Inflammation and Nutrition in Renal Insufficiency

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Protein-energy malnutrition (PEM) and inflammation are common in patients with chronic kidney disease (CKD) and worsen as the CKD progresses toward the end-stage renal disease (ESRD). These conditions are major predictors of poor clinical outcome in kidney failure, as reflected by a strong association between hypoalbuminemia and cardiovascular disease (CVD). It has been suggested that inflammation is the cause of both PEM and CVD and, hence, the main link among these conditions, but these hypotheses are not well established. Increased release or activation of inflammatory cytokines, such as interleukin-6 or tumor necrosis factor alpha, may suppress appetite, cause muscle proteolysis and hypoalbuminemia, and may be involved in atherogenesis. Increasing serum levels of proinflammatory cytokines caused by reduced renal function, volume overload, oxidative or carbonyl stress, decreased levels of antioxidants, increased susceptibility to infection in uremia, and the presence of comorbid conditions may lead to inflammation in CKD patients. In hemodialysis patients, the exposure to dialysis tubing and dialysis membranes, poor quality of dialysis water, back-filtration or back-diffusion of contaminants, and foreign bodies in dialysis access maybe additional causes of inflammation. Similarly, episodes of overt or latent peritonitis, peritoneal dialysis (PD) catheter and its related infections, and constant exposure to PD solution may contribute to inflammation in these patients. The degree to which PEM in dialysis patients is caused by inflammation is not clear. Because both PEM and inflammation are strongly associated with each other and can change many nutritional measures and outcome concurrently in the same direction, the terms malnutrition-inflammation complex syndrome (MICS) and/or malnutrition-inflammation-atherosclerosis (MIA) have been suggested to denote the important contribution of both of these conditions to poor clinical outcome. Maintenance dialysis patients who are underweight or who have low serum levels of cholesterol, creatinine, or homocysteine may be suffering from the MICS/MIA and its subsequent poor outcome. Consequently, obesity and hypercholesterolemia may appear protective, which is known as reverse epidemiology. Although MICS/MIA may have a significant contribution in reversing the traditional CVD risk factors in dialysis patients, it is not clear whether PEM or inflammation and their complications can be effectively managed in CKD and ESRD or whether their management improves clinical outcome.

Index Words: Chronic kidney disease; End-stage-renal disease; Inflammation; Protein-energy malnutrition; Malnutrition-inflammation complex syndrome; Reverse epidemiology

Renal failure has been established as an independent risk factor for cardiovascular disease (CVD).[1-4] Although the pathophysiologic link between renal failure and CVD is not well understood, the elements of chronic inflammation and/or protein-energy malnutrition (PEM) may be major contributors to this association. With the progression of chronic kidney disease (CKD), PEM and inflammation develop and worsen as the CKD advances toward the end-stage renal disease (ESRD).[5-8] There appears to be a strong association between PEM and inflammation in dialysis patients. In these individuals both PEM and inflammation are associated with increased morbidity and mortality, including enhanced risk of CVD and cardiovascular death.[6,9-12] The

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nature of the relationships between PEM and inflammation and the relative contributions of these 2 entities to clinical outcome have not been clearly elucidated.[6,13] These considerations are of major importance because the annual mortality rate among dialysis patients in the United States continues to remain unacceptably high (ie, approximately 20%), despite many recent improvements in dialysis technology and treatment.[14] The confounding effects of PEM and inflammation on outcome appear to be so stark that they may even reverse the conventional associations between such traditional risk factors as obesity or hypercholesterolemia and clinical outcome in individuals with kidney failure.[15-17] Hence, in contrast to the general population in which elements of overnutrition are strong predictors of CVD and death, decreased nutritional measures such as a low weight or body mass or a reduced serum cholesterol, creatinine, or possibly homocysteine concentrations are correlated with increased morbidity and mortality including higher risk of CVD in dialysis patients.[15-18] This paradoxical phenomenon has also been observed with regard to the association of low blood pressure, which is more often observed in inflamed or malnourished dialysis patients, and increased mortality.[19-21] These inverse associations are strongly suggestive of the central role of PEM and/or inflammation in poor outcome of patients with chronic renal failure and known as reverse epidemiology (Table 1).

PEM

There are significant associations between measures of PEM and such clinical outcomes as increased rate of hospitalization, mortality, and worsened quality of life in dialysis patients.[11,12] Indicators of PEM in maintenance dialysis patients include decreased dietary protein and energy intake; reduced serum albumin, prealbumin, transferrin, cholesterol, creatinine, and insulin-like growth factor-1 (IGF-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.[6,11,12,16] Many other tools for assessment of the nutritional status of the dialysis population are available. However, these methods are not exclusive detectors of PEM and may also detect conditions that are associated with chronic inflammation. For example, serum albumin, transferrin, and prealbumin are negative acute phase reactants,[13] and the Subjective Global Assessment and its refinements may also be a marker of the degree of sickness in maintenance dialysis patients.[23,24] During acute catabolic states, the urea nitrogen appearance may transiently increase independently of food intake.[25]

A low normalized protein equivalent of total nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR), reflects the daily protein intake.[26] The nPNA, which may be confounded because to its mathematical coupling with Kt/V, has been shown in some but not all studies to be a predictor of hospitalization and mortality in dialysis patients.[6,22,27] A recent study showed that even among maintenance hemodialysis (MHD) patients who have a reportedly adequate Kt/V ($>$1.20), the nPNA still maintains a strong association with dialysis outcome.[28] In this study, 122 MHD patients with a delivered Kt/V $>$1.20 at the start of the study were followed for 12 months. Serum albumin and nPNA were the only variables with significant correlations with both mortality and three measures of hospitalization (total days of and total number of hospitalizations and time to first hospital admission). The relative risk of first hospitalization for each 0.3 g/kg/d (standard deviation) decrease

Table 1. Reverse Epidemiology of Cardiovascular Risk Factors in Maintenance Dialysis Patients

	Direction of the Associations Between Risk Factors and Outcomes	
Risk Factors of CVD	*General Population*	*Maintenance Dialysis Patients*
Weight and body mass	High BMI and obesity are associated with increased CVD and mortality	High BMI and weight-for-height appear to be protective; low BMI is associated with increased mortality
Serum cholesterol	Hyperchlesterolemia, high LDL, and low HDL are deleterious	Moderate hypercholesterolemia is protective; hypocholesterolemia increases mortality
BP	Hypertension leads to increased CVD and mortality	A low (and not a high) predialysis BP correlates with increased mortality
Serum creatinine	A mild to moderate increase in serum creatinine is an independent risk factor of CVD	An increased creatinine level is associated with better survival
Plasma homocysteine	A high total plasma homocysteine level is a risk factor of increased CVD and mortality	Some recent studies have found that a low homocysteine level is associated with increased risk of CVD and mortality in dialysis patients
Serum iron	A high serum iron level is a risk factor of iron overload (hemochromatosis) and poor outcome	A recent study has found that a low serum iron and transferrin saturation is associated with increased risk of hospitalization and mortality in hemodialysis patients
Energy and/or protein intake	A high energy and food intake may be associated with risk of obesity and increased mortality	Increased protein intake and higher nPNA (nPCR) improves survival

NOTE. Effect and direction of traditional CVD risks factors are compared between dialysis patients and the general population.
Abbreviations: BMI, body mass index; CVD, cardiovascular disease; LDL, low density lipoprotein; HDL, high density lipoprotein; BP, blood pressure; nPNA, normalized protein catabolic rate; nPCR, normalized protein catabolic rate.

in nPNA was 1.43 (95% confidence interval: 1.06-1.93, $P = .02$), and the relative risk of death was 3.29 (95% confidence interval: 1.57-6.91, $P = .002$).[28]

In another study using food frequency questionnaires, it was shown that hemodialysis patients consumed significantly lower amounts of potassium, vitamin C, and dietary fibers as well as some carotenoids.[29] Thus, it is possible that prescribed restrictions in potassium in maintenance hemodialysis (MHD) 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 and increased cardiovascular morbidity and mortality in these patients. Further-

more, increased blood levels of the atheroprotective isoflavones such as genistein and daidzein may be beneficial for dialysis patients.[30] Nonobese Asian-American dialysis patients are found in some but not all studies to have a better outcome compared with their obese counterparts (ie, reversal of the reverse epidemiology, see later), which may be related to the fact that Asian Americans more often ingest isoflavone-rich foods such as soy products.[17] The effect of health-enhancing diets on clinical outcome in maintenance dialysis patients is an important question that will require well designed clinical trials.

Inflammation in Renal Failure

Inflammation is a physiologic response and contributes to defense mechanisms in living organisms. An inflammatory response to an acute event, such as infection, trauma, or toxic injury, helps the body to defend against pathological insults.[31,32] However, if inflammation becomes prolonged, it may lead to adverse consequences such as a decline in appetite, increased rate of protein depletion in skeletal muscle and other tissues, muscle and fat wasting, hypercatabolism, vascular endothelial damage, and atherosclerosis.[32] Thus, the acute-phase inflammatory process that is a normal host defense mechanism may play a detrimental role in renal patients and contribute to the increased risk for cardiovascular events.

Inflammatory processes are common in individuals with both CKD and ESRD and are closely related to PEM and accelerated atherosclerosis.[7,9,10,13,33] ESRD-associated inflammation has been observed in both North American,[7,34,35] European,[10,36] and Asian[37-39] dialysis patients, and 30% to 60% of ESRD patients in European and North American countries are found to have increased serum levels of inflammatory markers. Interestingly, dialysis patients in Asian countries may have a lower prevalence of inflammation,[38,39] suggesting that genetic factors and/or differences in cultural practices (such as diet) may influence the inflammatory response. Moreover, recent data suggest that female patients with chronic inflammatory response have a better outcome than their male counterparts; female sex hormones may have important protective effects that limit the impact of inflammation on vascular injury in ESRD patients.[40] In recent years, more attention has been focused on the inflammatory processes as a possible cause of accelerated atherosclerosis as well as a wasting syndrome[7,9,33] and refractory anemia.[41,42] Thus, inflammation may lead to a poor outcome in individuals with underlying kidney disease and renal insufficiency.

There is no uniform approach to assess the severity of inflammation in individuals with kidney disease. Several serum and blood measures of inflammation have been commonly used in both CKD and ESRD patients as well as in other groups of patients.[33,43] Serum levels of "positive acute-phase reactants," such as serum C-reactive protein (CRP) or ferritin, are markers that are elevated during an acute episode of inflammation. The serum levels of "negative acute-phase reactants," such as albumin or transferrin, decrease during an inflammatory process.[31,32] Many negative acute-phase reactants are also traditionally known as nutritional markers because their serum levels are decreased with a decline in nutritional status.

Occult or overt inflammation may be chronic or recurrent; hence, they have occasionally been referred to as "chronic" acute-phase responses.[23,44] Such chronic inflammatory states are associated with an elevation of serum acute phase proteins, including CRP, serum amyloid A, and some proinflammatory cytokines including a variety of interleukins. Among

Table 2. Causes of Inflammation in Renal Failure

Causes of inflammation in CKD or because of decreased GFR
Decreased clearance of proinflammatory cytokines
Volume overload
Oxidative stress
Carbonyl stress
Increased level of endotoxins
Decreased levels of antioxidants
Deteriorating protein-energy nutritional state and food intake
Increased susceptibility to infection in uremia
Genetic factors such as low production of anti-inflammatory cytokines
Coexistence of Comorbid Conditions in CKD Patients
1. Inflammatory diseases with kidney involvement (SLE, HIV, and so on)
2. Increased prevalence of other comorbid conditions
Additional Inflammatory Factors Related to Dialysis Treatment
Hemodialysis:
1. Exposure to dialysis tubing
2. Dialysis membranes with decreased biocompatiblility (eg, cuprophane)
3. Impurities in dialysis water and/or dialysate
4. Back-filtration or back-diffusion of contaminants
5. Foreign bodies (such as PTFE) in dialysis access grafts
6. Intravenous catheter
Peritoneal Dialysis:
1. Episodes of overt or latent peritonitis
2. PD catheter as a foreign body and its related infections
3. Constant exposure to PD solution

Abbreviations: CKD, chronic kidney disease; GFR, glomerular filtration rate; SLE, systemic lupus erythematosus; HIV, human immuno-deficiency virus; PTFE, poly-tetra-fluoro-ethylene; PD, peritoneal dialysis.

proinflammatory cytokines, interleukin (IL)-6 is reported to play a central role in the pathophysiology of adverse effects of inflammation in patients with renal disease.[9,45-48] Increased serum levels of tumor necrosis factor α (TNF-α) and IL-6 may be associated with reduced appetite in dialysis patients.[49] Renal failure may lead to increased inflammatory responses through a number of mechanisms as presented later (Table 2).

CKD and Inflammation

Deteriorating renal function may promote inflammatory responses by several mechanisms that are related to a reduced glomerular filtration rate. Decreasing renal clearances of factors that are directly or indirectly involved in inflammation may be a main factor. The serum half-lives of such proinflammatory cytokines as TNF-α or IL-1 are greater in nephrectomized as compared to sham-operated rats.[50,51] Moreover, Descamps-Latscha et al[52] have shown strong negative correlations between serum concentrations of various inflammatory markers, such as neopterin, TNF-α TNF-sR55, and creatinine clearance. Declining renal function may affect other inflammatory markers as well because serum CRP, IL-6 and hyaluronan levels have been found to have an inverse correlation with creatinine clearance.[53,54] Even among ESRD patients with some degree of residual renal function, those with a lower glomerular filtration rate have higher serum CRP concentrations.[55] In addition, accumulation of substances that are products of carbonyl stress such as advanced glycosylated end products in CKD patients may provoke inflammation.[56-58] Fluid overload and

congestive heart failure may be other contributors to increased inflammatory responses in CKD patients. It has been suggested that vascular congestion may alter the permeability of the gastrointestinal tract, leading to accumulation of endotoxins such as lipopolysaccharides.[33] Moreover, there is a greater susceptibility to infection in uremic patients as compared to healthy controls. The foregoing processes may in turn stimulate monocytes leading to increased release of proinflammatory cytokines.[59,60]

Oxidative stress, which occurs when there is an excessive free-radical production or low antioxidant levels, has emerged as an important promoter of endothelial dysfunction and possibly inflammation and atherogenesis.[61,62] Lower plasmalogen levels have been found in malnourished and inflamed CKD patients, indicating increased oxidative stress.[63] Hence, it may be speculated that oxidative stress could result in an increased production of proinflammatory cytokines and an acute-phase response. An acute-phase response also has been shown to be associated with decreased plasma levels of several antioxidants in nonrenal patients.[64] A lower intake of various antioxidants in ESRD patients might also contribute to oxidative stress.[29]

The common occurrence of superimposed illnesses frequently encountered in renal patients plays a role in the etiology of the hypercatabolic state and the development of inflammation in these individuals.[65] Hence, comorbid conditions may be the major contributors to the development of chronic inflammation in CKD patients. Underlying kidney disease (such as lupus erythematosus or some of the glomerulonephritides associated with inflammatory conditions), genetic factors (for example in diabetic patients), cardiac disease per se, unrecognized persistence infections, and atherosclerosis per se may also engender inflammation in renal failure. However, even in the absence of overt clinical illness, these patients may continue to have inflammatory processes, although not as severely as observed in multimorbid patients.

ESRD and Inflammation

An increased level of inflammatory markers has been reported in patients undergoing both MHD and chronic peritoneal dialysis (CPD). In addition to the causes of inflammation that are described in CKD patients (see earlier), proinflammatory cytokines are overtly increased in dialysis patients when compared to the general population. Kimmel et al[43] measured serum levels of several pro-inflammatory cytokines in 230 MHD patients and compared the data with those in 28 nondialytic controls and found that serum levels of interleukins 1, 2, 4, 5, 6, 12, and 13 as well as tumor necrosis factor alpha were significantly increased in MHD patients.[43] Kaysen et al[44] have shown that CRP levels varies over time in MHD patients and that these fluctuations are unrelated to the dialysis procedure.[44] This may suggest that factors unrelated to the dialysis procedure may be the most important cause for inflammation in dialysis patients. However, it should be pointed out that various dialysis-related factors may also contribute to inflammation (Table 3). First, exposure to dialysis membranes, especially those that are less biocompatible (eg, cuprophane membranes) as well as exposure to dialysis tubing during dialysis treatment may be a cause of inflammation.[48,66] Second, also the quality of dialysis water[67-69] and back-filtration or back-diffusion because of exposure to endotoxins that are possibly available in the dialysate fluid may be a cause of inflammation.[70] Finally, it should be emphasized that implanted foreign bodies in those who have an arteriovenous graft, which may harbor chronic

or recurrent latent infection or intravenous catheter in those who do not have a peripheral dialysis access may contribute to inflammation.[71,72] In CPD patients, the following additional factors may play a role in the development of chronic inflammation: episodes of overt or subclinical peritonitis, CPD catheter-related infections,[39,73] and constant exposure to PD solution, which may include bioincompatible substances or endotoxins (Table 3).[73]

Inflammation and Outcome

Markers of inflammation and malnutrition predict poor outcome including increased mortality in CKD and ESRD patients. Ironically, infection, which usually leads to an overt inflammatory response, or malnutrition per se are not the common causes of death in these patients. Most individuals with chronic renal failure die of CVD.[14] Inflammation predisposes dialysis patients to atherosclerotic CVD as well as to a net catabolic state and hypoalbuminemia.[9,10,13,74] ESRD patients with coronary heart disease often have elevated levels of acute-phase reactants.[10] Epidemiological studies indicate that in ESRD patients increased serum CRP is at least as a strong predictor of morbidity and mortality as is serum albumin.[34,35] Increased serum levels of IL-6 also is reported to be associated with increased mortality in both MHD[74] and CPD patients.[47] Progression of carotid atherosclerosis during dialysis may be related to IL-6 levels.[45]

It should be noted that the cascade of inflammatory factors leading to an acute-phase reaction is counter-regulated by various anti-inflammatory cytokines, such as IL-10. Recently Girndt et al[75] showed that the −1082A allele, which is associated with a low production of IL-10, is related to an increased risk of cardiovascular events in 300 MHD patients. Data indicate that inflammatory processes may promote proliferation and infiltration of inflammatory cells into the tunica intima of small arteries, including the coronary arteries. This may result in atherosclerosis and stenosis of the blood vessels and subsequent occlusive vascular events.[76,77] Epidemiological evidence suggests that inflammation may be linked to CVD via some specific low-grade infections, such as is caused by *Chlamydia pneumoniae*.[76,77] *C pneumoniae* infection is shown to predict adverse vascular outcome in CPD patients,[78] and elevated *C pneumoniae* IgA titres predict progression of carotid atherosclerosis in ESRD patients.[45] Myeloperoxidase, an abundant enzyme secreted by neutrophils, may also link inflammation to oxidative stress and atherosclerosis in ESRD patients.[79] Indeed, recent data have shown that a functional variant of the myeloperoxidase gene is associated with cardiovascular disease in end-stage renal disease patients.[80] It should be noted that inflammation might also cause direct endothelial dysfunction via a stimulation of intercellular adhesion molecules in CKD patients.[62]

The association between inflammation and increased rate of CVD is not restricted to renal disease. Women with systemic lupus erythematosus are several times more likely to have myocardial infarction than age-matched women,[81] the incidence of myocardial infarction is 50% higher in individuals with rheumatoid arthritis than in controls matched for age and sex,[82] and accelerated coronary atherosclerosis has been observed in young patients with HIV disease.[83]

Inflammation might also cause other adverse outcomes in renal disease such as refractory anemia, laboratory signs of iron overload, or poor quality of life.[11] Maintenance dialysis patients with evidence of inflammation frequently display increased serum ferritin, which, under these circumstances, is not a reliable indicator

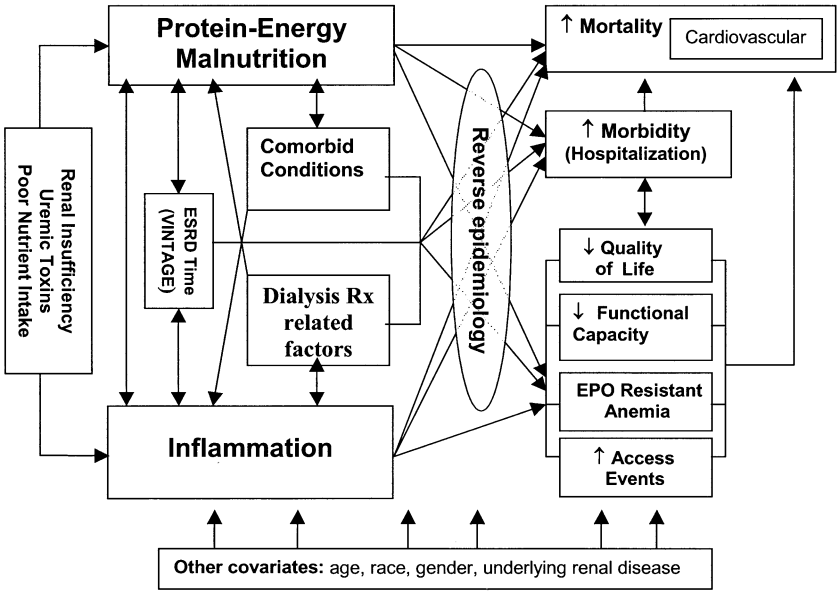

Figure 1. A hypothetical model of the complex interrelationships among the predictors (inflammation and PEM) and outcomes (quality of life, morbidity, and mortality) in individuals undergoing maintenance dialysis.

of increased iron burden but more a positive acute-phase reactant.[41,84] Serum ferritin has been shown to correlate with hospitalization rates, and a recent increase in serum ferritin concentration in MHD patients may carry a greater risk of death.[84] Hence, the association between a high serum ferritin and poor outcome in dialysis patients may be entirely because of inflammation and not iron overload.

Malnutrition-Inflammation Complex

The term malnutrition-inflammation complex syndrome (MICS) indicates the close association between PEM and inflammation in dialysis patients.[6,17,85,86] Alternatively, malnutrition-inflammation-atherosclerosis (MIA) has been used to emphasize the importance of atherosclerotic diseases as a major consequence of this disorder.[87] Renal failure and uremic toxins, as well as comorbid conditions and dialysis related factors, may lead to inflammation and PEM, which per se are major determinants of the low quality of life and increased hospitalization and mortality in dialysis patients (Fig 1).

The theory of reverse epidemiology in dialysis patients is compatible with the existence of MICS or MIA and its interplay with the traditional risk factors; patients who are underweight or who have a low serum cholesterol, creatinine, or homocysteine may be suffering from the MICS/MIA and its subsequent poor outcome[17] (Table 1). Several scoring systems have been proposed to assess the degree of MICS or MIA in dialysis patients, such as malnutrition-inflammation score (MIS),[24] which has been found to correlate strongly with both measures of nutritional status and inflammation and anemia. The MIS is significantly associated with hospitalization rates and mortality in HD patients.[24]

The association of PEM with inflammation in ESRD patients may be an explanation for PEM associated mortality.[6,7,9,10] Indeed, several investigators suggest that PEM is a consequence of chronic inflammatory processes in ESRD patients.[7,87,88] Thus, chronic inflammation may be the missing link or factor that causally ties PEM to morbidity and mortality. The fol-

lowing arguments have been advanced in support of this thesis: inflammation is associated with a rise in plasma and probably tissue levels of catabolic cytokines. TNF-α, also known as cachexin, not only promotes catabolic processes, engendering both protein degradation and suppression of protein synthesis, but also induces anorexia.[49,89,90] Elevation of inflammatory proteins and catabolic cytokines are observed in both nondialyzed patients with advanced chronic renal insufficiency and in dialysis patients who have signs of PEM. Dialysis patients with evidence of inflammation are reported to develop weight loss and a negative protein balance even with an intact appetite because there may be a shift in protein synthesis from muscle to acute-phase proteins as renal function declines.[8] Inflamed patients appear to lose more body weight during dialysis when they are compared with noninflamed patients.[91] Evidence suggests that albumin synthesis is suppressed when serum CRP is elevated.[44,92] In CKD patients, serum albumin decreases as renal function deteriorates,[5] and this phenomenon occur concurrently with the accumulation of proinflammatory cytokines.[53-55] Serum albumin may be influenced by factors other than malnutrition and high concentrations of acute-phase proteins, such as CRP, are correlated with low serum albumin in malnourished dialysis patients.[93] Inflammation may also lead to hypocholesterolemia, a strong mortality risk factor in dialysis patients and a marker of poor nutritional status.[74]

Although proinflammatory cytokines may be one common link between malnutrition, inflammation, and atherosclerosis, it should be emphasized that other factors such as oxidative stress, carbonyl stress, and uremic toxins may play a direct role as well.[61,62] The extent to which PEM and inflammation may be a cause of each other and the degree to which they can each independently induce adverse outcomes in patients with kidney diseases has not been clearly defined. The following arguments have questioned the role of inflammation as a cause of PEM: serum albumin and other indicators of protein-energy nutritional status correlate with indicators of protein intake irrespective of inflammatory status.[87,93] During studies of PEM induced in normal individuals by reducing their nutrient intake or in HD patients fed with low protein diets, the serum albumin decreases modestly, suggesting clearly that serum albumin is a reflection of protein intake.[94] In dialysis patients, the association of serum albumin and CRP is not precise, and the reported correlation coefficients are usually less than 0.50.[13,93] Serum albumin concentrations usually do not fluctuate on a month-to-month basis, whereas serum CRP appears to do so.[44] At least in some acute or chronic illnesses, the provision of adequate nutrition without treatment of the inflammation improves hypoalbuminemia and clinical outcome.[95] Malnourished dialysis patients may be deficient of antioxidants such as vitamin C or carotenoids,[29] which may lead to increased oxidative stress leading to inflammation.[6] There is evidence that certain nutrients, such as arginine and glutamine, may enhance the immune response.[96] Moreover, preliminary data suggest that levocarnitine may protect against endotoxins and also suppress elaboration of TNF-α from monocytes.[97] Thus, PEM may decrease host resistance and predispose to infection, which is an inflammatory disorder. Finally, the positive association of measures of PEM with inflammation may be caused, in part, by the generation of cytokines in the setting of low protein and energy intake.[6]

These considerations, although not conclusive, indicate that factors other than the catabolic consequences of inflammation may also affect serum albumin

and other nutritional measures and that nutrient intake is almost certainly such a factor. In summary, although in dialysis patients PEM may be associated with poor outcome because of the primary contribution of inflammation, existing data remain consistent with the possibility that nutrient intake may independently affect outcome.

Management of Malnutrition and Inflammation in Kidney Failure

The evidence as to whether nutritional treatment may improve morbidity and mortality in dialysis patients is quite limited. There are no large-scale randomized prospective interventional studies that have examined these questions. Among studies based on food intake, Kuhlmann et al[98] 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 hemodialysis patients. In this study, weight change correlated with mean dietary energy intake but not with mean dietary protein intake. Leon et al[95] reported that tailored nutritional intervention improved serum albumin levels in 52 MHD patients, and this effect was observed even among patients with high serum CRP levels. Caglar et al[99] recently showed that oral nutritional supplementation given during hemodialysis improves nutritional markers such as Subjective Global Assessment and serum albumin concentration in malnourished MHD patients.

A limited number of retrospective studies evaluated the effect of intradialytic parenteral nutrition (IDPN) on clinical outcome.[100,101] Even though the correction of hypoalbuminemia by IDPN was associated with improved outcome in these studies, a number of other interventional studies fail to show evident improvement of nutritional status or clinical outcome in dialysis patients receiving IDPN or other nutritional interventions.[102] However, recently Pupim et al[103] showed that IDPN promoted a large increase in whole-body protein synthesis and a significant decrease in whole-body proteolysis in 7 MHD patients without evidence of inflammation. 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 of time, and followed up patients for only short intervals. Until large-scale, prospective randomized interventional studies are conducted, it will be difficult to ascertain the potential benefits of increasing nutritional intake in malnourished dialysis patients.

Although epidemiological evidence strongly links inflammation to poor outcome in individuals with renal insufficiency, it must be recognized that there are not yet randomized clinical trials to indicate improvement of outcomes by inflammation-reducing measures. Hence, there is currently no consensus concerning the management strategies for the treatment of chronic inflammation in patients with renal failure. However, possible treatment modalities may target inflammation directly, or they may focus on oxidative stress or endothelial dysfunction. The following therapeutic approaches may be considered:

1. Statins (HMG-CoA reductase inhibitors) have been suggested for chronically inflamed patients. Statins are shown to decrease CRP levels independently of their effects on lipids and may be associated with reduced mortality in ESRD patients.[37,104]
2. Angiotensin-converting enzyme inhibitors may have anti-inflammatory properties in both the general popula-

tion and in CKD and ESRD patients[105] and are associated with delayed progression of chronic renal failure and improved outcome in these individuals.[1]

3. Vitamin E may have anti-inflammatory effects, and vitamin E administration is associated with a decreased risk for cardiovascular mortality in dialysis patients.[106]
4. Optimization of dialysis treatment may improve inflammatory status in dialysis patients, and the type of dialysis membrane may have a bearing on mortality.[107]

The use of ultra-pure dialysate and biocompatible membranes may decrease CRP, even though such interventions may not completely normalize the serum levels of CRP.[48,66] Of note, a major clinical trial (the HEMO Study)[108] recently failed to show an improvement in clinical outcomes by use of high-flux membranes. However, this finding does not ipso facto refute the role of dialysis membrane biocompatibility in the development of chronic inflammation in ESRD patients.

Clinical Implications and Future Steps

Individuals with renal failure, especially those undergoing maintenance dialysis treatment, are a group of highly selected individuals whose high rate of CVD and mortality does not appear to be caused by such traditional risk factors as hypertension, obesity, hypercholesterolemia, or hyperhomocysteinemia. Indeed these factors are associated with improved survival.[17] Such paradoxical associations appear to have major clinical implications in our patients.[17] To that end, the extrapolation of data on traditional risk factors in the general population to prognostic and management considerations in maintenance dialysis patients without adequate evidence may be flawed. Intense management of traditional risk factors, which is quite important, does not appear to lead to major improvements of CVD or poor clinical outcome in dialysis patients.[14] Increasing dialysis dose or use of high-flux dialysis membranes also failed to show any improvement in survival according to HEMO study.[108] Hence, it may be time to shift the focus of clinical studies and dialysis patient management to such nontraditional factors as nutritional status and inflammation. Although the PEM and inflammation may confound the effect of traditional risk factors on clinical outcome of maintenance dialysis patients, these conditions in themselves may be among the main causes of death in this group of patients. Hence, they deserve attention. Maintenance dialysis patients appear to be a unique population with their own (nonconventional) risk factors as is the case with the phenomenon of reverse epidemiology.[17] To that end, more epidemiological studies and well-designed clinical trials are needed to verify the existence and precise nature of nontraditional risk factors in chronic renal insufficiency and to examine the role of nutritional support and anti-inflammatory interventions as a treatment for high CVD and mortality rate in these individuals.

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