

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, hypocreatinemia, 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.**

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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

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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 utmost 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

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 malnutrition¹⁵⁻¹⁸ 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) syndrome²⁴ 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

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.

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-

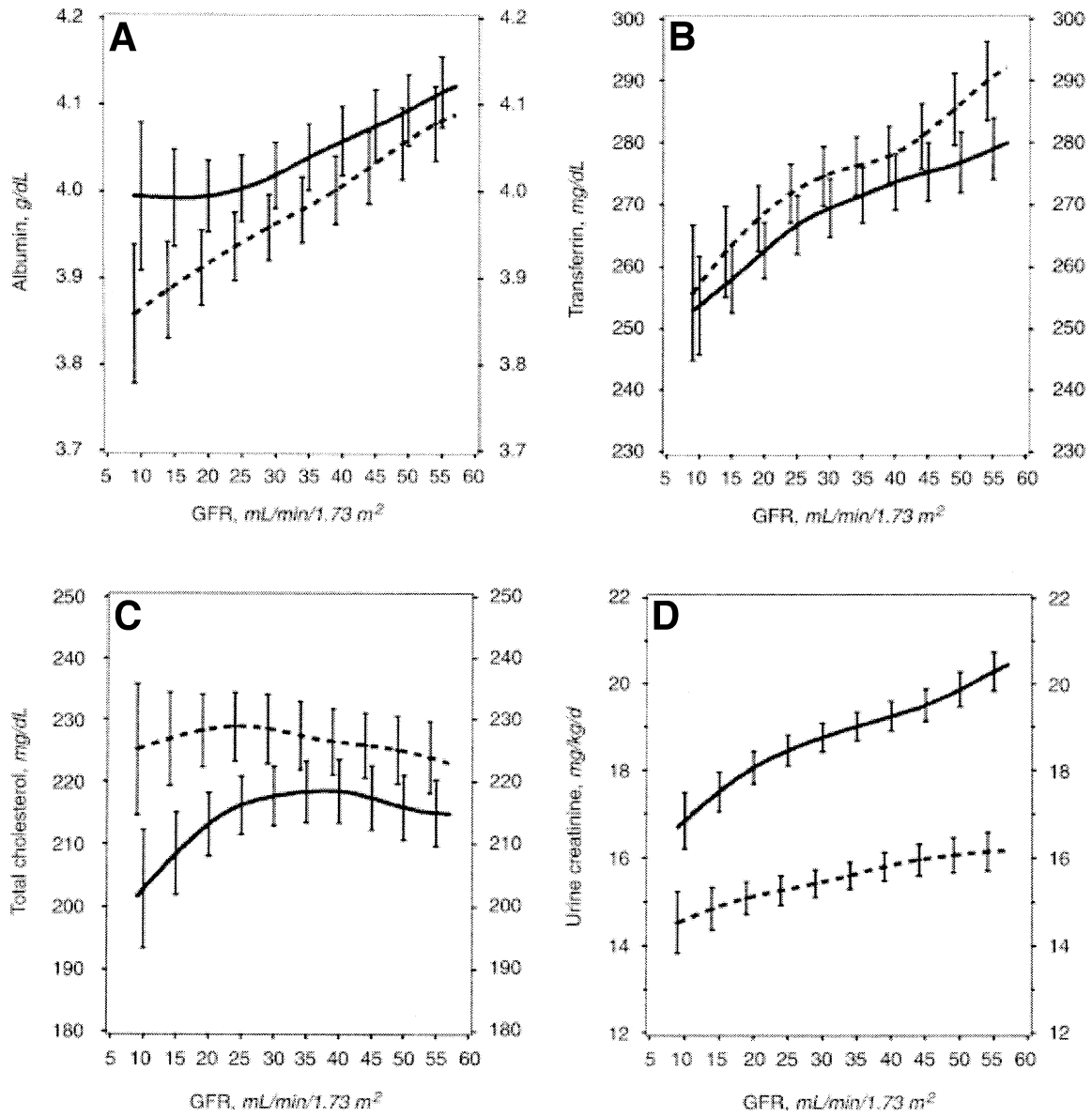


Fig 1. Mean levels of biochemical measures of nutritional status as a function of glomerular filtration rate (GFR) in the Modification of Diet in Renal Disease Study. Estimated mean levels with 95% confidence limits of biochemical nutritional markers are shown as a function of GFR (males, solid line; 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 m² than 55 mL/min/1.73 m² 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 mL/min.^{36,37} Hypoalbuminemia, hypo-

transferrinemia, and hypocholesterolemia have been shown to develop along with the progression of CKD stages, as shown in the Modification of Diet in Renal Disease Study³⁶ (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 absorptiometry; 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 levels⁴⁴; reduced midarm muscle mass and skinfold thicknesses⁵⁵; low serum concentrations of albumin,⁵⁶ prealbumin (transthyretin),^{57,58} transferrin (total iron-binding capacity [TIBC]),^{38,59} cholesterol,^{60,61} and creatinine⁶²; 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 polytetrafluoroethylene) in dialysis access grafts
Intravenous catheter
Peritoneal dialysis:
Episodes of overt or latent peritonitis*
Peritoneal 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 (cachectin)	Transferrin or TIBC
Other interleukins (IL-1 β , 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 -antitrypsin 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 ($\sim 10\%/y$ 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 individuals¹¹¹ (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-

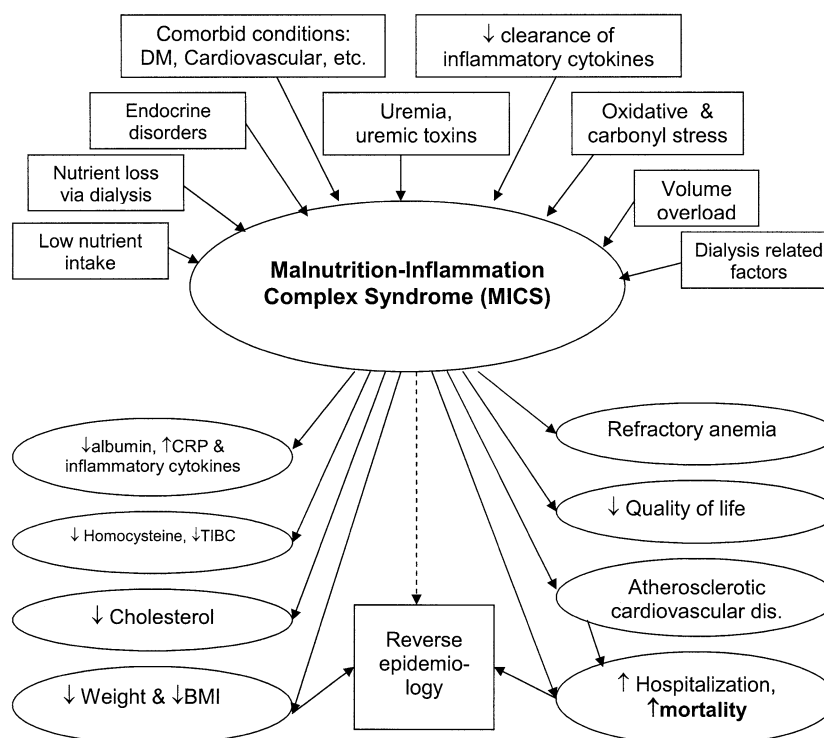


Fig 2. Schematic representation of the causes and consequences of MICS. Abbreviation: DM, diabetes mellitus.

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 repre-

sent 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 Druke 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 al¹³⁵ 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 hypoalbuminemia 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 hypocreatinemia, 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 sev-

eral 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 al¹⁴⁹⁻¹⁵¹ 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 al¹⁵³ 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 nutri-

tional 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 al¹⁵⁵ introduced a composite score based on body weight, midarm muscle circumference, and serum albumin level and found that 70% of hemodialysis patients were malnourished. Marckmann¹⁵⁴ 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-USA¹⁵⁸ and other studies¹⁵⁹ 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 al¹⁰³ 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 al¹⁰² 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 al¹⁶³ 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 al¹⁰⁴ 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 acetate¹⁷⁰; 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-methylglutaryl 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 ESRD¹⁷⁸ 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 outcome¹⁸⁰; 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.

REFERENCES

1. US Renal Data Systems: The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2003
2. Devereaux PJ, Schunemann HJ, Ravindran N, et al: Comparison of mortality between private for-profit and private not-for-profit hemodialysis centers: A systematic review and meta-analysis. *JAMA* 288:2449-2457, 2002
3. Eggers PW, Frankenfield DL, Greer JW, McClellan W, Owen WF Jr, Rocco MV: Comparison of mortality and intermediate outcomes between Medicare dialysis patients in HMO and fee for service. *Am J Kidney Dis* 39:796-804, 2002
4. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH: Association among SF-36 quality of life measures and nutrition, hospitalization, and mortality in hemodialysis. *J Am Soc Nephrol* 12:2797-2806, 2001

5. Carlson DM, Duncan DA, Naessens JM, Johnson WJ: Hospitalization in dialysis patients. *Mayo Clin Proc* 59:769-775, 1984
6. Fried L, Abidi S, Bernardini J, Johnston JR, Piraino B: Hospitalization in peritoneal dialysis patients. *Am J Kidney Dis* 33:927-933, 1999
7. Habach G, Bloembergen WE, Mauger EA, Wolfe RA, Port FK: Hospitalization among United States dialysis patients: Hemodialysis versus peritoneal dialysis. *J Am Soc Nephrol* 5:1940-1948, 1995
8. Foley RN, Parfrey PS, Sarnak MJ: Epidemiology of cardiovascular disease in chronic renal disease. *J Am Soc Nephrol* 9:S16-S23, 1998 (suppl 3)
9. Foley RN, Parfrey PS, Sarnak MJ: Clinical epidemiology of cardiovascular disease in chronic renal disease. *Am J Kidney Dis* 32:S112-S119, 1998 (suppl 3)
10. US Renal Data System: The National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2001
11. Hirth RA, Held PJ, Orzol SM, Dor A: Practice patterns, case mix, Medicare payment policy, and dialysis facility costs. *Health Serv Res* 33:1567-1592, 1999
12. Garella S: The costs of dialysis in the USA. *Nephrol Dial Transplant* 12:S10-S21, 1997 (suppl 1)
13. Morbidity and mortality of dialysis. NIH Consensus Statement 11:1-33, 1993
14. Eknoyan G, Beck GJ, Cheung AK, et al: Effect of dialysis dose and membrane flux in maintenance hemodialysis. *N Engl J Med* 347:2010-2019, 2002
15. Fung F, Sherrard DJ, Gillen DL, et al: Increased risk for cardiovascular mortality among malnourished end-stage renal disease patients. *Am J Kidney Dis* 40:307-314, 2002
16. Kalantar-Zadeh K, Supasyndh O, Lehn RS, McAllister CJ, Kopple JD: Normalized protein nitrogen appearance is correlated with hospitalization and mortality in hemodialysis patients with Kt/V greater than 1.20. *J Ren Nutr* 13:15-25, 2003
17. Bergstrom J, Lindholm B: Malnutrition, cardiac disease, and mortality. *Perit Dial Int* 19:S309-S314, 1999 (suppl 2)
18. Kalantar-Zadeh K, Kopple JD: Relative contributions of nutrition and inflammation to clinical outcome in dialysis patients. *Am J Kidney Dis* 38:1343-1350, 2001
19. Qureshi AR, Alvestrand A, Divino-Filho JC, et al: Inflammation, malnutrition, and cardiac disease as predictors of mortality in hemodialysis patients. *J Am Soc Nephrol* 13:S28-S36, 2002 (suppl 1)
20. Zimmermann J, Herrlinger S, Pruy A, Metzger T, Wanner C: Inflammation enhances cardiovascular risk and mortality in hemodialysis patients. *Kidney Int* 55:648-658, 1999
21. Stenvinkel P, Heimburger O, Paulre F, et al: Strong association between malnutrition, inflammation, and atherosclerosis in chronic renal failure. *Kidney Int* 55:1899-1911, 1999
22. Bergstrom J: Inflammation, malnutrition, cardiovascular disease and mortality in end-stage renal disease. *Pol Arch Med Wewn* 104:641-643, 2000
23. Kalantar-Zadeh K, Kopple JD, Block G, Humphreys MH: A malnutrition-inflammation score is correlated with morbidity and mortality in maintenance hemodialysis patients. *Am J Kidney Dis* 38:1251-1263, 2001
24. Pecoits-Filho R, Lindholm B, Stenvinkel P: The malnutrition, inflammation, and atherosclerosis (MIA) syndrome—The heart of the matter. *Nephrol Dial Transplant* 17:S28-S31, 2002 (suppl 11)
25. Torun B, Chew F: Protein-energy malnutrition, in Shils M, Olson J, Shike M, Ross A (eds): *Modern Nutrition in Health and Disease* (ed 9). Baltimore, MD, Williams & Wilkins, 1999, pp 963-988
26. Kopple JD: Nutritional status as a predictor of morbidity and mortality in maintenance dialysis patients. *ASAIO J* 43:246-250, 1997
27. Kopple JD, Zhu X, Lew NL, Lowrie EG: Body weight-for-height relationships predict mortality in maintenance hemodialysis patients. *Kidney Int* 56:1136-1148, 1999
28. Mehrotra R, Kopple JD: Nutritional management of maintenance dialysis patients: Why aren't we doing better? *Annu Rev Nutr* 21:343-379, 2001
29. Kalantar-Zadeh K, Kopple J: Nutritional management of hemodialysis patients, in Massry S (ed): *Nutritional Management of Renal Disease* (ed 2). Philadelphia, PA, Lippincott, Williams & Wilkins, 2003, pp 183-198
30. Kalantar-Zadeh K, Kopple JD, Deepak S, Block D, Block G: Food intake characteristics of hemodialysis patients as obtained by food frequency questionnaire. *J Ren Nutr* 12:17-31, 2002
31. Kopple JD: McCollum Award Lecture, 1996: Protein-energy malnutrition in maintenance dialysis patients. *Am J Clin Nutr* 65:1544-1557, 1997
32. Kopple JD: Pathophysiology of protein-energy wasting in chronic renal failure. *J Nutr* 129:S247-S251, 1999 (suppl 1)
33. Mehrotra R, Kopple J: Causes of protein-energy malnutrition in chronic renal failure, in Kopple J, Massry S (eds): *Nutritional Management of Renal Disease* (ed 2). Philadelphia, PA, Lippincott, Williams & Wilkins, 2003, pp 167-182
34. Qureshi AR, Alvestrand A, Danielsson A, et al: Factors predicting malnutrition in hemodialysis patients: A cross-sectional study. *Kidney Int* 53:773-782, 1998
35. Bergstrom J: Why are dialysis patients malnourished? *Am J Kidney Dis* 26:229-241, 1995
36. Kopple JD, Greene T, Chumlea WC, et al: Relationship between nutritional status and the glomerular filtration rate: Results from the MDRD study. *Kidney Int* 57:1688-1703, 2000
37. Ikizler TA, Greene JH, Wingard RL, Parker RA, Hakim RM: Spontaneous dietary protein intake during progression of chronic renal failure. *J Am Soc Nephrol* 6:1386-1391, 1995
38. Kalantar-Zadeh K, Kleiner M, Dunne E, et al: Total iron-binding capacity-estimated transferrin correlates with the nutritional Subjective Global Assessment in hemodialysis patients. *Am J Kidney Dis* 31:263-272, 1998
39. Enia G, Sicuso C, Alati G, Zoccali C: Subjective Global Assessment of nutrition in dialysis patients. *Nephrol Dial Transplant* 8:1094-1098, 1993
40. Chertow GM: Estimates of body composition as intermediate outcome variables: Are DEXA and BIA ready for prime time? *J Ren Nutr* 9:138-141, 1999

41. Dumler F: Use of bioelectric impedance analysis and dual-energy X-ray absorptiometry for monitoring the nutritional status of dialysis patients. *ASAIO J* 43:256-260, 1997
42. Pollock CA, Allen BJ, Warden RA, et al: Total body nitrogen by neutron activation analysis in maintenance dialysis patients. *Am J Kidney Dis* 16:38-45, 1990
43. Arora P, Strauss BJ, Borovnicar D, Stroud D, Atkins RC, Kerr PG: Total body nitrogen predicts long-term mortality in haemodialysis patients—A single-centre experience. *Nephrol Dial Transplant* 13:1731-1736, 1998
44. Boddy K, King PC, Lindsay RM, Briggs JD, Winchester JF, Kennedy AC: Total body potassium in non-dialysed and dialysed patients with chronic renal failure. *Br Med J* 1:771-775, 1972
45. Ikizler TA, Hakim RM: Nutrition in end-stage renal disease. *Kidney Int* 50:343-357, 1996
46. Kalantar-Zadeh K, Dunne E, Nixon K, et al: Near infra-red interactance for nutritional assessment of dialysis patients. *Nephrol Dial Transplant* 14:169-175, 1999
47. Kalantar-Zadeh K, Block G, Kelly MP, Schroeffer C, Rodriguez RA, Humphreys MH: Near infra-red interactance for longitudinal assessment of nutrition in dialysis patients. *J Ren Nutr* 11:23-31, 2001
48. Kalantar-Zadeh K, Kopple J: Malnutrition as a cause of morbidity and mortality in dialysis patients, in Kopple J, Massry S (eds): *Nutritional Management of Renal Disease* (ed 2). Philadelphia, PA, Lippincott, Williams & Wilkins, 2003, pp 433-466
49. Kalantar-Zadeh K, Block G, McAllister C, Kopple M: Association between appetite and inflammation, anemia, EPO dose, and quality of life in dialysis. *J Am Soc Nephrol* 13:S223A, 2002 (suppl; abstr P0797).
50. Culp K, Flanigan M, Dudley J, Taylor L, Bissen T, Garrison S: Using the Quetelet body mass index as a mortality indicator for patients starting renal replacement therapy. *ANNA J* 25:321-330; discussion, 331-322, 1998
51. Leavey SF, McCullough K, Hecking E, Goodkin D, Port FK, Young EW: Body mass index and mortality in 'healthier' as compared with 'sicker' haemodialysis patients: Results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant* 16:2386-2394, 2001
52. Port FK, Ashby VB, Dhingra RK, Roys EC, Wolfe RA: Dialysis dose and body mass index are strongly associated with survival in hemodialysis patients. *J Am Soc Nephrol* 13:1061-1066, 2002
53. Blumenkrantz MJ, Kopple JD, Gutman RA, et al: Methods for assessing nutritional status of patients with renal failure. *Am J Clin Nutr* 33:1567-1585, 1980
54. Pollock CA, Ibels LS, Allen BJ, et al: Total body nitrogen as a prognostic marker in maintenance dialysis. *J Am Soc Nephrol* 6:82-88, 1995
55. Wolfson M, Strong CJ, Mintum D, Gray DK, Kopple JD: Nutritional status and lymphocyte function in maintenance hemodialysis patients. *Am J Clin Nutr* 39:547-555, 1984
56. Kaysen GA, Levin NW: Why measure serum albumin levels? *J Ren Nutr* 12:148-150, 2002
57. Sreedhara R, Avram MM, Blanco M, Batish R, Mittman N: Prealbumin is the best nutritional predictor of survival in hemodialysis and peritoneal dialysis. *Am J Kidney Dis* 28:937-942, 1996
58. Kopple JD, Mehrotra R, Suppasyndh O, Kalantar-Zadeh K: Observations with regard to the National Kidney Foundation K/DOQI clinical practice guidelines concerning serum transthyretin in chronic renal failure. *Clin Chem Lab Med* 40:1308-1312, 2002
59. Neyra NR, Hakim RM, Shyr Y, Ikizler TA: Serum transferrin and serum prealbumin are early predictors of serum albumin in chronic hemodialysis patients. *J Ren Nutr* 10:184-190, 2000
60. Avram MM, Fein PA, Antignani A, et al: Cholesterol and lipid disturbances in renal disease: The natural history of uremic dyslipidemia and the impact of hemodialysis and continuous ambulatory peritoneal dialysis. *Am J Med* 87:55N-60N, 1989
61. Iseki K, Yamazato M, Tozawa M, Takishita S: Hypocholesterolemia is a significant predictor of death in a cohort of chronic hemodialysis patients. *Kidney Int* 61:1887-1893, 2002
62. Lowrie EG, Lew NL: Death risk in hemodialysis patients: The predictive value of commonly measured variables and an evaluation of death rate differences between facilities. *Am J Kidney Dis* 15:458-482, 1990
63. Cooper BA, Bartlett LH, Aslani A, Allen BJ, Ibels LS, Pollock CA: Validity of Subjective Global Assessment as a nutritional marker in end-stage renal disease. *Am J Kidney Dis* 40:126-132, 2002
64. Visser R, Dekker FW, Boeschoten EW, Stevens P, Krediet RT: Reliability of the 7-point Subjective Global Assessment scale in assessing nutritional status of dialysis patients. *Adv Perit Dial* 15:222-225, 1999
65. Kaysen GA: The microinflammatory state in uremia: Causes and potential consequences. *J Am Soc Nephrol* 12:1549-1557, 2001
66. Kaysen GA, Dubin JA, Muller HG, Mitch WE, Rosales LM, Levin NW: Relationships among inflammation nutrition and physiologic mechanisms establishing albumin levels in hemodialysis patients. *Kidney Int* 61:2240-2249, 2002
67. Grodstein GP, Blumenkrantz MJ, Kopple JD: Nutritional and metabolic response to catabolic stress in uremia. *Am J Clin Nutr* 33:1411-1416, 1980
68. Newman Dorland W, Anderson D: *Dorland's Illustrated Medical Dictionary*, Philadelphia, PA, Saunders, 2000
69. Gabay C, Kushner I: Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med* 340:448-454, 1999
70. Kushner I: Acute phase proteins, in Rose B, Wellesley MA (eds): *UpToDate*. Boston, MA, UpToDate, 2003
71. Stretz KL, Wustefeld T, Klein C, Manns MP, Trautwein C: Mediators of inflammation and acute phase response in the liver. *Cell Mol Biol (Noisy-le-grand)* 47:661-673, 2001
72. Suffredini AF, Fantuzzi G, Badolato R, Oppenheim JJ, O'Grady NP: New insights into the biology of the acute phase response. *J Clin Immunol* 19:203-214, 1999
73. Owen WF, Lowrie EG: C-Reactive protein as an outcome predictor for maintenance hemodialysis patients. *Kidney Int* 54:627-636, 1998
74. Yeun JY, Levine RA, Mantadilok V, Kaysen GA:

C-Reactive protein predicts all-cause and cardiovascular mortality in hemodialysis patients. *Am J Kidney Dis* 35:469-476, 2000

75. Zoccali C, Benedetto FA, Mallamaci F, et al: Inflammation is associated with carotid atherosclerosis in dialysis patients. Creed Investigators. Cardiovascular Risk Extended Evaluation in Dialysis Patients. *J Hypertens* 18:1207-1213, 2000

76. Iseki K, Tozawa M, Yoshi S, Fukiyama K: Serum C-reactive protein (CRP) and risk of death in chronic dialysis patients. *Nephrol Dial Transplant* 14:1956-1960, 1999

77. Noh H, Lee SW, Kang SW, et al: Serum C-reactive protein: A predictor of mortality in continuous ambulatory peritoneal dialysis patients. *Perit Dial Int* 18:387-394, 1998

78. Fanti P, Sawaya BP, Custer LJ, Franke AA: Serum levels and metabolic clearance of the isoflavones genistein and daidzein in hemodialysis patients. *J Am Soc Nephrol* 10:864-871, 1999

79. Mann JF, Gerstein HC, Pogue J, Bosch J, Yusuf S: Renal insufficiency as a predictor of cardiovascular outcomes and the impact of ramipril: The HOPE randomized trial. *Ann Intern Med* 134:629-636, 2001

80. Shlipak MG, Chertow GC, Massie BM: Beware the rising creatinine level. *J Card Fail* 9:26-28, 2003

81. Shlipak MG, Heidenreich PA, Noguchi H, Chertow GM, Browner WS, McClellan MB: Association of renal insufficiency with treatment and outcomes after myocardial infarction in elderly patients. *Ann Intern Med* 137:555-562, 2002

82. Lowbeer C, Stenvinkel P, Pecoits-Filho R, et al: Elevated cardiac troponin T in predialysis patients is associated with inflammation and predicts mortality. *J Intern Med* 253:153-160, 2003

83. Kalantar-Zadeh K, Kopple J: Inflammation in renal failure, in Rose BD, Post TW (eds): *UpToDate*, vol 10.2. Boston, MA, UpToDate, 2003

84. Kalantar-Zadeh K, Stenvinkel P, Barba L, Pillon L, Kopple J: Nutrition and inflammation in renal insufficiency. *Adv Ren Replace Ther* (in press)

85. Kalantar-Zadeh K, Rodriguez R, Humphreys M: Association between serum ferritin and measures of inflammation, nutrition, and iron in hemodialysis patients. *Nephrol Dial Transplant* (in press)

86. Pecoits-Filho R, Heimbürger O, Barany P, et al: Associations between circulating inflammatory markers and residual renal function in CRF patients. *Am J Kidney Dis* 41:1212-1218, 2003

87. Kimmel PL, Phillips TM, Simmens SJ, et al: Immunologic function and survival in hemodialysis patients. *Kidney Int* 54:236-244, 1998

88. Bologa RM, Levine DM, Parker TS, et al: Interleukin-6 predicts hypoalbuminemia, hypocholesterolemia, and mortality in hemodialysis patients. *Am J Kidney Dis* 32:107-114, 1998

89. Pecoits-Filho R, Barany P, Lindholm B, Heimbürger O, Stenvinkel P: Interleukin-6 is an independent predictor of mortality in patients starting dialysis treatment. *Nephrol Dial Transplant* 17:1684-1688, 2002

90. Stenvinkel P, Barany P, Heimbürger O, Pecoits-Filho R, Lindholm B: Mortality, malnutrition, and atherosclerosis

in ESRD: What is the role of interleukin-6? *Kidney Int* 80:S103-S108, 2002 (suppl)

91. Tatli MM, Vural H, Koc A, Koscecik M, Atas A: Altered anti-oxidant status and increased lipid peroxidation in marasmic children. *Pediatr Int* 42:289-292, 2000

92. Yeun JY, Kaysen GA: Factors influencing serum albumin in dialysis patients. *Am J Kidney Dis* 32:S118-S125, 1998 (suppl 4)

93. Stenvinkel P, Barany P, Chung SH, Lindholm B, Heimbürger O: A comparative analysis of nutritional parameters as predictors of outcome in male and female ESRD patients. *Nephrol Dial Transplant* 17:1266-1274, 2002

94. Kaizu Y, Kimura M, Yoneyama T, Miyaji K, Hibi I, Kumagai H: Interleukin-6 may mediate malnutrition in chronic hemodialysis patients. *Am J Kidney Dis* 31:93-100, 1998

95. Flores EA, Bistrian BR, Pomposelli JJ, Dinarello CA, Blackburn GL, Istfan NW: Infusion of tumor necrosis factor/cachectin promotes muscle catabolism in the rat. A synergistic effect with interleukin 1. *J Clin Invest* 83:1614-1622, 1989

96. Espat NJ, Copeland EM, Moldawr LL: Tumor necrosis factor and cachexia: A current perspective. *Surg Oncol* 3:255-262, 1994

97. McCarthy DO: Tumor necrosis factor alpha and interleukin-6 have differential effects on food intake and gastric emptying in fasted rats. *Res Nurs Health* 23:222-228, 2000

98. Kaysen GA, Chertow GM, Adhikarla R, Young B, Ronco C, Levin NW: Inflammation and dietary protein intake exert competing effects on serum albumin and creatinine in hemodialysis patients. *Kidney Int* 60:333-340, 2001

99. Kaysen GA, Stevenson FT, Depner TA: Determinants of albumin concentration in hemodialysis patients. *Am J Kidney Dis* 29:658-668, 1997

100. Ginn HE, Frost A, Lacy WW: Nitrogen balance in hemodialysis patients. *Am J Clin Nutr* 21:385-393, 1968

101. Kaysen GA, Dubin JA, Muller HG, Rosales LM, Levin NW: The acute-phase response varies with time and predicts serum albumin levels in hemodialysis patients. The HEMO Study Group. *Kidney Int* 58:346-352, 2000

102. Leon JB, Majerle AD, Soinski JA, Kushner I, Ohri-Vachaspati P, Sehgal AR: Can a nutrition intervention improve albumin levels among hemodialysis patients? A pilot study. *J Ren Nutr* 11:9-15, 2001

103. Kuhlmann MK, Schmidt F, Kohler H: High protein/energy vs standard protein/energy nutritional regimen in the treatment of malnourished hemodialysis patients. *Miner Electrolyte Metab* 25:306-310, 1999

104. Pupim LB, Flakoll PJ, Brouillette JR, Levenhagen DK, Hakim RM, Ikizler TA: Intradialytic parenteral nutrition improves protein and energy homeostasis in chronic hemodialysis patients. *J Clin Invest* 110:483-492, 2002

105. Caglar K, Fedje L, Dimmitt R, Hakim RM, Shyr Y, Ikizler TA: Therapeutic effects of oral nutritional supplementation during hemodialysis. *Kidney Int* 62:1054-1059, 2002

106. Stenvinkel P, Holmberg I, Heimbürger O, Diczfalussy U: A study of plasmalogen as an index of oxidative stress in patients with chronic renal failure. Evidence of increased oxidative stress in malnourished patients. *Nephrol Dial Transplant* 13:2594-2600, 1998

107. Hulsewe KW, van Acker BA, von Meyenfeldt MF,

Soeters PB: Nutritional depletion and dietary manipulation: Effects on the immune response. *World J Surg* 23:536-544, 1999

108. De Simone C, Famularo G, Tzantzoglou S, Trinchieri V, Moretti S, Sorice F: Carnitine depletion in peripheral blood mononuclear cells from patients with AIDS: Effect of oral L-carnitine. *AIDS* 8:655-660, 1994

109. Ridker PM, Rifai N, Rose L, Buring JE, Cook NR: Comparison of C-reactive protein and low-density lipoprotein cholesterol levels in the prediction of first cardiovascular events. *N Engl J Med* 347:1557-1565, 2002

110. Kaysen GA: Malnutrition and the acute-phase reaction in dialysis patients—How to measure and how to distinguish. *Nephrol Dial Transplant* 15:1521-1524, 2000

111. Kalantar-Zadeh K, Block G, Humphreys MH, Kopple JD: Reverse epidemiology of cardiovascular risk factors in maintenance dialysis patients. *Kidney Int* 63:793-808, 2003

112. Ifudu O, Uribarri J, Rajwani I, et al: Low hematocrit may connote a malnutrition-inflammation syndrome in hemodialysis patients. *Dial Transplant* 845 31:845-878, 2002

113. Stenvinkel P, Heimbürger O, Lindholm B, Kaysen GA, Bergström J: Are there two types of malnutrition in chronic renal failure? Evidence for relationships between malnutrition, inflammation and atherosclerosis (MIA syndrome). *Nephrol Dial Transplant* 15:953-960, 2000

114. Riella MC: Malnutrition in dialysis: Malnourishment or uremic inflammatory response? *Kidney Int* 57:1211-1232, 2000

115. Barany P, Divino Filho JC, Bergström J: High C-reactive protein is a strong predictor of resistance to erythropoietin in hemodialysis patients. *Am J Kidney Dis* 29:565-568, 1997

116. Stenvinkel P, Alvestrand A: Inflammation in end-stage renal disease: Sources, consequences, and therapy. *Semin Dial* 15:329-337, 2002

117. Gunnell J, Yeun JY, Depner TA, Kaysen GA: Acute-phase response predicts erythropoietin resistance in hemodialysis and peritoneal dialysis patients. *Am J Kidney Dis* 33:63-72, 1999

118. Goicoechea M, Martin J, de Sequera P, et al: Role of cytokines in the response to erythropoietin in hemodialysis patients. *Kidney Int* 54:1337-1343, 1998

119. Sitter T, Bergner A, Schiffl H: Dialysate related cytokine induction and response to recombinant human erythropoietin in haemodialysis patients. *Nephrol Dial Transplant* 15:1207-1211, 2000

120. Kalantar-Zadeh K, McAllister C, Lehn R, Lee G, Nissenson A, Kopple J: Effect of malnutrition-inflammation complex syndrome on EPO hyporesponsiveness in maintenance hemodialysis patients. *Am J Kidney Dis* 42:761-773, 2003.

121. Hurot JM, Cucherat M, Haugh M, Fouque D: Effects of L-carnitine supplementation in maintenance hemodialysis patients: A systematic review. *J Am Soc Nephrol* 13:708-714, 2002

122. Navarro JF, Mora C: In-depth review: Effect of androgens on anemia and malnutrition in renal failure: Implications for patients on peritoneal dialysis. *Perit Dial Int* 21:14-24, 2001

123. Brox AG, Zhang F, Guyda H, Gagnon RF: Subthera-

peutic erythropoietin and insulin-like growth factor-1 correct the anemia of chronic renal failure in the mouse. *Kidney Int* 50:937-943, 1996

124. Voulgari PV, Kolios G, Papadopoulos GK, Katsaraki A, Seferiadis K, Drosos AA: Role of cytokines in the pathogenesis of anemia of chronic disease in rheumatoid arthritis. *Clin Immunol* 92:153-160, 1999

125. Stenvinkel P: The role of inflammation in the anaemia of end-stage renal disease. *Nephrol Dial Transplant* 16:S36-S40, 2001 (suppl 7)

126. Stenvinkel P, Barany P: Anaemia, rHuEPO resistance, and cardiovascular disease in end-stage renal failure; Links to inflammation and oxidative stress. *Nephrol Dial Transplant* 17:S32-S37, 2002 (suppl 5)

127. Kalantar-Zadeh K, Don BR, Rodriguez RA, Humphreys MH: Serum ferritin is a marker of morbidity and mortality in hemodialysis patients. *Am J Kidney Dis* 37:564-572, 2001

128. Kalantar-Zadeh K, Luft FC, Humphreys MH: Moderately high serum ferritin concentration is not a sign of iron overload in dialysis patients. *Kidney Int* 56:758-759, 1999

129. Miller CB, Jones RJ, Piantadosi S, Abeloff MD, Spivak JL: Decreased erythropoietin response in patients with the anemia of cancer. *N Engl J Med* 322:1689-1692, 1990

130. Jelkmann W, Pagel H, Wolff M, Fandrey J: Monokines inhibiting erythropoietin production in human hepatoma cultures and in isolated perfused rat kidneys. *Life Sci* 50:301-308, 1992

131. Means RT Jr, Krantz SB: Progress in understanding the pathogenesis of the anemia of chronic disease. *Blood* 80:1639-1647, 1992

132. Schooley JC, Kullgren B, Allison AC: Inhibition by interleukin-1 of the action of erythropoietin on erythroid precursors and its possible role in the pathogenesis of hypoplastic anaemias. *Br J Haematol* 67:11-17, 1987

133. Druke T, Witko-Sarsat V, Massy Z, et al: Iron therapy, advanced oxidation protein products, and carotid artery intima-media thickness in end-stage renal disease. *Circulation* 106:2212-2217, 2002

134. Becker AE, de Boer OJ, van Der Wal AC: The role of inflammation and infection in coronary artery disease. *Annu Rev Med* 52:289-297, 2001

135. Girndt M, Kaul H, Sester U, et al: Anti-inflammatory interleukin-10 genotype protects dialysis patients from cardiovascular events. *Kidney Int* 62:949-955, 2002

136. Kaplan N: Risk factor for atherosclerotic disease, in Braunwald EZD, Libby P (eds): *Heart Disease: A Textbook of Cardiovascular Medicine*. Philadelphia, PA, Saunders, 2001, pp 1010-1039

137. Haubitz M, Brunkhorst R: C-Reactive protein and chronic *Chlamydia pneumoniae* infection—Long-term predictors for cardiovascular disease and survival in patients on peritoneal dialysis. *Nephrol Dial Transplant* 16:809-815, 2001

138. Stenvinkel P, Heimbürger O, Jogestrand T: Elevated interleukin-6 predicts progressive carotid artery atherosclerosis in dialysis patients: Association with *Chlamydia pneumoniae* seropositivity. *Am J Kidney Dis* 39:274-282, 2002

139. Daugherty A, Dunn JL, Rateri DL, Heinecke JW: Myeloperoxidase, a catalyst for lipoprotein oxidation, is

expressed in human atherosclerotic lesions. *J Clin Invest* 94:437-444, 1994

140. Pecoits-Filho R, Stenvinkel P, Marchlewska A, et al: A functional variant of the myeloperoxidase gene is associated with cardiovascular disease in end-stage renal disease patients. *Kidney Int Suppl* 84:S172-S176, 2003
141. Mezzano D, Pais EO, Aranda E, et al: Inflammation, not hyperhomocysteinemia, is related to oxidative stress and hemostatic and endothelial dysfunction in uremia. *Kidney Int* 60:1844-1850, 2001
142. Chung SH, Stenvinkel P, Heimburger O, Bergstrom J, Lindholm B: Prevention and treatment of the malnutrition, inflammation and atherosclerosis (MIA) syndrome in uremic patients. *Pol Arch Med Wewn* 104:645-654, 2000
143. Foley RN, Parfrey PS, Harnett JD, Kent GM, Murray DC, Barre PE: Hypoalbuminemia, cardiac morbidity, and mortality in end-stage renal disease. *J Am Soc Nephrol* 7:728-736, 1996
144. Fleischmann E, Teal N, Dudley J, May W, Bower JD, Salahudeen AK: Influence of excess weight on mortality and hospital stay in 1346 hemodialysis patients. *Kidney Int* 55:1560-1567, 1999
145. Iseki K, Ikemiya Y, Fukiyama K: Predictors of end-stage renal disease and body mass index in a screened cohort. *Kidney Int Suppl* 63:S169-S170, 1997
146. Lowrie EG: History and organization of the National Cooperative Dialysis Study. *Kidney Int Suppl* 1:S1-S7, 1983
147. Ritz E: Why are lipids not predictive of cardiovascular death in the dialysis patient? *Miner Electrolyte Metab* 22:9-12, 1996
148. Lowrie E: Conceptual model for a core pathobiology of uremia with special reference to anemia, malnourishment, and mortality among dialysis patients. *Semin Dial* 10:115-129, 1997.
149. Suliman ME, Lindholm B, Barany P, Bergstrom J: Hyperhomocysteinemia in chronic renal failure patients: Relation to nutritional status and cardiovascular disease. *Clin Chem Lab Med* 39:734-738, 2001
150. Suliman ME, Qureshi AR, Barany P, et al: Hyperhomocysteinemia, nutritional status, and cardiovascular disease in hemodialysis patients. *Kidney Int* 57:1727-1735, 2000
151. Suliman ME, Stenvinkel P, Barany P, Heimburger O, Anderstam B, Lindholm B: Hyperhomocysteinemia and its relationship to cardiovascular disease in ESRD: Influence of hypoalbuminemia, malnutrition, inflammation, and diabetes mellitus. *Am J Kidney Dis* 41:S89-S95, 2003 (suppl 2)
152. Bostom A, Brosnan JT, Hall B, Nadeau MR, Selhub J: Net uptake of plasma homocysteine by the rat kidney in vivo. *Atherosclerosis* 116:59-62, 1995
153. Iseki K, Miyasato F, Tokuyama K, et al: Low diastolic blood pressure, hypoalbuminemia, and risk of death in a cohort of chronic hemodialysis patients. *Kidney Int* 51:1212-1217, 1997
154. Marckmann P: Nutritional status and mortality of patients in regular dialysis therapy. *J Intern Med* 226:429-432, 1989
155. Lawson JA, Lazarus R, Kelly JJ: Prevalence and prognostic significance of malnutrition in chronic renal insufficiency. *J Ren Nutr* 11:16-22, 2001
156. Canada-USA Peritoneal Dialysis Study Group: Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcomes. *J Am Soc Nephrol* 7:198-207, 1996
157. National Kidney Foundation: K/DOQI Clinical Practice Guidelines for Nutrition in Chronic Renal Failure. *Am J Kidney Dis* 35:S1-S140, 2000 (suppl 2)
158. Canada-USA (CANUSA) Peritoneal Dialysis Study Group: Adequacy of dialysis and nutrition in continuous peritoneal dialysis: Association with clinical outcomes. *J Am Soc Nephrol* 7:198-207, 1996
159. Kalantar-Zadeh K, Kleiner M, Dunne E, Lee GH, Luft FC: A modified quantitative subjective global assessment of nutrition for dialysis patients. *Nephrol Dial Transplant* 14:1732-1738, 1999
160. Kopple JD, Massry SG: Nutritional management of renal disease, in Kopple JD (ed): *Nutritional Management of Nondialyzed Patients With Chronic Renal Failure*. Baltimore, MD, William & Wilkins, 1996, pp 479-531
161. Mortelmans AK, Duym P, Vandenbroucke J, et al: Intradialytic parenteral nutrition in malnourished hemodialysis patients: A prospective long-term study. *JPEN J Parenter Enteral Nutr* 23:90-95, 1999
162. Koretz RL: Does nutritional intervention in protein-energy malnutrition improve morbidity or mortality? *J Ren Nutr* 9:119-121, 1999
163. Sharma M, Rao M, Jacob S, Jacob CK: A controlled trial of intermittent enteral nutrient supplementation in maintenance hemodialysis patients. *J Ren Nutr* 12:229-237, 2002
164. Foulks CJ: The effect of intradialytic parenteral nutrition on hospitalization rate and mortality in malnourished hemodialysis patients. *J Ren Nutr* 4:5-10, 1994
165. Chertow GM, Owen WF, Lazarus JM: Outcomes of older patients receiving chronic dialysis. *JAMA* 272:274, 1994
166. Capelli JP, Kushner H, Camiscioli TC, Chen SM, Torres MA: Effect of intradialytic parenteral nutrition on mortality rates in end-stage renal disease care. *Am J Kidney Dis* 23:808-816, 1994
167. Siskind MS, Lien YH: Effect of intradialytic parenteral nutrition on quality of life in hemodialysis patients. *Int J Artif Organs* 16:599-603, 1993
168. Pupim LB, Kent P, Hakim R: The potential of intradialytic parenteral nutrition: A review. *Miner Electrolyte Metab* 25:317-323, 1999
169. Foulks CJ: An evidence-based evaluation of intradialytic parenteral nutrition. *Am J Kidney Dis* 33:186-192, 1999
170. Boccanfuso JA, Hutton M, McAllister B: The effects of megestrol acetate on nutritional parameters in a dialysis population. *J Ren Nutr* 10:36-43, 2000
171. Semeniuk J, Shalansky KF, Taylor N, Jastrzebski J, Cameron EC: Evaluation of the effect of intravenous L-carnitine on quality of life in chronic hemodialysis patients. *Clin Nephrol* 54:470-477, 2000
172. Chazot C, Laurent G, Charra B, et al: Malnutrition in long-term haemodialysis survivors. *Nephrol Dial Transplant* 16:61-69, 2001
173. Johannsson G, Bengtsson BA, Ahlmen J: Double-blind, placebo-controlled study of growth hormone treatment in elderly patients undergoing chronic hemodialysis:

Anabolic effect and functional improvement. *Am J Kidney Dis* 33:709-717, 1999

174. Fouque D, Peng SC, Shamir E, Kopple JD: Recombinant human insulin-like growth factor-1 induces an anabolic response in malnourished CAPD patients. *Kidney Int* 57:646-654, 2000
175. Johnson CA: Use of androgens in patients with renal failure. *Semin Dial* 13:36-39, 2000
176. Chang JW, Yang WS, Min WK, Lee SK, Park JS, Kim SB: Effects of simvastatin on high-sensitivity C-reactive protein and serum albumin in hemodialysis patients. *Am J Kidney Dis* 39:1213-1217, 2002
177. Seliger SL, Weiss NS, Gillen DL, et al: HMG-CoA reductase inhibitors are associated with reduced mortality in ESRD patients. *Kidney Int* 61:297-304, 2002
178. Stenvinkel P, Andersson P, Wang T, et al: Do ACE-inhibitors suppress tumour necrosis factor-alpha production in advanced chronic renal failure? *J Intern Med* 246:503-507, 1999
179. Boaz M, Smetana S, Weinstein T, et al: Secondary Prevention With Antioxidants of Cardiovascular Disease in Endstage Renal Disease (SPACE): Randomised placebo-controlled trial. *Lancet* 356:1213-1218, 2000
180. Abbey M: The importance of vitamin E in reducing cardiovascular risk. *Nutr Rev* 53:S28-S32, 1995 (suppl 1)
181. Hoogwerf BJ, Young JB: The HOPE study. Ramipril lowered cardiovascular risk, but vitamin E did not. *Cleve Clin J Med* 67:287-293, 2000
182. Lonn E, Yusuf S, Hoogwerf B, et al: Effects of vitamin E on cardiovascular and microvascular outcomes in high-risk patients with diabetes: Results of the HOPE study and MICRO-HOPE substudy. *Diabetes Care* 25:1919-1927, 2002
183. Clermont G, Lecour S, Cabanne JF, et al: Vitamin E-coated dialyzer reduces oxidative stress in hemodialysis patients. *Free Radic Biol Med* 31:233-241, 2001
184. Bloembergen WE, Hakim RM, Stannard DC, et al: Relationship of dialysis membrane and cause-specific mortality. *Am J Kidney Dis* 33:1-10, 1999
185. Schindler R, Boenisch O, Fischer C, Frei U: Effect of the hemodialysis membrane on the inflammatory reaction in vivo. *Clin Nephrol* 53:452-459, 2000
186. Memoli B, Minutolo R, Bisesti V, et al: Changes of serum albumin and C-reactive protein are related to changes of interleukin-6 release by peripheral blood mononuclear cells in hemodialysis patients treated with different membranes. *Am J Kidney Dis* 39:266-273, 2002
187. Beto JA, Bansal VK, Hart J, McCarthy M, Roberts D: Hemodialysis prognostic nutrition index as a predictor for morbidity and mortality in hemodialysis patients and its correlation to adequacy of dialysis. Council on Renal Nutrition National Research Question Collaborative Study Group. *J Ren Nutr* 9:2-8, 1999
188. Merkus MP, Jager KJ, Dekker FW, de Haan RJ, Boeschoten EW, Krediet RT: Predictors of poor outcome in chronic dialysis patients: The Netherlands Cooperative Study on the Adequacy of Dialysis. The NECOSAD Study Group. *Am J Kidney Dis* 35:69-79, 2000
189. Pecoits-Filho R, Lindholm B, Stenvinkel P: End-stage renal disease: A state of chronic inflammation and hyperleptinemia. *Eur J Clin Invest* 33:527-528, 2003
190. Harty JC, Boulton H, Curvell J, et al: The normalized protein catabolic rate is a flawed marker of nutrition in CAPD patients. *Kidney Int* 45:103-109, 1994