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REVIEWS

Malnutrition-Inflammation Complex Syndrome in Dialysis Patients: Causes and Consequences

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• Protein-energy malnutrition (PEM) and inflammation are common and usually concurrent in maintenance dialysis patients. Many factors that appear to lead to these 2 conditions overlap, as do assessment tools and such criteria for detecting them as hypoalbuminemia. Both these conditions are related to poor dialysis outcome. Low appetite and a hypercatabolic state are among common features. PEM in dialysis patients has been suggested to be secondary to inflammation; however, the evidence is not conclusive, and an equicausal status or even opposite causal direction is possible. Hence, malnutrition-inflammation complex syndrome (MICS) is an appropriate term. Possible causes of MICS include comorbid illnesses, oxidative and carbonyl stress, nutrient loss through dialysis, anorexia and low nutrient intake, uremic toxins, decreased clearance of inflammatory cytokines, volume overload, and dialysis-related factors. MICS is believed to be the main cause of erythropoietin hyporesponsiveness, high rate of cardiovascular atherosclerotic disease, decreased quality of life, and increased mortality and hospitalization in dialysis patients. Because MICS leads to a low body mass index, hypocholesterolemia, hypocreatininemia, and hypohomocysteinemia, a "reverse epidemiology" of cardiovascular risks can occur in dialysis patients. Therefore, obesity, hypercholesterolemia, and increased blood levels of creatinine and homocysteine appear to be protective and paradoxically associated with a better outcome. There is no consensus about how to determine the degree of severity of MICS or how to manage it. Several diagnostic tools and treatment modalities are discussed. Successful management of MICS may ameliorate the cardiovascular epidemic and poor outcome in dialysis patients. Clinical trials focusing on MICS and its possible causes and consequences are urgently required to improve poor clinical outcome in dialysis patients. *Am J Kidney Dis* 42:864-881.

INDEX WORDS: Malnutrition-inflammation complex syndrome (MICS); dialysis; inflammation; protein-energy malnutrition (PEM); cardiovascular disease; reverse epidemiology; anemia; erythropoietin (EPO); atherosclerosis; outcome.

DESPITE MANY years of efforts and improvement in dialysis technique and patient care, the mortality rate in the more than one quarter of a million maintenance dialysis patients in the United States continues to be unacceptably high, currently at approximately 20% per year.[1-3] They also have a high hospitalization rate and low self-reported quality of life.[4-7] Cardiovascular diseases cause the bulk of morbidity and mortality in dialysis patients.[8,9] The number of patients with end-stage renal disease (ESRD) grows constantly and fast, predicted to reach more than half a million by 2010 in the United States,[10] and continues to consume a disproportionately large component of the Medicare budget.[11,12] Therefore, discovering factors that lead to poor dialysis outcome and their successful management is of outmost importance.[13] It once was believed that factors related to dialysis treatment and technique were the main causes of poor clinical outcome; however, a recent multicenter, randomized clinical trial known as the HEMO Study failed to show an improvement in mortality or hospitalization by increasing dialysis dose or using high-flux dialysis membranes.[14] Therefore, the questions of what causes poor dialysis

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outcome and how to manage it remain essentially unanswered.

Among potential candidates for the high rate of hospitalization and mortality in maintenance dialysis patients, both protein-energy malnutrition (PEM) and inflammation continue to be at the top of the list. Epidemiological studies repeatedly and consistently have shown a strong association between clinical outcome and measures of both malnutrition[15-18] and inflammation in dialysis patients.[19,20] Moreover, many investigators have observed that these 2 conditions tend to occur concurrently and coexist in individuals with ESRD, and many factors that engender 1 of these conditions also lead to the other.[18,19,21,22] Therefore, the terms malnutrition-inflammation complex syndrome (MICS)[18,23] or malnutrition, inflammation, and atherosclerosis (MIA) syndrome[24] have been proposed to indicate the combination of these 2 conditions in these patients. The MICS increasingly has become the main focus of attention of outcome research concerning maintenance dialysis patients. This report has been advanced with the hope that a systematic review may provide better insight to explicate the elements of MICS and what is known about their possible causes and consequences in the ESRD population.

PROTEIN-ENERGY MALNUTRITION

To differentiate various causes of wasting syndrome, it is important to attempt to define more clearly what is meant by PEM. A workable definition is as follows: PEM is the state of decreased body pools of protein with or without fat depletion or a state of diminished functional capacity, caused at least partly by inadequate nutrient intake relative to nutrient demand and/or which is improved by nutritional repletion. We believe this definition is applicable to individuals with chronic kidney disease (CKD) or ESRD. Hence, PEM is engendered when the body's need for protein or energy fuels or both cannot be satisfied by the diet.[25] PEM is a common phenomenon in maintenance dialysis patients and a risk factor for poor quality of life and increased morbidity and mortality, including cardiovascular death, in these individuals.[26,27] Various studies using different criteria have been used to establish the presence of PEM in the dialysis population. Its reported prevalence varies between 18% and 75% in dialysis patients according to type of dialysis modality, nutritional assessment tools, and origin of the patient population.[18,28,29] Although per definition, PEM should not involve micronutrients believed to be adequate or even abundantly retained in the setting of renal insufficiency, many malnourished dialysis patients also may have a relative deficiency in vitamins and trace elements.[30]

The cause of PEM in dialysis patients is not very clear, but some probable causes are listed in Table 1 and reviewed in detail elsewhere.[31-35] As shown in Table 1, some of these factors also can lead to inflammation. Hence, the known overlap between malnutrition and inflammation in dialy-

Table 1. Causes of Wasting and PEM in Dialysis Patients

Inadequate nutrient intake
Anorexia* caused by
Uremic toxicity
Impaired gastric emptying
Inflammation with/without comorbid conditions*
Emotional and/or psychological disorders
Dietary restrictions
Prescribed restrictions: low-potassium low-phosphate regimens
Social constraints: poverty, inadequate dietary support
Physical incapacity: inability to acquire or prepare food or to eat
Nutrient losses during dialysis
Loss through hemodialysis membrane into hemodialysate
Adherence to hemodialysis membrane or tubing
Loss into peritoneal dialysate
Hypercatabolism caused by comorbid illnesses
Cardiovascular diseases*
Diabetic complications
Infection and/or sepsis*
Other comorbid conditions*
Hypercatabolism associated with dialysis treatment
Negative protein balance
Negative energy balance
Endocrine disorders of uremia
Resistance to insulin
Resistance to growth hormone and/or IGF-1
Increased serum level of or sensitivity to glucagons
Hyperparathyroidism
Other endocrine disorders
Acidemia with metabolic acidosis
Concurrent nutrient loss with frequent blood losses

*The given factor may also be associated with inflammation.

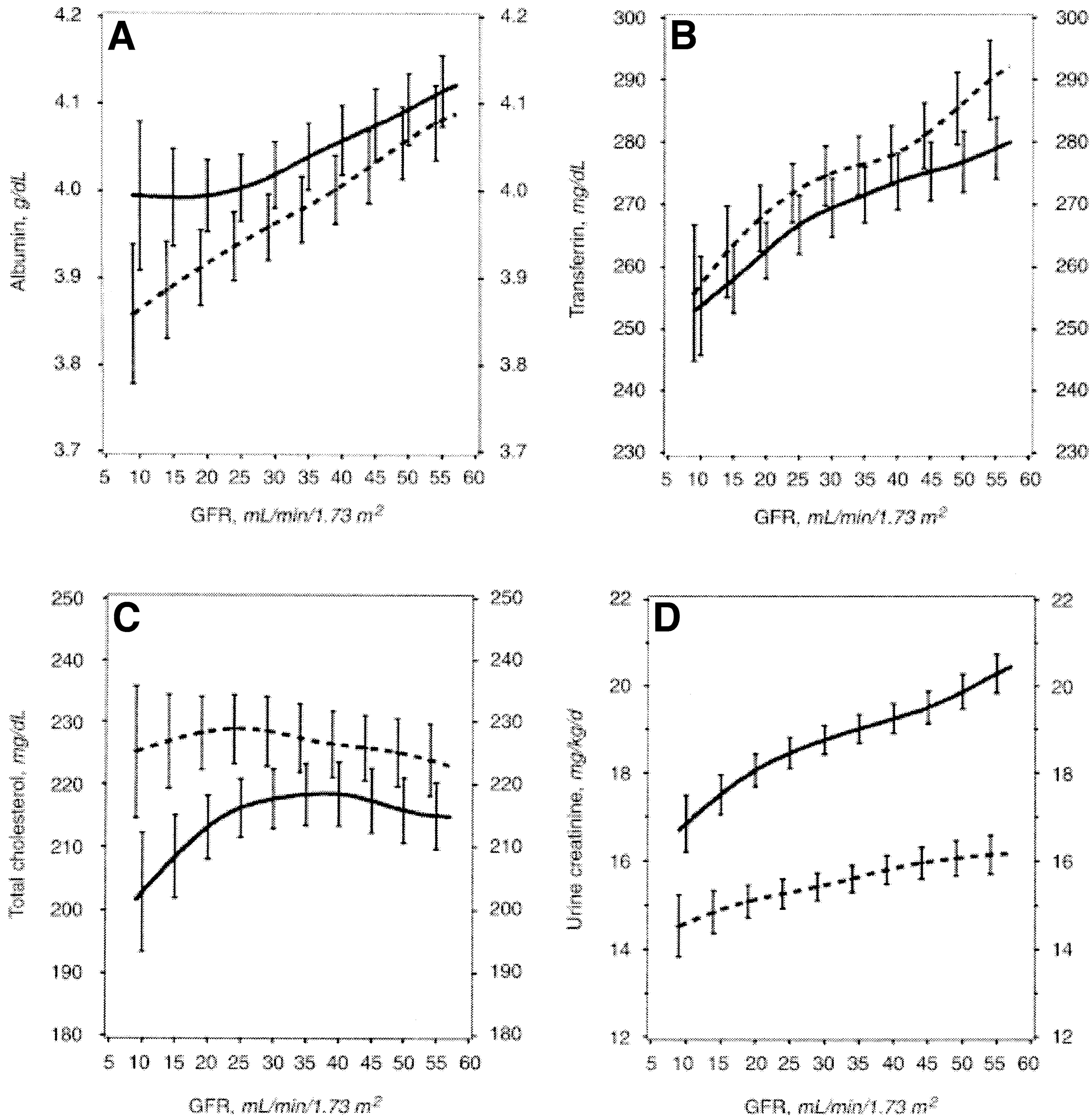

Fig 1. Mean levels of biochemical measures of nutritional status as a function of glomerular filtration rate (GFR) in the Modification of Diet in Renal Disease Study. Estimated mean levels with 95% confidence limits of biochemical nutritional markers are shown as a function of GFR (males, solid line; females, dashed line) controlling for age, race, and use of protein- and energy-restricted diets. In men, the slope of the relationship was greater at a GFR of 12 mL/min/1.73 m^2 than 55 mL/min/1.73 m^2 for serum total cholesterol (P = 0.014). (A) Males, N = 1,065 (P = 0.004); females, N = 698 (P < 0.001); (B) males, N = 1,065 (P < 0.001); females, N = 698 (P < 0.001); (C) males, N = 1,063 (P = 0.052); females, N = 694 (P = 0.63); (D) males, N = 1,017 (P < 0.001); females, N = 664 (P < 0.001). To convert albumin in g/dL to g/L, multiply by 10; transferrin in mg/dL to g/L, multiply by 0.01; cholesterol in mg/dL to mmol/L, multiply by 0.02586. Used with permission from *Kidney International*, vol 57, pages 1688-1703, 2000.[36]

sis patients may have its root at the causal level. The origin of PEM appears to precede dialysis treatment, and it is engendered progressively as glomerular filtration rate (GFR) decreases to less than 55 mg/min.[36,37] Hypoalbuminemia, hypotransferrinemia, and hypocholesterolemia have been shown to develop along with the progression of CKD stages, as shown in the Modification of Diet in Renal Disease Study[36] (Fig 1) and other studies.[37]

Table 2. Systematic Classification of Assessment Tools for Evaluation of PEM in Maintenance Dialysis Patients

Nutritional intake
Direct: diet recalls and diaries, food-frequency questionnaires*
Indirect: based on urea nitrogen appearance: nPNA (nPCR)*
Body composition
Weight-based measures: BMI, weight for height, edema-free fat-free weight*
Skin and muscle anthropometry by caliper: skinfolds, extremity muscle mass*
Total-body elements: total-body potassium
Energy-beam–based methods: DEXA, BIA, NIR*
Other energy-beam-related methods: total-body nitrogen
Other methods: underwater weighing
Scoring systems
Conventional SGA and its modifications (eg, Dialysis Malnutrition Score,[159] MIS, Canada-USA-version)*
Other scores: Hemodialysis Prognostic Nutritional Index, others (eg, Wolfson et al,[55] Merkus et al,[188] Merckman et al,[154] Harty et al[190])*
Laboratory values
Visceral proteins (negative acute-phase reactants): albumin, prealbumin, transferrin*
Lipids: cholesterol, triglycerides, other lipids and lipoproteins*
Somatic proteins and nitrogen surrogates: creatinine, serum urea nitrogen
Growth factors: IGF-1, leptin
Peripheral-blood cell count: lymphocyte count

Abbreviations: nPNA, normalized protein nitrogen appearance; nPCR, normalized protein catabolic rate, DEXA, dual-energy X-ray absoptiometry; BIA, bioelectrical impedance analysis, NIR, near-infra red interactance.

*The given tool may also detect inflammation.

Data from Kalantar-Zadeh and Kopple.[18,48]

Classically, 3 major lines of inquiries, ie, dietary intake, biochemical means, and body composition, are used to assess protein-energy nutritional status. Composite indices that include a combination of assessment measures within these categories also are used, such as the Subjective Global Assessment of Nutrition (SGA)[38,39] or Malnutrition-Inflammation Score (MIS).[23] More technologically based nutritional measures that have been used in dialysis patients include dual-energy X-ray absorptiometry,[40,41] total-body nitrogen or potassium measurements,[42-44] underwater weighing,[45] bioelectrical impedance analysis,[41] and near-infrared interactance.[46,47] The 4 categories of nutritional assessment tools are listed in Table 2 and have been reviewed in detail elsewhere.[18,48]

As shown in Table 2, many of these nutritional assessment tools also detect the presence of inflammation and measure its severity. Hence, the overlap between malnutrition and inflammation also exists at the diagnostic level, in addition to their overlapping causes. No uniform approach has been agreed on for rating the overall severity of PEM. Of these 4 categories, dietary assessment is probably the most nutrition-specific entity. A low normalized protein equivalent of total nitrogen appearance (nPNA), also known as normalized protein catabolic rate (nPCR), is associated with increased hospitalization and mortality in maintenance hemodialysis (MHD) patients, even when the dose of dialysis is high (single-pool $Kt/V > 1.20$).[16] Although it has been argued that inflammation is a cause of diminished appetite in dialysis patients,[49] reduced dietary intake from other causes (Table 1, first item) still induces malnutrition and its consequences independent of inflammation.

Some more frequently studied indicators of malnutrition in dialysis patients that are associated with clinical outcome include decreased dietary protein and energy intake[16,30]; reduced weight for height,[27] body mass index (BMI),[50-52] and total-body fat percentage[47,53]; decreased total-body nitrogen[43,54] and total-body potassium levels[44]; reduced midarm muscle mass and skinfold thicknesses[55]; low serum concentrations of albumin,[56] prealbumin (transthyretin),[57,58] transferrin (total iron-binding capacity [TIBC]),[38,59] cholesterol,[60,61] and creatinine[62]; and a more abnormal score by some nutritional assessment tools, such as the SGA[63,64] and MIS.[23] Although the foregoing measures of nutritional status have practical value, it should be recognized that each of these methods has its limitations. For example, serum albumin, transferrin, and prealbumin are negative acute-phase reactants and may reflect inflammation.[38,65,66] SGA also may be a marker of degree of sickness and comorbidity in maintenance dialysis patients.[38] During acute catabolic states, urea nitrogen appearance may increase transiently independently of food intake.[67]

INFLAMMATION

Inflammation is defined as a localized protective response elicited by injury or destruction of tissues that serves to destroy, dilute, or sequester both the injurious agent and injured tissue.[68] The acute-phase response (or reaction) is a major pathophysiological phenomenon that accompanies inflammation and is associated with increased activity of proinflammatory cytokines.[69] With this reaction, normal homeostatic mechanisms are replaced by new set points that presumably contribute to defensive or adaptive capabilities.[70] Hence, inflammation is a physiological response, and in the form of an acute response to infections, trauma, or toxic injury, it helps the body to defend against pathophysiological insults.[71,72] Inflammation can become more subtle and less organ specific and may involve many body organs or the entire organism. If inflammation becomes prolonged and persistent in the form of the so-called *chronic* acute-phase reaction, it may lead to such adverse consequences as decline in appetite, increased rate of protein depletion in skeletal muscle and other tissues, muscle and fat wasting, hypercatabolism, endothelial damage, and atherosclerosis.[72]

Inflammatory processes are common in individuals with both CKD and ESRD. Approximately 30% to 60% of Northern American[73,74] and European[20,75] dialysis patients have increased levels of inflammatory markers, although dialysis patients in Asian countries may have a lower prevalence of inflammation,[76,77] which may be caused by genetic factors or environmental entities, including diet.[78] In recent years, more attention has been focused on inflammatory processes as the possible cause of accelerated atherosclerosis, as well as PEM and concurrent wasting syndrome, which lead to a poor outcome in those with underlying kidney disease. Renal insufficiency per se now is considered an independent risk factor for cardiovascular diseases.[79-81] It is believed that inflammation may have an important role in the increased prevalence of cardiovascular disease and mortality associated with renal insufficiency.[19,20,22,23,82] Renal failure may lead to increased inflammatory responses through a number of mechanisms, which are listed in Table 3 and reviewed comprehensively elsewhere.[65,83-86] As shown in Table 3, some of these factors also may result in PEM and consequently cause the overlap between malnutrition and inflammation. Comorbid conditions may contribute considerably to the development and maintenance of inflammation in dialysis patients. Because of a very high prevalence of comorbid conditions in these individuals, it seems very difficult to ascertain the role of inflammation without preexisting comorbidity.

There is no uniform approach to assess the degree of severity of inflammation in individuals with kidney disease.[87] Such positive acute-phase reactants as serum C-reactive protein (CRP) or ferritin are markers for which serum levels are elevated during an acute episode of inflammation (Table 4). Serum levels of such negative acute-phase reactants as albumin or transferrin decrease during an inflammatory process.[71,72,83,85] Many negative acute-phase reactants also are traditionally known as nutritional markers because their serum levels decrease with a decline in nutritional status (Table 4). Hence, it is not clear if these markers have specificity in the detection of either of these 2 conditions. Among proinflammatory cytokines, interleukin-6 (IL-6) is reported to have a central role in the pathophysiological process of adverse effects of inflammation in patients with renal disease.[88-90] However, even these proinflammatory cytokines may be engendered during oxidative stress, which can happen in the setting of PEM.[91]

RELATIONSHIP BETWEEN MALNUTRITION AND INFLAMMATION

The foregoing discussions, along with Tables 1 through 4, indicate a major overlap among possible etiologic factors and assessment tools for PEM and inflammation. The association between PEM and inflammation in patients with CKD and ESRD may be an explanation for malnutrition-associated mortality.[18,19,66] Several investigators suggested that PEM is a consequence of chronic inflammatory processes in patients with renal insufficiency.[21,92-94] Thus,

Table 3. Possible Causes of Inflammation in Patients With CKD and ESRD

Causes of inflammation from CKD or decreased glomerular filtration rate
Decreased clearance of proinflammatory cytokines
Volume overload*
Oxidative stress (eg, oxygen radicals)*
Carbonyl stress (eg, pentosidine and advanced glycation end products)
Decreased levels of antioxidants (eg, vitamin E, vitamin C, carotenoids, selenium, glutathione)*
Deteriorating protein-energy nutritional state and food intake*
Coexistence of comorbid conditions
Inflammatory diseases with kidney involvement (eg, systemic lupus erythematosus; AIDS)
Increased prevalence of comorbid conditions (eg, cardiovascular disease; diabetes mellitus; advanced age)*
Additional inflammatory factors related to dialysis treatment
Hemodialysis:
Exposure to dialysis tubing
Dialysis membranes with decreased biocompatibility (eg, cuprophane)
Impurities in dialysis water and/or dialysate
Backfiltration or backdiffusion of contaminants
Foreign bodies (such as polytetonfluoroethylene) in dialysis access grafts
Intravenous catheter
Peritoneal dialysis:
Episodes of overt or latent peritonitis*
Pcritoneal dialysis catheter as a foreign body and its related infections
Constant exposure to peritoneal dialysis solution

*The given factor may also be associated with PEM.

chronic inflammation may be the missing link that causally ties PEM to morbidity and mortality in these individuals. The following arguments have been proposed to indicate that the development of PEM is secondary to inflammation.

1. Proinflammatory cytokines, such as tumor necrosis factor-α (TNF-α), not only promote catabolic processes, engendering both protein degradation and suppression of protein synthesis, but also induce anorexia.[95-97] Low appetite has been associated with increased levels of inflammatory markers in hemodialysis patients.[49]
2. Dialysis patients with 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.[94]
3. In patients with CKD and ESRD, albumin synthesis is suppressed when serum CRP level is elevated.[66,98]
4. Inflammation also may lead to hypocholesterolemia, a strong mortality risk factor in dialysis patients and a marker of poor nutritional status.[88]

Table 4. Some Acute-Phase Reactants for Which Blood Concentrations Are Measured as Markers of Inflammation in Patients With Renal Insufficiency

Positive Acute-Phase Reactants	Negative Acute-Phase Reactants
Proinflammatory cytokines	Nutritional markers
IL-6	Albumin
TNF-α (cachechtin)	Transferrin or TIBC
Other interleukins (IL-1β, etc)	Prealbumin (transthyretin)
Other positive acute-phase reactants	Cholesterol
CRP	Leptin*
Serum amyloid A	Other negative acute-phase reactants
Ferritin	Histidine-rich glycoprotein
Fibrinogen, α_1-antitrgpsin T, haptoglobin	

*A recent report has questioned the role of leptin as an acute-phase protein.[189]

The following counterarguments have questioned the role of inflammation as a primary cause of PEM:

1. Serum albumin and other indicators of protein-energy nutritional status correlate with indicators of protein intake irrespective of inflammatory status.[98-100]
2. In dialysis patients, the association of serum albumin and CRP is not precise, and the reported correlation coefficients are usually less than 0.50.[98,99]
3. Serum albumin concentrations usually do not fluctuate on a month-to-month basis, whereas levels of serum CRP and other inflammatory markers do.[101]
4. At least in some acute or chronic illnesses, provision of nutritional support without management of inflammation improves hypoalbuminemia and clinical outcome.[102-105]
5. Malnourished dialysis patients may be deficient in such antioxidants as vitamin C or carotenoids, which may lead to increased oxidative stress, leading to inflammation.[30] A recent study using food-frequency questionnaires to compare food intake of dialysis patients with that of healthy individuals detected such dietary inadequacies, which could be related to such prescribed nutritional restrictions as low-potassium low-phosphorus diets.[30] Studies of malnourished children have shown that PEM may lead to oxidative stress, which can lead to increased activity of proinflammatory cytokines.[91] Moreover, in dialysis patients, a reverse association has been reported between serum vitamin C (ascorbate) and CRP levels.[106]
6. There is evidence that certain nutrients, such as arginine and glutamine, may enhance the immune response.[107] Moreover, preliminary data suggest that levocarnitine may protect against endotoxins and also suppress elaboration of TNF-α from monocytes.[108] Thus, PEM may decrease host resistance and predispose to latent or overt infection, which is an inflammatory disorder.
7. Nutritional intervention may ameliorate inflammation. In a recent nonrandomized pilot study in a group of MHD patients, infusion of L-carnitine, 20 mg/kg body weight, at the end of each hemodialysis session for 6 months was associated with a moderate, but statistically significant, decrease in serum CRP levels and increase in mean serum albumin and transferrin levels and BMI (V. Savica and J.D. Kopple, unpublished data).

In summary, given that mortality is still very high in dialysis patients (~10%/y to 20%/y in Westernized countries), inflammation, independent of clinically evident comorbid conditions or malnutrition, cannot fully explain this extremely poor clinical outcome, especially because in otherwise healthy individuals, inflammation has been associated with an annual mortality rate in only the 2% to 3% range.[109]

These considerations indicate lack of conclusive consensus with regard to the nature and direction of the association between PEM and inflammation in renal insufficiency. Hypoalbuminemia, a strong and reliable predictor of cardiovascular disease and mortality in patients with renal insufficiency, is caused by both inflammation and PEM, and it is not clear which 1 of these 2 conditions has a greater influence on serum albumin concentration.[18,98,110] Furthermore, both inflammation and malnutrition have been associated with cardiovascular disease and atherosclerosis in the ESRD population, overwhelming and even reversing the effect of traditional cardiovascular risk factors in these individuals[111] (discussed later). Hence, the term MICS denotes the close ties between these 2 relatively common, often concurrent, and outcome-predicting conditions.[18,111,112] Some investigators have used other terms, such as MIA, to emphasize the importance of atherosclerosis as the consequence of MICS.[24,113]

According to Stenvinkel et al,[113] there are 2 forms of PEM in dialysis patients: a malignant form essentially caused by inflammation and associated with poor clinical outcome; and a more benign form unrelated to inflammation, with little or no important consequences for clinical outcome,[113] a concept that may have special implications in developing countries.[114] No matter what it is called or caused by, MICS is related to such known common morbid conditions in dialysis patients as decreased appetite and hypercatabolism. MICS also has such relevant clinical consequences as refractory ane-

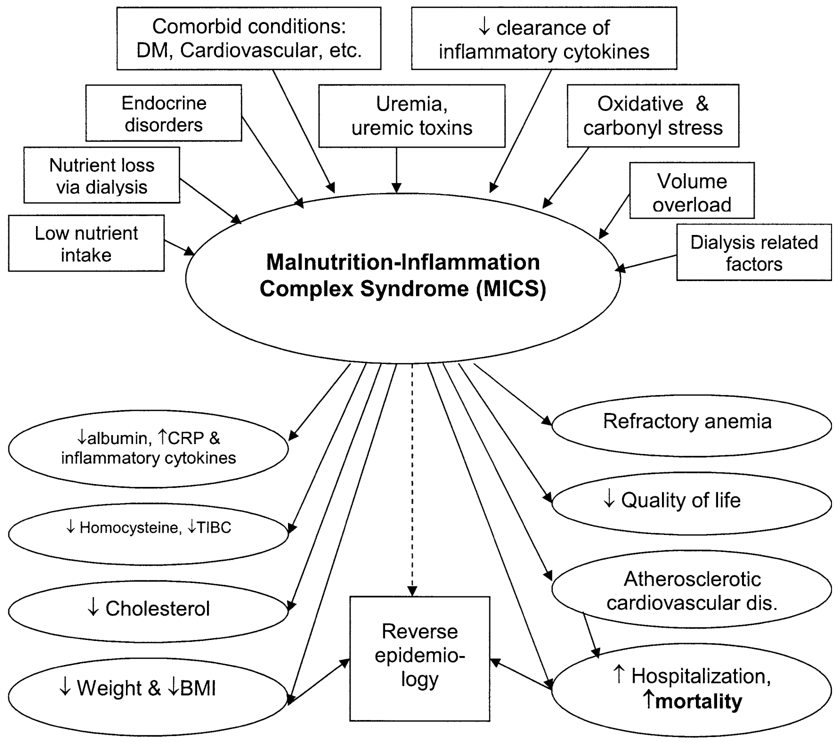

Fig 2. Schematic representation of the causes and consequences of MICS. Abbreviation: DM, diabetes mellitus.

mia, increased rate of atherosclerotic cardiovascular disease, and poor outcome, including low quality of life and increased hospitalization and mortality, and may be the cause of "reverse epidemiology" in patients with renal failure (Fig 2).

REFRACTORY ANEMIA

Elements of MICS may blunt the responsiveness of anemia of ESRD to recombinant human erythropoietin (EPO). Refractory anemia appears to be more common in dialysis patients who also have PEM and/or inflammation.[38,115,116] Several previous studies reported an association between anemia and inflammation in dialysis patients, reflected by a high serum concentration of CRP[115,117] or such proinflammatory cytokines as IL-6 and TNF-α.[118,119] We recently reported that the logarithm of serum IL-6 level had the strongest correlation with required EPO dose in 339 hemodialysis patients, and the association remained statistically significant in different statistical analyses and after multivariate adjustments.[120] Both serum CRP and TNF-α levels also showed a similar trend, and their associations with EPO dose remained significant in some, but not all, analysis modalities we conducted in this study.[120]

An inverse association between such markers of nutritional state as serum prealbumin, transferrin (TIBC), and total cholesterol concentrations and blood lymphocyte count and required EPO dose also has been reported.[120] Such associations are less well described in the literature compared with the association between EPO dose and inflammation. Improving nutritional state in dialysis patients also may improve anemia and lead to a lower required EPO dose. A cross-sectional study of 59 MHD patients showed that the required EPO dose was greater in poorly nourished patients according to SGA scoring.[38] In a meta-analysis by Hurot et al,[121] L-carnitine administration, used to improve nutritional state, was associated with improved hemoglobin level and decreased EPO dose and EPO resistance in anemic dialysis patients.[121] Moreover, anabolic steroids have been administered successfully to simultaneously improve both nutritional state and anemia in dialysis patients.[122] Insulin-like growth factor 1 (IGF-1) is reported to enhance bone marrow progenitor-cell proliferation in uremic mice.[123] Hence, ESRD anemia may represent both an EPO- and a functional IGF-1–deficient state.[123]

It is not completely clear how MICS is related to dialysis-associated refractory anemia pathophysiologically. It has long been known that anemia frequently is observed in patients with chronic inflammatory disorders, even with normal kidney function.[124] Several mechanisms for cytokine-induced anemia have been proposed, including impaired iron metabolism and suppression of bone marrow erythropoiesis and EPO production.[125,126] Serum levels of ferritin, a marker of iron stores and also a positive acute-phase reactant, have been shown to be paradoxically high in patients with ESRD with refractory anemia.[127,128] Increased ferritin production may prevent iron delivery to erythrocyte precursors.[127] Moreover, uptake of iron is lower than usual in inflammation.[125] Patients with inflammatory diseases have inappropriately low EPO levels in their blood.[129] IL-1 and TNF-α have been shown to inhibit EPO production in vitro.[130] Furthermore, increased release or activation of such inflammatory cytokines as IL-6 or TNF-α has been shown to have a suppressive effect on erythropoiesis.[131] IL-6 and IL-1 have been found to antagonize the ability of EPO to stimulate bone marrow proliferation in culture.[132] Moreover, patients with inflammation may be more prone to gastrointestinal bleeding.[125,126] Finally, it is important to mention that use of intravenous iron for anemia treatment in dialysis patients per se may lead to oxidative stress, inflammation, and consequent atherosclerosis, as indicated by Drueke et al.[133]

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

In the general population, it recently was shown that such indicators of inflammation as an increased serum CRP level are stronger predictors of cardiovascular events than low-density lipoprotein hypercholesterolemia.[109] Hence, at least by virtue of its inflammatory component, MICS predisposes dialysis patients to atherosclerotic cardiovascular disease.[20,88,90] Patients with ESRD with coronary heart disease often have hypoalbuminemia and elevated levels of acute-phase reactants.[20] Moreover, progression of carotid atherosclerosis during dialysis may be related to IL-6 levels.[134] It should be noted that the cascade of inflammatory factors leading to an acute-phase reaction is counterregulated by various anti-inflammatory cytokines, such as IL-10. Recently, Girndt et al[135] showed that the -1082A allele, associated with low IL-10 production, was associated with increased risk for cardiovascular events in 300 hemodialysis 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, which leads to atherosclerosis and stenosis of these blood vessels and consequent coronary and other vascular diseases.[134,136] Epidemiological evidence suggests that inflammation may be linked to cardiovascular disease through some specific low-grade infections, such as those caused by *Chlamydia pneumoniae*.[134,136] *C pneumoniae* infection is shown to predict adverse outcomes in dialysis patients,[137] and elevated *C pneumoniae* immunoglobulin A titers predict progression of carotid atherosclerosis in these individuals.[138]

Myeloperoxidase, an abundant enzyme secreted by neutrophils, also may link inflammation to oxidative stress and atherosclerosis in patients with ESRD.[139] Recent data have shown that a functional variant of the myeloperoxidase gene is associated with cardiovascular disease in patients with ESRD.[140] Inflammation also might cause direct endothelial dysfunction through stimulation of intercellular adhesion molecules in patients with CKD.[141] The association between elements of MICS and atherosclerosis has been underscored by some investigators who have chosen the term MIA syndrome for this entity as stated above.[24,142]

POOR CLINICAL OUTCOME AND REVERSE EPIDEMIOLOGY

Many recent studies suggested that PEM and inflammation in dialysis patients are associated with decreased quality of life and increased hospitalization and mortality, especially from cardiovascular disease.[4,22,23] Epidemiological studies indicated that hypoalbumineamia and increased serum CRP levels are strong predictor of poor clinical outcome in patients with ESRD.[73,74] Compared with such traditional risk factors as obesity, hypercholesterolemia, and hypertension, hypoalbuminemia per se, generally considered an indicator of MICS, has one of the most striking and consistent associations with clinical outcome in these individuals.[143]

In highly industrialized affluent countries, PEM is an uncommon cause of poor outcome in the general population, whereas overnutrition is associated with a greater risk for cardiovascular disease and has an immense epidemiological impact on the burden of this disease and shortened survival. Conversely, in maintenance dialysis patients, undernutrition is one of the most common risk factors for adverse cardiovascular events.[18,111,144] Hence, certain markers that predict a low likelihood of cardiovascular events and improved survival in the general population, such as decreased BMI[50-52,145] or lower serum cholesterol levels,[61,88] are risk factors for increased cardiovascular morbidity and death in dialysis patients.[111] Paradoxically, obesity, hypercholesterolemia, and hypertension appear to be protective features associated with greater survival among dialysis patients. A similar protective role has been described for high serum creatinine and possibly homocysteine levels in patients with ESRD. The association between undernutrition and adverse cardiovascular outcome in dialysis patients, in contrast to that in individuals without ESRD, has been referred to as reverse epidemiology.[111]

The cause of this inverse association between conventional risk factors and clinical outcome in dialysis patients is not clear. Several possible causes are hypothesized, including survival bias and time discrepancy between competitive risk factors (undernutrition versus overnutrition). However, the presence of MICS in dialysis patients offers the most plausible explanation for the existence of reverse epidemiology. Both PEM and inflammation or the combination of the 2 are much more common in dialysis patients than in the general population, and many elements of MICS, such as low weight for height or BMI, hypocholesterolemia, or hypocreatininemia, are known risk factors for poor outcome in dialysis patients.[111] The existence of reverse epidemiology may have a bearing on the management of dialysis patients. It is possible that new standards or goals for such traditional risk factors as body mass, serum cholesterol level, and blood pressure should be considered for these individuals.

The phenomenon of risk factor paradox is caused or at least accentuated by MICS in several ways. First, patients who are underweight or have low serum cholesterol, creatinine, or homocysteine levels may have MICS and its poor outcome. Thus, MICS may both cause these alterations and be associated with increased mortality, caused by either the illnesses that engender MICS or the atherosclerotic cardiovascular diseases that seem to be promoted by MICS.[22,146,147] Second, these paradoxical factors may indicate a state of undernutrition, which may predispose to infection or other inflammatory processes.[18] Finally, it has been argued that when individuals are malnourished, they are more susceptible to the ravages of inflammatory diseases.[148] Hence, a condition that potentially attenuates the magnitude of PEM or inflammation should be favorable to dialysis patients.

Suliman et al[149-151] reported a more specific example of the contribution of MICS to risk-factor reversal concerned with hyperhomocysteinemia in dialysis patients. In their study, plasma total homocysteine levels were shown to be dependent on nutritional status, protein intake, and serum albumin levels in hemodialysis patients. Dialysis patients with cardiovascular disease had lower plasma homocysteine levels, as well as a greater prevalence of malnutrition and hypoalbuminemia, than those without cardiovascular disease. Furthermore, in another study, plasma total homocysteine level increased during treatment of malnourished peritoneal dialysis patients with an amino acid–containing peritoneal dialysate (methionine, 1.7 g/d).[152] The puzzling inverse relationship between low blood pressure and poor outcome in the dialysis population also might be accounted for by nutritional status and/or inflammation. Iseki et al[153] showed a significant association between low diastolic blood pressure, hypoalbuminemia, and risk for death in a cohort of 1,243 hemodialysis patients followed up for up to 5 years. Death rate correlated inversely with diastolic blood pressure, which per se correlated positively with serum albumin level and negatively correlated with age. Hence, in some cases, hypotension may be a manifestation of MICS in patients with ESRD.

DIAGNOSIS AND MANAGEMENT OF MICS

Because various markers of nutritional state and inflammation may independently predict outcome and may assess different aspects of nutritional status, several researchers tried to develop composite scores to identify MICS. Ideally, such a scoring system would not only reflect the overall nutritional status and inflammation of a dialysis patient, but also predict outcome. Wolfson et al[55] introduced a composite score based on body weight, midarm muscle circumference, and serum albumin level and found that 70% of hemodialysis patients were malnourished. Marckmann[154] developed a nutritional scoring system based on serum transferrin level, relative body weight, triceps skinfold, and midarm muscle circumference. The SGA of Nutritional Status was designed primarily to evaluate surgical patients with gastrointestinal diseases.[38] It has been used in a number of epidemiological studies and clinical trials in dialysis patients.[39] SGA score correlated significantly with morbidity and mortality in dialysis patients.[155,156] The National Kidney Foundation–Kidney Disease and Dialysis Outcomes Quality Initiative (DOQI) recommended the SGA as an appropriate nutritional assessment tool for dialysis patients.[157] The Canada-USA[158] and other studies[159] have led to improved more quantitative versions of the SGA. The MIS recently was developed and is based on the SGA, but also includes BMI and serum albumin and transferrin concentrations in an incremental fashion.[23] In a longitudinal study of hemodialysis patients, the MIS correlated strongly with 12-month hospitalization rates and mortality.[23] The MIS is believed to reflect the degree of severity of MICS in dialysis patients.[23]

PEM and inflammation are powerful predictors of death risk for dialysis patients, and if they are treatable, it is possible that nutritional and anti-inflammatory interventions improve poor outcome in dialysis patients. Experience with nutritional support of sick or malnourished individuals who do not have ESRD may provide some insight into the independent role of PEM on clinical outcome in dialysis patients. Ample evidence suggests that maintaining adequate nutritional intake in patients with a number of acute or chronic catabolic illnesses may improve their nutritional status irrespective of its cause.[160,161] In some of these studies, such improvement is associated with reduced morbidity and mortality and improved quality of life.[162]

However, evidence about whether nutritional treatment may improve morbidity and mortality in dialysis patients is limited. There are no large-scale, randomized, prospective, interventional studies that have examined these questions. Among studies based on food intake, Kuhlmann et al[103] reported that prescription of 45 kcal/kg/d and 1.5 g protein/kg/d induced weight gain and improved serum albumin levels and other measures of nutritional status in malnourished hemodialysis patients. Leon et al[102] reported that tailored nutritional intervention improved serum albumin levels in 52 hemodialysis patients, and this effect was observed even among patients with high serum CRP levels. Sharma et al[163] conducted a randomized clinical trial in 40 MHD patients and showed that short-term enteral nutrient supplementation using a high-calorie and high-protein blend formula not only improved hypoalbuminemia, but also functional capacity measured by a 10-point Karnofsky scale.

Several retrospective studies showed a beneficial effect of intradialytic parenteral nutrition (IDPN) on clinical outcome.[164-167] Recently, Pupim et al[104] showed that IDPN promoted a large increase in whole-body protein synthesis and a significant decrease in whole-body proteolysis in 7 hemodialysis patients without inflammation. However, a number of other studies of IDPN failed to show improvement in nutritional status or clinical outcome in dialysis patients.[168,169] Many of these 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 only short periods, or had only a short period of follow-up. 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.[169]

A number of other techniques have been used for the prevention or treatment of PEM in dialysis patients. Routine methods include preventing PEM before the onset of dialysis therapy, dietary counseling, maintenance of an adequate dose of dialysis, avoidance of acidemia, and aggressive treatment of superimposed catabolic illness.[26] More novel nondietary interventions in addition to IDPN include an appetite stimulant, such as megestrol acetate[170]; L-carnitine[171,172]; and growth factors, including recombinant human growth hormone,[173] IGF-1,[174] and anabolic steroids.[175] Nonetheless, although these treatments have improved nutritional status, with the probable exception of the effect of L-carnitine administration on quality of life, none of these treatments have yet been shown to improve quality of life, morbidity, or mortality in 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 in outcomes by inflammation-reducing approaches. However, possible treatment modalities may target inflammation directly or focus on oxidative stress or endothelial dysfunction. The following agents may be considered:

1. Statins (3-hydroxy-3-methylglutarlyl coenzyme A reductase inhibitors) have been suggested for use in patients with chronic inflammation. Statins are shown to decrease CRP levels irrespective of their effects on lipid levels and may be associated with reduced mortality in patients with ESRD.[176,177]
2. Angiotensin-converting enzyme inhibitors may have anti-inflammatory properties in both the general population and patients with CKD and ESRD[178] and are associated with delayed progression of chronic renal failure and improved outcome in these individuals.[79]
3. Vitamin E may have anti-inflammatory effects, and vitamin E administration may be associated with a decreased risk for cardiovascular mortality in dialysis patients.[179] In the general population, some epidemiological studies indicated that a vitamin E–rich diet was associated with better cardiovascular outcome[180]; however, such large clinical trials as the HOPE Study did not confirm such results.[181,182] There are several forms of vitamin E, and it is possible that purified supplements do not show the benefits of natural dietary vitamin E components. A number of preliminary studies indicated that vitamin E–coated dialyzers may have a favorable effect.[183]
4. Optimization of dialysis treatment may improve inflammatory status in dialysis patients, and type of dialysis membrane may have a bearing.[184] Ultrapure dialysate and biocompatible membranes have been shown to decrease CRP levels.[185,186]

FUTURE STEPS

There is a paucity of information concerning the effect of nutritional therapy or anti-inflammatory modalities on morbidity and mortality in dialysis patients. Interventional studies of the effect of nutritional support and inflammation-reducing approaches on outcome are often difficult to interpret because of small sample sizes, short durations of study, and other limitations. New treatment strategies are needed to treat the unacceptably high rate of PEM and inflammation associated with increased cardiovascular morbidity and mortality in patients with ESRD. Different nutritional support modalities should be studied systematically, and novel anti-inflammatory and anticytokine agents need to be tested in patients with renal diseases. In hemodialysis patients, more biocompatible membranes, and in peritoneal dialysis patients, more biocompatible solutions should be developed and tried. Genetic approaches for identifying genes or polymorphisms that may be associated with phenotypes with a greater predisposition to MICS should be attempted. Randomized clinical trials are needed to compare the effect of nutritional support and anti-inflammatory agents, both independently and combined with each other, in patients with MICS to determine the most optimal treatment modality and improve the poor outcome from the cardiovascular epidemic in patients with CKD and ESRD.

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