR
Scoring systems	
Conventional SGA and its modifications	(DMS, MIS, CANUSA)
Other scores:	HD-PNI
Laboratory values	
Negative acute-phase reactants:	albumin, transferrin, prealbumin
Lipids:	cholesterol, other lipids, and lipoproteins
Nitrogen surrogates:	creatinine, SUN
Growth factors:	IGF-1*
Positive acute-phase reactants and cytokines:	CRP, IL, TNF- α , SAA, ferritin

Abbreviations: nPNA, normalized protein nitrogen appearance; nPCR, normalized protein catabolic rate; BMI, body mass index; DEXA, dual-energy x-ray absorptiometry; BIA, bioelectrical impedance analysis; NIR, near-infrared interactance; SGA, subjective global assessment of nutritional status; DMS, Dialysis Malnutrition Score; MIS, malnutrition inflammation score; CANUSA, Canada-USA study based modification of the SGA; HD-PNI, hemodialysis prognostic nutritional index; SUN, serum urea nitrogen; IGF-1, insulin-like growth factor 1; CRP, C-reactive protein; IL, interleukin (eg, IL-1 and IL-6); TNF- α , tumor necrosis factor- α ; SAA, serum amyloid A.

*IGF-1 indicates recent (eg, 2 to 5 day) intake of protein and energy.

and increased cardiovascular morbidity and mortality in these patients. The effect of dietary intake on clinical outcome in MD patients requires more studies.

INFLAMMATION AND OXIDATIVE STRESS

Epidemiologic evidence suggests that inflammation, including but not limited to some specific low-grade infections, such as *Chlamydia pneumoniae*, is a risk factor for cardiovascular diseases and mortality in the general population.^{21,22} The mechanisms by which inflammation promotes cardiovascular disease are the subject of intense investigation in nonuremic populations. Data indicate that inflammatory processes promote proliferation and infiltration of inflammatory cells into the tunica intima of small arteries, including the coronary arteries. Proliferation of the tunica intima and acceleration of atherosclerosis are the result and lead to stenosis of these blood vessels and consequent coronary heart disease.²²

Studies indicate that many MD patients are in a state of inflammation that is associated with elevated levels of positive acute-phase proteins, including C-reactive protein (CRP); increased concentrations of certain circulating cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor- α ; and decreased levels of negative acute-phase proteins, including albumin, transferrin, and prealbumin.^{23,24} These findings provide evidence that inflammation, as manifested by altered serum acute-phase proteins and certain cytokines, is another major risk factor for increased morbidity and mortality in MD patients.^{10,23,24} The acute-phase inflammatory process that is a normal host defense mechanism may play a detrimental role in MD patients and contribute to the risk for cardiovascular events.²⁴

Infection or inflammation or both may predispose MD patients to atherosclerosis and a net catabolic state and hypoalbuminemia.²³⁻²⁶ It has been suggested that the abundance of superimposed illnesses frequently encountered in MD patients plays a role in the cause of the hypercatabolic state and the development of inflammation.^{27,28} There now is increasing evidence, however, that even in the absence of overt clinical illness, ESRD patients may continue to have inflammatory processes that may be associated with a state of acute-phase response.²³ These

episodes of occult inflammation may be recurrent,²⁹ and it is possible that they may be chronic—a *chronic* acute-phase response.¹⁴ Such inflammation is associated with elevation of serum acute-phase proteins, including CRP, serum amyloid A, and some proinflammatory cytokines, and may be related to bioincompatible dialysis components.³⁰ Epidemiologic studies indicate that in ESRD patients increased serum CRP is at least as strong a predictor of morbidity and mortality as is serum albumin.^{24,31,32} Models to investigate mechanisms causing inflammation and its adverse effects have been developed in nonuremic patients.^{21,22} These mechanisms also need to be reexamined in uremic patients.

INTERACTION BETWEEN PROTEIN-ENERGY MALNUTRITION AND INFLAMMATION

The pathophysiology by which PEM is associated with increased mortality, particularly from cardiovascular disease, has not been well defined in MD patients.^{4,5,33} The association of PEM with inflammation in these patients may explain this dilemma.¹⁰⁻¹³ Several investigators suggest that PEM is a consequence of chronic inflammatory processes in ESRD patients.^{10,33} According to this model, inflammation is associated with a rise in plasma and probably tissue levels of catabolic cytokines. Tumor necrosis factor- α not only promotes catabolic processes, engendering protein degradation and suppression of protein synthesis,³⁴ but also induces anorexia.³⁵ These effects of inflammation may promote PEM in MD patients. Elevations of inflammatory proteins and catabolic cytokines are observed in nondialyzed patients with advanced chronic renal insufficiency and in MD patients.³⁶ Evidence suggests that albumin synthesis is suppressed when serum CRP is elevated.³⁷ Morbid conditions that are associated temporally with PEM or chronic inflammation may be a major determinant of the low quality of life and adverse events in MD patients (Fig 1).⁴ Chronic inflammation may be the missing link or factor that causally ties PEM to morbidity and mortality.

ESRD patients with coronary heart disease often have elevated levels of acute-phase reactants, refractory anemia, and PEM.^{38,39} MD patients with refractory anemia frequently display increased serum ferritin, which is not only an indicator of increased iron burden, but also a

Fig 1. A hypothetical model of the complex interrelationships among the predictors (inflammation and malnutrition) and outcomes (quality of life, morbidity, and mortality).

positive acute-phase reactant.^{38,40} Serum ferritin has been shown to correlate with hospitalization rates, and a recent increase in serum ferritin concentration in MD patients may carry a greater risk of death.⁴⁰ Malnourished MD patients with worse SGA scores are reported to have higher levels of serum ferritin.¹⁴ These observations suggest that inflammation may cause refractory anemia, laboratory signs of iron overload, and poor clinical outcome in MD patients with PEM.

The paradoxical relationship between protein-energy undernutrition and cardiovascular disease in MD patients, which appears to be connected causally through inflammation, has been referred to as the *malnutrition inflammation complex syndrome*.^{40,41} Several scoring systems have been proposed to obtain a summated rating of an MD patient's nutritional status (Table 1). Among the most currently used systems is the SGA and its refinements.^{42,43} Additional scoring systems have been developed to provide a unified rating for nutritional status and the morbid and inflammatory states. These scoring systems include the Prognostic Nutritional Index⁴⁴ and Malnutrition Inflammation Score (MIS).⁴¹ The MIS correlates strongly with measures of nutritional status, such as near-infrared⁴⁵ measured body fat, and inflammation and anemia. The MIS is associated significantly with hospitalization rates and mortality in MHD patients.⁴¹ The MIS may be a useful measure of the severity of the malnutrition inflammation complex syndrome in MD patients. Further research may be helpful to develop more sensitive and specific scoring systems and to assess whether they have clinical usefulness.

IS PROTEIN-ENERGY MALNUTRITION AN INDEPENDENT CAUSE OF ADVERSE OUTCOME?

The extent to which PEM and inflammation may be causes of each other and the degree to which they can cause adverse outcomes independently in MD patients has not been defined clearly. The data that so far connect PEM to inflammation are epidemiologic in nature, and there is a paucity of interventional studies that could evaluate more definitively the interrelationships between PEM, inflammation, and outcome in MD patients. It also is unclear as to the degree to which PEM is an independent cause of poor outcome in MD patients. It has been argued that PEM is a result rather than the cause of inflammation and that PEM may be a secondary marker itself and not a causal agent of poor outcome.^{10,33} It has been suggested that there are two forms of PEM in MD patients: (1) a malignant form that essentially is due to inflammation and is associated with poor clinical outcome and (2) a more benign form unrelated to inflammation with little or no important consequences for clinical outcome.⁴⁶

Evidence suggests that PEM is not caused exclusively by chronic inflammatory processes and circulating inflammatory cytokines in ESRD patients. In MD patients, the association of serum albumin and CRP is not precise, and the reported correlation coefficients are usually less than 0.50.^{37,47} Low serum albumin concentrations occur in the presence of normal serum CRP and vice versa.³⁷ Serum albumin concentrations usually do not fluctuate on a month-to-month basis, whereas serum CRP appears to do so.^{10,29} In some but not all studies, serum albumin and other indicators of protein-energy nutritional status correlate with nPNA, an indicator of protein intake.²⁹

The fact that inflammatory cytokines may cause anorexia does not indicate that a low protein-energy intake resulting from this anorexia may not have its own adverse effects. The entire field of nutritional support is based on the tenet that acutely or chronically ill patients who do not eat because they are anorexic or who are physically incapable of ingesting, digesting, or processing food may benefit from nutritional support.⁴⁸ Evidence shows that at least in some

acute or chronic illnesses, the provision of adequate nutrition does improve hypoalbuminemia⁴⁹ and clinical outcome.⁵⁰ Inflammation or morbid events may be caused in part by inadequate nutritional intake, as has been shown to be the case in other illnesses associated with an inflammatory response.⁴⁹

During studies of PEM induced in normal individuals by reducing their nutrient intake or in MD patients fed low-protein diets, the serum albumin decreases modestly, suggesting that serum albumin is a reflection of protein intake.^{51,52} The positive association of measures of PEM with inflammation may be due in part to the generation of cytokines in the setting of low protein and energy intake. Ling and Bistrian observed that otherwise normal rats randomized to receive a diet low in protein and energy experience a rise in acute-phase proteins and cytokines, which is not seen in control fed rats (P-R Ling and B Bistrian, personal communication). In addition, there is evidence that certain nutrients may enhance the immune response.^{48,53} Arginine and glutamine are reported to be such nutrients.⁵⁴ Preliminary data suggest that levocarnitine may protect against endotoxins and suppress elaboration of tumor necrosis factor- α from monocytes.^{55,56} PEM may decrease host resistance and predispose to infection, which is an inflammatory disorder. These considerations, although not conclusive, indicate that factors other than the catabolic consequences of inflammation also affect serum albumin and other nutritional measures and that nutrient intake almost certainly is such a factor.

The epidemiologic association between indicators of PEM and indicators of inflammation in ESRD patients cannot indicate the direction of causality. Epidemiologic analyses of cross-sectional data are associated inherently with several types of errors.^{57,58} The selection at one point in time of a study population that includes incident and prevalent dialysis patients may lead to a significant degree of survival bias.⁵⁹ Patients with severe PEM and higher mortality and hospitalization rates may be underrepresented, whereas those with ongoing mild inflammation caused by nonnutritional factors may have survived to be overrepresented in such studies.⁵⁹ Multivariate analyses can be associated with the risk of overmatching and the elimination of significant asso-

ciations. An investigator might wish to study the impact of food intake on clinical outcome in MD patients with anorexia, a low protein-energy intake, hypoalbuminemia, and increased serum CRP and cytokines that might be caused by the anorexia and inadequate diet. In these circumstances, serum CRP and cytokines would be expected to covary with nutritional intake. Using such secondary markers as serum CRP and cytokines as predicting variables in multivariate regression equations to study the simultaneous impact of food intake and inflammation on outcome variables diminishes the true epidemiologic effect of food intake on the outcome in question. The use of longitudinal studies based on incident dialysis patients may circumvent the former conundrum of the interfering role of survival bias. The latter dilemma concerning the application of multivariate analyses may be resolved by designing and performing prospective randomized interventional trials. Until the results of such studies are available, inferences concerning the relative causal roles of inflammation and PEM on clinical outcome should be regarded with caution. Although in MD patients PEM may be associated with poor outcome because of the primary contribution of inflammation, existing data are consistent with the possibility that nutrient intake may affect outcome independently.

NUTRITIONAL SUPPORT AND DIALYSIS OUTCOME

Experience with nutritional support of sick or malnourished individuals may provide some insight as to the independent role of PEM on clinical outcome in MD patients. Ample evidence suggests that maintaining an adequate nutritional intake in patients with many acute or chronic catabolic illnesses may improve their nutritional status⁶⁰ and, in some studies, reduce morbidity and mortality and improve quality of life.⁵⁰ The evidence as to whether nutritional treatment may improve morbidity and mortality in MD patients is limited, however. There are no large-scale randomized prospective interventional studies that have examined these questions. Among studies based on food intake, Kuhlmann et al⁶¹ reported that prescription of 45 kcal/kg/d and 1.5 g protein/kg/d induced weight gain and improved nutritional status, including serum albumin in malnourished MD patients.⁶¹

In this study, prealbumin and cholesterol levels were unaffected. Weight change correlated with mean dietary energy intake, but not with mean dietary protein intake. Leon et al⁴⁹ reported that tailored nutritional intervention improved serum albumin levels in 52 MD patients, and this effect was observed among patients with high serum CRP levels.

At least two retrospective studies evaluated the effect of intradialytic parenteral nutrition (IDPN) on clinical outcome. Chertow et al⁶² examined mortality in 1,679 MD patients who received IDPN for 12 months versus 22,517 control MD patients who did not undergo treatment with IDPN. They showed that in undernourished MD patients, IDPN could affect the serum levels of biochemical surrogates of visceral and somatic protein nutrition. Among patients who received IDPN, those whose serum albumin was less than or equal to 3.4 g/dL displayed a significant reduction in the relative risk of death. The authors concluded that, albeit retrospective, the improvement in survival at year's end among patients with serum albumin less than or equal to 3.4 g/dL suggested that PEM and its attendant ill effects in MD patients might respond to aggressive therapeutic intervention, such as IDPN. Capelli et al⁶³ conducted a study involving 81 MD patients who had decreased serum albumin and a low nPCA to compare the effect of IDPN on mortality rates. Fifty patients received IDPN and 31 did not. The average length of IDPN treatment was 9 months. The results of the study revealed a better survival rate (64% versus 52%) in the patients treated with IDPN. Serum albumin increased by 12% in the survivors of the IDPN-treated group. Capelli et al⁶³ concluded that correction of hypoalbuminemia by IDPN reduced mortality rates significantly.

Many other interventional studies failed to show evident improvement of nutritional status or clinical outcome in MD patients receiving IDPN or other nutritional interventions.⁶⁴ Many investigators of such studies used small sample sizes, failed to restrict study subjects to those with PEM, did not control for concurrent food intake, did not define or adjust appropriately for comorbid conditions, performed nutritional interventions for short periods, and followed patients for only short intervals. Until large-scale, prospective randomized interventional studies are con-

ducted, it will be difficult to ascertain the potential benefits of increasing nutritional intake in malnourished MD patients.

In conclusion, PEM, a common problem in MD patients, is associated strongly with high morbidity and mortality. The pathophysiology of PEM as it relates to poor clinical outcome and methods of treating this condition are unclear. Epidemiologic evidence suggests that inflammation is a cause of PEM and the association of PEM with morbidity and mortality; however, much of this association could be due to anorexia and poor nutrient intake. Independent contribution of PEM to adverse outcomes, the mechanisms for these relationships, and potential benefits of nutritional therapy in MD patients with PEM are unclear. Preliminary data suggest that PEM independently may promote inflammation and increase the risk of clinical illness. There is a possibility that not only may inflammation induce PEM, but also that PEM may predispose to inflammatory state. To define the relative contribution of PEM and inflammation to clinical outcome, large-scale randomized prospective interventional trials are required. Such trials may include treatment arms that provide nutritional support, anti-inflammatory intervention, or both treatments.

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