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NEPHROLOGY FORUM

Malnutrition in dialysis: Malnourishment or uremic inflammatory response?

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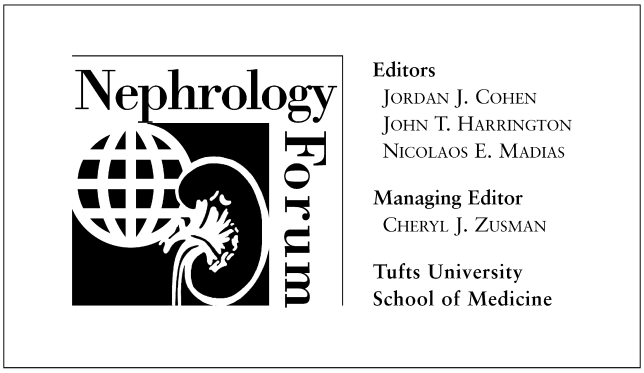

CASE PRESENTATIONS

Patient 1. A 50-year-old woman had chronic renal failure secondary to long-standing arterial hypertension. When she started hemodialysis thrice weekly 10 years ago, she had a "dry weight" of 49 kg; height, 1.54 m; body mass index, 20.7; and serum albumin, 3.1 g/dL. She had been anorectic and asthenic, and peripheral edema was present. Eight years ago, her dry weight was 51.5 kg; body mass index, 21.7; and serum albumin, 3.1 g/dL. Despite good appetite, dietary evaluation revealed that she was taking 22 kcal/kg/day and her normalized protein catabolic rate was 0.68 g/kg/day. Her urea reduction ratio (URR) was 61.2%. Six years ago, her dry weight was 52 kg; body mass index, 21.9; and serum albumin, 3.1 g/dL. Ten months later, nutritional oral supplementation was initiated. Her dry weight had dropped to 48 kg, and the body mass index was 21.1. It became apparent to the social worker and dietitian that she could not afford to purchase her basic nutrients and that she had difficulty chewing the food because of poor teeth.

Ten months ago, her dry weight had reached 56 kg; body mass index, 24.5; and serum albumin, 4.0 g/dL. Her normalized protein catabolic rate was 0.82 g/kg/day; URR, 72.8%; and Kt/V_{urea}, 1.56. She is still receiving oral nutritional supplementation and doing well after almost 10 years on dialysis.

Patient 2. A 51-year-old woman presented to the Renal Clinic at the Evangelic School of Medicine of Parana 11 months ago with a history of edema and weakness. She was a retired teacher and had been undergoing peritoneal dialysis for four years. The cause of her chronic renal failure was polycystic kidney disease, and she had started dialysis with a creatinine clearance of 10 mL/min. In the beginning of the therapy, she used a 2-liter exchange three times daily. The patient had felt well during the first year of treatment and showed no signs of underdialysis. She was 1.58 m tall and her weight was 67 kg (body mass index, 26.8) when she started dialysis. She had normal blood pressure, no edema, and her appetite was good. The same pattern was present after one year of treatment.

Laboratory examination showed: hematocrit, 30%; albumin, 4.0 g/dL; urea, 128 mg/dL; and creatinine, 11.2 mg/dL. She had been seen in the clinic two years earlier with her first episode of exit-site infection. In the following month, she presented with a *Staphylococcus aureus* peritonitis, which was treated with a first-generation cephalosporin and an aminoglycoside. Another episode of peritonitis occurred three months later and was characterized as a recurrent infection. The same bacteria grew in an exit-site smear culture. The infection was treated with a new course of the same antibiotic regimen. A tunnel infection was diagnosed two months later and the catheter was replaced. Two months after the tunnel infection, she weighed 66 kg, her albumin was 3.2 g/dL, and the serum urea was 108 mg/dL. Her appetite decreased throughout the following months, despite an uneventful dialysis treatment. The albumin level did not increase, and she lost 2 kg during the calendar year. Two years ago, the dialysis prescription was changed to 8 liters per day, with one hypertonic exchange at night. Four months later, she had another episode of *Staphylococcus aureus* peritonitis. Despite the increased dialysis dose, she developed hypertension and had problems keeping her dry weight. Edema was noticeable at most of her clinic appointments. A standard peritoneum equilibrium test showed a high transport pattern, with a 4-hour dialysate/plasma ratio of creatinine of 0.81. Analysis of the adequacy of dialysis showed a total corrected creatinine clearance of 42 liters/week and a Kt/V of 1.74. At that time her normalized protein catabolic rate was 1.2 g/kg/day. The albumin level 11 months ago was 2.9 g/dL and her weight was 63.8 kg (estimated dry weight, 62 kg; body mass index, 24.8) and edema was still present. She was admitted to the hospital for control of her edema and hypertension, and she was switched to daytime chronic ambulatory peritoneal dialysis.

DISCUSSION

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gelic School of Medicine of Parana, Curitiba, Parana, Brazil): These two patients illustrate the spectrum of malnutrition in our current dialysis population. At one end of the spectrum is malnutrition due to poor nutrient intake (malnourishment); at the other end of the spectrum is malnutrition due to a reduction in somatic and visceral proteins as a result of a hypercatabolic state (an inflammatory response). In this Forum, I will examine both sides of this spectrum.

Malnutrition has been reported to vary from 10% to 70% in hemodialysis patients and from 18% to 51% in continuous ambulatory peritoneal dialysis (CAPD) patients [1]. The signs of malnutrition are reduced subcutaneous fat stores (reduced energy stores) and decreased muscle mass (as assessed by anthropometric methods), low total-body nitrogen determined by in vivo neutron activation analysis [2], hypoalbuminemia, low transferrin and other visceral proteins, low alkaline-soluble protein in muscle in relation to dry fat-free weight and DNA [3], and abnormal plasma amino acids and intracellular amino acid profiles [4]. However, some hemodialysis patients have a normal nutritional status [5]. The anthropometric data indicate that energy malnutrition is more prevalent than is protein malnutrition in hemodialysis patients, but these anthropometric methods may underestimate protein depletion [6]. In one study, total-body nitrogen determined by neutron activation analysis was more sensitive in detecting protein depletion than were anthropometric measurements [7].

The anthropometric measurement of body mass index (BMI), calculated as an individual's weight in kilograms divided by the square of the individual's height in meters (kg/m^2), correlates with measures of body fat and is used as a marker of energy nutritional status (energy stores). Comparisons of BMI among female and male hemodialysis patients and the general U.S. population reveal that in all age groups and both genders, mean BMI is significantly lower in hemodialysis patients than in the respective general population samples [8]. Young et al examined the nutritional status of 224 CAPD patients from six centers in Europe and North America and assessed the incidence of protein-energy malnutrition. Using a subjective nutritional assessment, the authors found that 8% of the patients were severely malnourished, 33% were mildly to moderately malnourished, and 59% showed no evidence of malnutrition [9].

Table 1. Nutritional evaluation in dialysis patients

Clinical
Medical history
Physical examination
Nutrient physical examination (NPE)
SGA: subjective global assessment
Nutritional intake
Dietary history and dietary records
Appetite assessment: Appetite and Diet Assessment tool (ADAT)
Urea appearance (estimation of protein intake)
Biochemical
Visceral protein stores: plasma proteins (albumin, prealbumin, transferrin, IGF-1)
Static protein reserves: serum creatinine, urinary creatinine output, creatinine-height index, 3-methylhistidine
Other plasma and blood chemistries (hemoglobin, urea, creatinine, lipids, amino acids)
Biochemical analysis of skeletal muscle: alkali-soluble protein, DNA, RNA, amino acids
Vitamins, minerals, and trace elements
Fluid, electrolyte, and acid-base status
Body weight
Actual, compared to standards and weight change
BMI (body mass index)
Body composition
Direct methods
Neutron activation analysis
Computed tomography
Magnetic resonance imaging
Dual energy X-ray absorptiometry (DEXA)
Total body water
Indirect methods
Hydrodensitometry
Bioelectric impedance
Anthropometry: skinfold thickness, midarm muscle circumference
Immunologic methods
Total lymphocyte count
Delayed hypersensitivity skin tests

Evaluating nutritional status in dialysis patients

The ideal protocol for diagnosing malnutrition in patients with renal disease has not been created. Many biochemical indicators of nutrition—such as serum albumin, creatinine, transferrin, and cholesterol—are useful in identifying high-risk groups but often are abnormal only late in the course of a deteriorating nutritional state. Moreover, they can be confounded by concomitant liver disease, iron-deficiency anemia, and chronic inflammation [10]. More sophisticated methods of body composition analysis, such as neutron activation analysis, can be used to quantify body cell mass and other body compartments but are costly and not widely available [7].

Ideal nutritional assessment should be able to detect the entire range of poor nutrition, from subclinical malnutrition to overt malnutrition, assess macro- and micronutrient deficiencies, and grade the overall nutritional status of the patient. Since no single measurement can accomplish all of these goals [11], many indices, each representing a specific data category, are measured independently and then evaluated collectively to ascertain the nutritional status of the patient (Table 1).

A good method for estimating the protein intake quantitatively is a determination of the "total nitrogen appearance" (TNA), which is defined as the sum of all nitrogen losses from the body plus the change in body nonprotein nitrogen (mainly urea nitrogen). Total nitrogen appearance reflects the net breakdown of protein which, in the steady state, is equal to the intake of nitrogen, the main source of which is ingested protein [11].

By measuring the urea losses in the urine and dialysate as well as the changes in blood urea nitrogen in CAPD patients, one can calculate the urea nitrogen appearance (UNA), which closely reflects TNA. In hemodialysis patients, one needs to measure urea concentrations before and after dialysis, dialyzer clearance, and dialysis time. The protein equivalent of nitrogen appearance, PNA (formerly protein catabolic rate), has been found to be 6.25 times TNA, which in the steady state reflects protein intake [11]. For CAPD patients, the Bergström et al I and II formulas are recommended [11]. Equation 1 might be simpler to use, as it does not require direct analysis of protein losses, but it can yield less-accurate values when the protein losses are high. In Equation 2, the protein losses in dialysate and urine should be added.

$$\text{PNA (g/24 h)} = 20.1 + 7.50\ \text{UNA (g/24 h)} \quad \text{(Eq. 1)}$$

$$\text{PNPNA (g/24 h)} = 15.1 + 6.95\ \text{UNA (g/24 h)} \quad \text{(Eq. 2)}$$

where PNPNA represents protein equivalent of nonprotein nitrogen appearance which, in the steady state, approximates the net protein intake, that is, total protein intake minus total protein losses.

What are an individual's protein and energy requirements? The protein requirement is defined as the lowest level of dietary protein intake that will balance the losses of nitrogen from the body in a person who maintains energy balance at modest levels of physical activity. Most estimates of human protein requirements have been obtained from measurements of nitrogen balance. The mean value obtained for adults has been 0.6 g/kg/day with a coefficient of variability of 12.5% [12]. Hence, a value of 25% (2 SD) above the mean physiologic requirement for the adult would meet the needs of all but 2.5% of people in the adult population. Thus, the mean requirement should be increased to 0.75 g/kg/day to provide a safe protein intake for healthy adults. Some adults may require as little as 0.45 g/kg/day of high-quality protein [12].

Surprisingly few studies have assessed the dietary protein requirements for patients on maintenance hemodialysis [13]. Most of the studies addressing protein requirements in hemodialysis patients were carried out several years ago and used dialyzers and dialyzer clearances that are no longer in use. Given the fact that (1) there is a high prevalence of protein malnutrition in maintenance hemodialysis patients, (2) metabolic studies clearly indicate that 0.75 g protein/kg/day is nutritionally adequate for many hemodialysis patients [13], and (3) 1.1 g protein/kg/day will maintain nitrogen balance in some but not all patients who are ingesting 25 or 35 kcal/kg/day, a dietary protein intake of 1.2 g/kg/day is recommended [13]. To ensure adequate intake of essential amino acids, at least one-half the protein ingested should be of high biologic value.

Low caloric energy intake appears to be more common and severe than is decreased protein intake in most patients on maintenance hemodialysis [13]. The low energy intake does not reflect a decrease in energy requirements. Indirect calorimetry studies have shown that energy expenditure in maintenance hemodialysis patients appears similar to that of normal individuals [14]. But a more recent study, using whole-room indirect calorimetry, reported that resting energy expenditure (REE) is actually higher in maintenance hemodialysis patients, even on non-dialysis days, compared to age-, gender-, and body-mass-index-matched normal controls [15]. This higher REE in hemodialysis patients was calculated to be 8% to 16% greater than that in normal individuals.

Most studies in patients on maintenance hemodialysis indicate that energy intake frequently is below the recommended level for normal healthy adults, usually averaging approximately 24 to 27 kcal/kg/day [13]. In the Hemo Clinical Trial, in which patients are seen periodically by renal dietitians, the energy intake averaged 22.8 $\pm$ 8.8 (mean $\pm$ SD) kcal/kg adjusted body weight/day [13]. The findings of low body fat and decreased skinfold thickness in maintenance hemodialysis patients [16] seem to support the thesis that the usual energy intake of these individuals is inadequate. Slomowitz et al carried out metabolic balance studies in six maintenance hemodialysis patients who lived in a clinical research center for 63 to 65 days and who underwent hemodialysis for four hours three times per week with Cuprophan or cellulose acetate dialyzers [17]. These patients were fed a constant-protein diet that provided 1.13 $\pm$ 0.02 (mean $\pm$ SEM) g/kg/day, but were fed three different dietary energy intakes (in a random fashion) for 21 to 23 days each that provided 25, 35, and 45 kcal/kg/day. Nitrogen balance was negative, neutral, and positive for the diets providing 25, 35, and 45 kcal/kg/day, respectively [17]. Nutritional surveys indicate that mean protein intake is less than 1 g/kg/day in a large proportion of patients on maintenance hemodialysis [3, 18]. However, many investigators have shown that chronic renal failure and ESRD patients can maintain nitrogen balance despite significantly lower protein intake [19]. Based on the available evidence, I believe it appropriate to recommend an energy intake of 35 kcal/kg/day for clinically stable patients on maintenance hemodialysis. Patients older than 60 years might need only 30 kcal/kg/day [13].

Causes of dialysis malnutrition

The multifactorial reasons for malnutrition in dialysis patients include disturbances in protein and energy metabolism, hormonal derangement, poor intake due to anorexia, and nausea and vomiting related to the uremic toxicity. Many underlying diseases such as diabetes melli-

Table 2. Causes of anorexia in maintenance dialysis patients

Dietary restriction (limited choice and palatability)
Frequent hospitalizations and surgical procedures
Psychosocial and economic factors: depression, loneliness, ignorance, poverty, poor dental status, alcohol and drug abuse
Inadequate dialysis (uremic toxicity)
Inflammation, infection, sepsis
Underlying diseases
Gastropathy (diabetics)
Medications
? Hyperleptinemia
? Cytokines
Effects of hemodialysis: cardiovascular instability, nausea and vomiting, postdialysis fatigue
Effects of peritoneal dialysis: abdominal discomfort, absorption of glucose and amino acids, peritonitis

tus, diffuse vascular disease (coined vascular cachexia), and superimposed illness (pericarditis, infection, congestive heart failure) also can contribute to malnutrition. Let us analyze first one end of the malnutrition spectrum: poor nutrient intake. The main reason for inadequate nutritional intake is a decrease in appetite (anorexia) that can have many causes (Table 2).

Although many of the causes of anorexia in dialysis patients are acceptable and understandable, some are poorly understood, particularly the anorexia related to uremic toxicity. A reasonable hypothesis is that inhibition of appetite is caused by retention of toxic substances as a consequence of reduced renal function. Low-protein diets ameliorate the uremic symptoms of anorexia, nausea, and vomiting. This finding suggests that some of these toxins are generated by dietary protein breakdown. Recent studies indicate that many patients decrease dietary protein intake with the progression of renal failure; protein intake can fall as low as 0.6 g/kg/day when creatinine clearance is less than 10 mL/min [20]. The observation that anorexia, nausea, and vomiting diminish or disappear at the start of dialysis suggests that a readily dialyzable substance is removed through conventional cellulosic dialysis membranes. Assuming that a dialyzable uremic toxin accumulates in severe renal failure and causes anorexia, it is understandable that underdialysis can affect the appetite and thus cause poor nutrient intake.

Several studies in dialysis patients report a significant correlation between dose of dialysis for small-molecule removal (Kt/V_{urea}) and the protein intake, especially in the lowest dose intervals [21, 22]. Nearly two decades ago, the National Cooperative Dialysis Study (NCDS) showed a correlation between protein intake and length of dialysis. The two groups on dialysis of shorter duration had lower mean protein intakes at the end of six months than did the two groups whose dialysis time was longer [23]. These results suggest that appetite suppression in uremia depends to some extent on the accumulation of uremic toxin (possibly a middle molecule). Studies both in maintenance hemodialysis patients and chronic peritoneal dialysis patients indicate that as the dialysis dose (indicated by Kt/V) increases, dietary protein intake increases [22]. Other data, however, show no relation between these variables in patients who are "adequately" dialyzed [24], defined as having a Kt/V of ≥ 0.9. Bergström and Lindholm illustrated the correlation between Kt/V_{urea} and the estimated protein intake in a group of 151 hemodialysis patients in whom the Kt/V was below 1.0 [1]. This group, reinvestigated two years later when the Kt/V was desirable, no longer showed this correlation. It appears that in well-dialyzed patients, the level of protein intake is independent of the dialysis dose [6]. If the patient has a very low Kt/V—to a point of producing uremic symptoms—increasing the dialysis dose should improve appetite and food intake. The question remains whether an increase in Kt/V above the previously acceptable levels will further increase protein and energy intake. No study has examined whether such an increase in the dialysis dose will enhance dietary energy intake. The relationship between Kt/V_{urea} and protein intake might simply reflect a mathematical coupling because both variables share several components: both are normalized to body size and both depend on urea in plasma before and after dialysis. However, some data show a relationship between the quantity of urea removed and protein intake that is calculated from the dietary records and interviews. In CAPD patients, this relationship could be demonstrated even when the quantity of urea or creatinine removed was not normalized to body size [21].

Hakim et al reported a prospective study in which the dialysis dose was increased progressively in 130 hemodialysis patients. During a four-year period, the dialysis dose (measured by delivered Kt/V) was gradually increased to 1.33. They found a strong positive correlation between the dialysis dose and protein intake. Moreover, nutritional indicators (serum albumin, transferrin, PCR) differed significantly between the groups with an average Kt/V below 0.86 and above 1.21 [25], higher values being found in the group with the latter Kt/V. However, Lowrie reported no significant correlation between the dose of hemodialysis, estimated as the urea reduction rate, and the serum albumin concentration [26]. In another study, hypoalbuminemic patients on hemodialysis were monitored longitudinally while receiving a Kt/V of 1.3. In these patients, the serum albumin increased significantly [27]. Although Owen et al failed to show a correlation between serum albumin levels and increasing dialysis dose in hemodialysis patients, the mortality rate improved with an increasing urea reduction rate [28]. Thus, it remains controversial whether the dialysis dose has an impact on nutrition and whether the correction of underdialysis improves the patient's nutritional status.

My own practice is to guarantee "adequate dialysis" through a Kt/V_{urea} of 1.3 or eKt/V_{urea} of 1.2. In patients with low nutritional indices and "adequate dialysis" for at least six months, lack of improvement suggests alternate factors in the genesis of these low nutritional indices. I don't believe that going beyond what now is considered "adequate dialysis" will improve these indices.

How does residual renal function affect nutrition?

Using multiple regression analysis, Bergström et al showed that the renal component of the total clearance of urea or creatinine correlated significantly with dietary protein intake in CAPD patients, whereas the dialytic clearance showed no such relationship. This finding suggests that in CAPD patients, residual renal function has a greater influence than does the dose of peritoneal dialysis on the appetite for protein [21]. Some longitudinal studies show that total-body nitrogen decreases during the first two years of CAPD treatment concomitantly with a decrease in protein and energy intake, and that protein intake decreases along with the loss of residual renal function [29]. An international cross-sectional multicenter study revealed that lack of residual renal function is associated with anorexia and symptoms of malnutrition [9]. These findings support the hypothesis that some compounds normally excreted in the urine (even in patients with severe renal failure) are retained in the plasma of CAPD patients and cause anorexia.

As I mentioned earlier, the improvement in appetite that occurs after initiation of dialysis substantiates the possibility that one or more uremic toxins cause anorexia. The report that protein intake increases proportionally more with a given increase in Kt/V_{urea} with a high-flux membrane than a low-flux membrane suggests that a middle-molecule compound causes anorexia [22]. Bergström's group has isolated and characterized factors in uremic plasma that suppress appetite. Injecting ultrafiltrate from uremic plasma of patients with end-stage renal failure into the peritoneum of rats inhibited the ingestion of both carbohydrate (sucrose) and protein; injection of normal plasma had no effect [30]. The authors isolated a fraction in the molecular weight range of 1 to 5 kD that suppressed appetite in rats in a dose-dependent way.

The obesity (*ob* or *lep*) gene has been cloned [31] and its protein product leptin (Greek *leptos*, thin) has been identified. The *lep* gene is expressed exclusively in fat cells that synthesize and secrete leptin into the circulation. Administration of recombinant leptin elicits impressive biologic effects in mice: inhibition of food intake, stimulation of energy expenditure, reversal of obesity, amelioration of insulin resistance, and acceleration of sexual maturation [32]. Leptin's site of action is thought to be the hypothalamic appetite center, although leptin receptors have been reported in pancreas, liver, and kidney [32]. In the hypothalamus, leptin appears to reduce the synthesis and release of neuropeptide Y, one of the most potent appetite stimulants yet demonstrated [33]. Thus, leptin is presumed to be a powerful regulator of the brain's satiety center [33].

Clinical studies have shown that obese patients have high circulating levels of leptin, suggesting resistance to the action of leptin [32]. This is a similar situation to the *db*/*db* mouse, which has a mutation in the leptin receptor gene and manifests hyperleptinemia due to leptin resistance [34]. Many patients with end-stage renal disease (ESRD) are hyperleptinemic due to impaired renal clearance and/or increased synthesis. Because of the high prevalence of malnutrition and reduced food intake in ESRD patients, understanding the regulation of leptin in uremia would be valuable. Previous studies have shown that insulin stimulates expression of the *ob* gene and increases plasma leptin levels; thus, hyperinsulinemia due to insulin resistance in uremia is expected to result in hyperleptinemia [35].

In normal individuals, the estimated net renal extraction of circulating leptin is approximately 12%; it is virtually 0% in patients with renal failure [36]. Leptin levels in CAPD patients appear to be higher than in hemodialysis patients because of less-efficient clearance or greater synthesis [37]. The pathophysiologic significance of increased circulating levels of leptin in ESRD patients is not clear. If leptin receptors are not down-regulated, chronic serum leptin elevation could affect appetite and nutritional status. Nishizawa et al measured plasma leptin levels in 103 patients on hemodialysis and found levels significantly higher than those in controls: 13.9 ± 2.1 ng/mL versus 7.6 ± 0.5 ng/mL ($P < 0.0001$) [38]. Women had higher levels in both groups, and leptin levels correlated with percentage of body fat, being higher in patients with 30% or more of body fat. Leptin levels did not correlate with lean body mass (Fig. 1). If impaired leptin clearance alone could explain the hyperleptinemia, it would not explain the observation that leptin is elevated only in obese patients on hemodialysis. Heimbürger and colleagues also demonstrated a good correlation between serum leptin levels and body fat and suggested that leptin could be a marker of body fat content in patients with chronic renal failure [39]. At present the significance of uremic hyperleptinemia is unknown. If future studies reveal the need to reduce leptin levels (or reduce the resistance to leptin) in ESRD patients, then control of body weight, use of high-flux dialyzers, and renal transplantation might be indicated [32].

Yet another group of compounds has been suggested as contributing to anorexia in dialysis patients. Several cytokines have been reported to suppress appetite and thus might contribute to malnutrition [40]. However, Kaizue et al did not find a difference in PCR, an indicator of dietary protein intake under stable conditions, be-

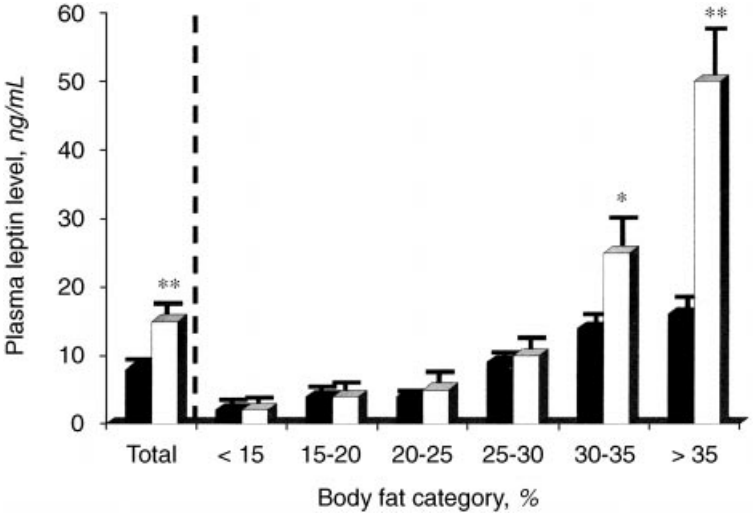

Fig. 1. Comparison of plasma leptin levels between hemodialysis patients (□) and control subjects (■) in the same range of percentage body fat. *P = 0.016 and **P = 0.005 by Student's t-test. (Used with permission from *Am J Kidney Dis* [38].)

tween patients with a high serum IL-6 level and those with a low level [41].

Protein catabolism

Because dialysis patients have increased protein requirements and reduced utilization of ingested protein compared to normal subjects, metabolic factors might stimulate net protein catabolism and impair utilization of ingested protein [42]. The literature contains ample evidence of marked protein catabolism in uremic rat models [43]. Dialysis, with its obligatory protein and amino acid losses, is inherently a catabolic stress [44]. Furthermore, during hemodialysis, protein degradation can be increased by bioincompatible membranes (Table 3). Using ^{13}C-leucine kinetics, Berkelhammer et al studied a group of well-nourished adult hemodialysis patients whose diet contained 1.0 g/kg/day of protein and 30 to 40 kcal/kg/day. Fasting rates of whole-body protein synthesis and breakdown were normal, whereas rates of amino acid oxidation (that is, net proteolysis) were increased [45]. However, the metabolic acidosis (serum bicarbonate, 18 ± 1 mEq/L) in this study might have been responsible for the increased oxidation rate. In kinetic leucine studies performed three months after initiation of CAPD, protein turnover and the rate of protein oxidation were lower than in controls [46]. The low protein intake in these patients might explain the low amino acid oxidation rates. Lim et al measured fasting whole-body protein turnover in seven patients before, during, and after high-efficiency hemodialysis using Cuprophan dialyzers [44]. Whole-body protein synthesis and leucine oxidation both were decreased during hemodialysis; in contrast, protein degradation was unchanged. Net leucine balance (the difference between synthesis and degradation) became more negative during dialysis; this change was attributed to impairment in protein synthesis and dialysate losses of amino acids. The increased protein catabolism observed during dialysis was attributed to a suppression of whole-body protein synthesis and dialysate losses of amino acids [44].

Table 3. Protein catabolic factors in dialysis patients[a]

General factors
Physical inactivity
Heart failure
Low energy intake
Endocrine abnormalities
Corticosteroid therapy
Inflammation, infection, sepsis
Acidosis
Amino acid abnormalities
Factors related to hemodialysis
Loss of amino acids, 9–13 g/session
Loss of glucose, 25 g/session (glucose-free dialysate)
Loss of protein (minor)
Inflammatory stimuli: blood-dialyzer contact
Complement activation
Endotoxins
Cytokines
Acetate
Factors related to CAPD
Loss of amino acids, 2–4 g/day
Loss of protein, 5–15 g/day
Inflammatory stimuli: ? particles, chemicals
Peritonitis
Cytokine release

[a] Based on work by Bergström J [6]

In healthy subjects, nitrogen balance depends greatly on energy intake. High energy intake has a protein-sparing effect; low energy intake results in negative nitrogen balance [42]. Bergström et al performed nitrogen balance studies in CAPD patients and verified that within two to six months after the start of CAPD, dietary protein intake and total energy intake significantly correlated with the nitrogen balance [21]. However, in later studies (9 to 16 months on CAPD), protein intake had

no influence on nitrogen utilization, and energy intake seemed to have an even stronger influence [21]. The findings indicate that energy deficiency is detrimental to the utilization of dietary protein in CAPD patients [21].

Metabolic acidosis also has been identified as an important stimulus of protein catabolism. Acidosis is the only metabolic factor ("uremic toxin") identified to date that induces catabolism and impairs nitrogen utilization in uremia [42]. Acidosis also induces insulin resistance, demineralizes bones, decreases the sensitivity of PTH to serum calcium concentration, and impairs growth in children [47].

Animal studies have demonstrated that chronic metabolic acidosis, rather than uremia per se, accelerates proteolysis [48]. This effect seems to be mediated by the stimulation of branched-chain keto-acid decarboxylation in skeletal muscle, which increases the catabolism of the branched-chain amino acids (valine, leucine, isoleucine) [48]. Evidence indicates that acidosis stimulates proteolysis in muscle by inducing the transcription of genes encoding for enzymes participating in the ATP-dependent cytosolic ubiquitin-proteasome proteolytic pathway and that cortisol is required for the activation to occur [48].

Human studies have demonstrated amino acid abnormalities that correlate with the degree of metabolic acidosis in hemodialysis patients [4] and also have shown that metabolic acidosis impairs nitrogen utilization and accelerates the loss of lean body mass in patients with chronic uremia [49]. Ammonium chloride-induced metabolic acidosis in healthy humans decreases albumin synthesis and induces negative nitrogen balance [50]. In non-dialyzed patients with chronic uremia, correction of metabolic acidosis improves nitrogen balance and reduces urea appearance, muscle proteolysis [49], and leucine oxidation [51]. Similarly, correction of metabolic acidosis in patients on peritoneal dialysis decreases whole-body protein degradation [52]. Lim et al recently measured in vivo whole-body protein turnover in nine patients with chronic renal failure before initiation of dialysis and 8 to 10 weeks later [53]. Leucine flux was measured when the patients were acidotic as well as after correction with sodium bicarbonate. The authors found that uremia per se was not a catabolic state, and protein turnover was in fact down-regulated. The data indicated that when acidosis was corrected, patients with chronic renal failure adapted to lower protein intake by reducing amino acid oxidation and protein degradation, and maintained protein synthesis at normal levels. Maintenance dialysis treatment over time restored protein flux to normal and increased protein synthesis [53].

Not all human data, however, are consistent with hypercatabolism. Goodship and colleagues did not find increased protein degradation or increased leucine oxidation in six mildly acidotic predialysis patients [54]. When Graham and coworkers corrected the acidosis of six mildly acidotic patients on hemodialysis, protein degradation and synthesis decreased but oxidation did not. The reduction in plasma urea that occurred after correction of the acidosis reflected the decrease in protein degradation. The authors noted no change in body composition but the study period was only 10 weeks [55].

The clinical significance of metabolic acidosis as a factor for the development of malnutrition has not been determined. Lowrie and Lew analyzed laboratory data and mortality rates in more than 12,000 hemodialysis patients. The death risk was significantly increased in patients with metabolic acidosis, but only in those in whom the serum total CO_2 levels were lower than 12.5 mmol/L [56]. No association was noted between total CO_2 levels and nutritional factors, as assessed by serum albumin and cholesterol levels. Bergström also found no correlation between standard bicarbonate and serum albumin levels in 133 hemodialysis patients [42]. It is conceivable that a high protein intake stimulates protein synthesis to the extent that the negative effect of the increased activation of proteolysis characteristic of metabolic acidosis is overcome [42]. Brady and Hasbargen studied 36 hemodialysis patients whose mean serum bicarbonate concentration was less than 18 mEq/L before dialysis [57]. They kept one-half of the patients on a conventional bicarbonate bath of 35 mEq/L but increased the bicarbonate bath concentration to 40 mEq/L in the other half. After four months, no difference in serum albumin and total lymphocyte count was apparent between the groups [57]. The protein catabolic rate (PCR) was unchanged in both groups during the study. However, the serum albumin in the control group was 3.88 ± 0.28 g/dL and 3.76 ± 0.26 g/dL in the experimental group, and this finding might explain a lack of improvement (low-normal serum albumin at start in both groups and not much difference between groups). Movilli et al administered oral sodium bicarbonate (mean dose, 2.7 ± 0.94 g/day; range, 1 to 4 g/day) to 12 hemodialysis patients for three months, raising the serum bicarbonate from 19.3 ± 0.6 mmol/L to 24.4 ± 1.2 mmol/L ($P < 0.0001$) [58]. Serum albumin increased from 3.49 ± 0.21 g/dL to 3.79 ± 0.29 g/dL ($P < 0.01$) during the study period. Of note is the fact that the normalized PCR (nPCR) decreased during the period; the authors attributed the fall to a decrease in catabolism of endogenous proteins [58]. Recent work also describes increases in triceps skinfold thickness and body weight after correction of metabolic acidosis in hemodialysis [59] and CAPD [60] patients. These findings suggest an associated improvement in nutritional status.

In conclusion, we have significant evidence both from animal and human studies that metabolic acidosis induces protein catabolism. However, the evidence that correction of acidosis in dialysis patients improves nutritional status comes from short-term studies that might have long-term implications: improvements in metabolic

bone disease, proper growth, and the sense of well-being felt by the dialysis patient. Bailey and Mitch have recommended that we maintain the predialysis serum bicarbonate as close to 24 mmol/L as possible through adjustments of the dialysis bath or the utilization of sodium bicarbonate supplements [47].

Dialysis alters glucose metabolism and thus affects nutrition. During a single dialysis session using conventional glucose-free dialysate, glucose losses have been estimated at 25 to 30 g [61]. To maintain glucose homeostasis, these losses, together with those arising from normal body utilization, are replaced by mobilization of liver glycogen stores and gluconeogenesis. In addition to the protein catabolism due to gluconeogenesis, further protein breakdown replaces amino acid losses. Dialysis therapy therefore would be expected to promote protein catabolism, as discussed earlier. This hypothesis is supported by the observation of an increase in urea generation and a negative total nitrogen balance on the day of dialysis when a glucose-free dialysate is used [61]. Gutierrez et al verified that after an overnight fast, the efflux of amino acids in the dialysate did not differ during hemodialysis, with or without glucose in the dialysis fluid [62], and thus the addition of glucose had no protein-sparing effect.

Amino acid losses also occur during dialysis. The total loss of amino acids is about 10 to 13 g per dialysis (5 to 8 g of free amino acids and 4 to 5 g of peptide-bound amino acids). Ikizler et al examined amino acid and protein losses in patients undergoing hemodialysis with three types of dialyzer membranes [63]. The patients on high-flux polysulfone membranes lost 8.0 ± 2.8 g (mean ± SD) of amino acid per dialysis session, as compared to patients dialyzed with low-flux polymethylmethacrylate membranes, who lost 6.1 ± 1.5 g of amino acids ($P < 0.05$), and those dialyzed with cellulose acetate membranes, who lost 7.1 g ± 2.6 g (NS). Protein losses during hemodialysis typically are very small, but they can be higher with high-flux (polysulfone) dialyzers and particularly after reuse with bleach and formaldehyde. Ikizler et al found that albumin losses became apparent after the sixth reuse of the high-flux polysulfone membrane, reached 1.5 ± 1.3 g per session by the 15th reuse, and peaked at 9.3 ± 5.5 g at the 20th reuse [63]. Kaplan and coworkers observed similar results [64]. The amino acid losses increased by 50% after the 6th reuse in the high-flux polysulfone membranes. The loss of free amino acids into the dialysate during CAPD is of the same magnitude (per week) or smaller than in hemodialysis [13]. However, protein losses are higher in CAPD when compared to hemodialysis and average 5 to 15 g per day. Variability is wide among patients, and dialysate protein loss can vary between 20 to 140 g per week. Peritonitis can increase losses by 50% to 100%.

Biocompatibility of the dialysis membrane is yet another factor contributing to the patient's nutritional status. The best evidence that blood-membrane contact induces protein catabolism and that biocompatibility of the membrane plays a role in nutrition comes from a series of experiments with sham dialysis in normal individuals [65, 66]. Blood-membrane contact within a dialyzer with Cuprophan membrane elicited an increased release of amino acids from the leg tissue that corresponded to an increased protein breakdown of 15 to 20 g. Dialysis with a more biocompatible membrane, AN 69S or polysulfone, produced no increase in amino acid release. Also, Cuprophan, but not the more biocompatible membranes, was associated with an increased release of methylhistidine from the leg muscles and an elevation of the plasma methylhistidine concentration. This efflux of methylhistidine from the leg implies that increased protein breakdown plays an important part in the net catabolic process induced by blood-membrane contact. Thus, the hemodialysis procedure likely elicits an inflammatory reaction depending on the membrane material used; this response is more marked with cellulosic than with synthetic membranes [42]. It appears that complement is activated with the release of anaphylatoxins (C3a, C5a); and monocyte activation releases cytokines (IL-1, TNF, and other cytokines) as a result of direct membrane contact, activated C5a, endotoxin fragments passing through the membrane, and dialysate acetate [42]. Despite these reports, Lim et al did not confirm increased catabolism after dialysis with an unsubstituted cellulose membrane [44]. Their study disclosed evidence of decreased anabolism during and after dialysis, which was attributed to amino acid removal during dialysis. Lindsay and Spanner showed in 1989 that the relationship between protein catabolic rate and Kt/V_{urea} can be separated according to patients dialyzed by devices containing cellulose acetate membranes and patients dialyzed by devices containing the synthetic AN 69S membrane [22]. The slope of the relationship for the former is significantly less than the slope for the latter. In a prospective study, they also showed that after six months, there was an increase in the slope when the patient's dialysis was changed from a cellulosic to an AN 69S membrane. These data indicate that patients using a more biocompatible membrane (AN 69S) achieve the same protein catabolic rate for less Kt/V_{urea} than do patients using cellulosic membranes [22].

Uremic inflammatory response

What about malnutrition as an expression of uremic inflammatory response? Kaysen et al measured albumin synthesis, fractional catabolic rate, and the distribution of albumin between the vascular and extravascular compartments from the turnover of [^{125}I] human albumin in six hemodialysis patients whose plasma albumin level was less than 3.5 g/dL and in six patients with a plasma albumin level greater than 4.0 g/dL [67]. Both groups

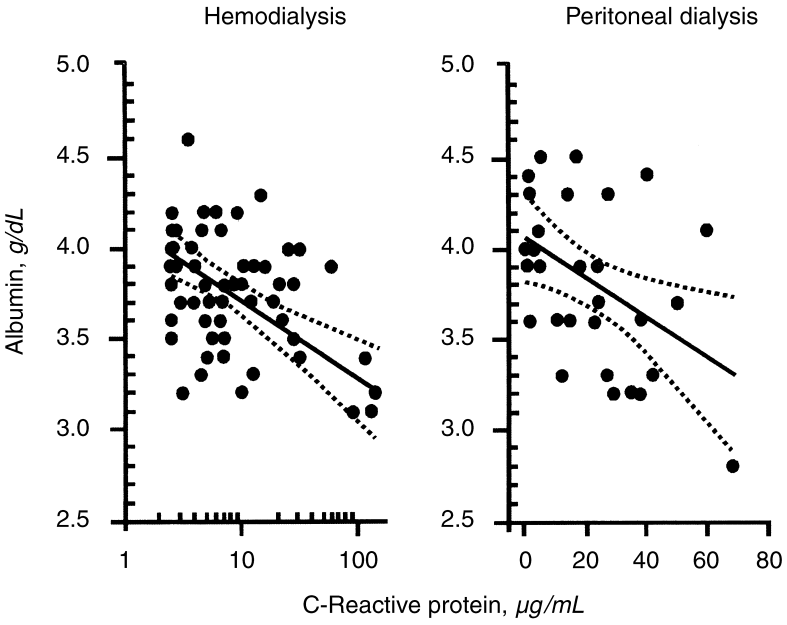

Fig. 2. Relationship between three-month average serum albumin concentration and C-reactive protein (CRP) concentration in hemodialysis patients (left panel; $r = 0.490$; $P < 0.001$) and between three-month average albumin concentration and CRP in peritoneal dialysis patients (right panel, $r = 0.436$; $P < 0.0016$). (Reproduced with permission from KAYSEN G: Biological basis of hypoalbuminemia in ESRD. *J Am Soc Nephrol* 9:2368–2376, 1998.)

were maintained with high-flux polysulfone dialyzers for longer than three months. The authors verified that albumin synthesis was significantly reduced in the low-albumin group. Plasma albumin concentration also correlated negatively with ferritin, C-reactive protein, and α_2-macroglobulin. Plasma albumin concentration and albumin synthesis rate were independent of PCR and other related nutritional variables. Thus, hypoalbuminemia was due to decreased albumin synthesis. To verify whether hypoalbuminemia is a result of the acute-phase response, Kaysen et al also measured serum albumin, C-reactive protein, serum amyloid A, Kt/V, and nPCR in 115 hemodialysis patients and found that most had normal C-reactive protein and serum amyloid A levels and that a significant minority had high levels [68]. A significant negative correlation existed between serum albumin and both C-reactive protein and serum amyloid A ($P < 0.001$); this correlation supports the hypothesis that a generalized acute-phase response lowers serum albumin (Fig. 2). Because none of the parameters correlated with Kt/V, it is likely that underdialysis was not a factor in the hypoalbuminemia. The specific cause of inflammation was not clear to the investigators, who noted the highest C-reactive protein levels in patients with transcutaneous catheters and arteriovenous grafts.

Acute phase reactants (APRs) are proteins secreted by the liver in the presence of stimuli such as infection and trauma. These proteins are classified as positive or negative when synthesis is increased or decreased in inflammatory states [69]. The positive APRs are: C-reactive protein, serum amyloid A, α_2-macroglobulin, α_1-acid glycoprotein, haptoglobin, ceruloplasmin, ferritin, and α_1-antitrypsin. Negative APRs are albumin, transferrin, and apoA_1. The positive APRs (C-reactive protein and serum amyloid A being the most important) have a variety of actions that modulate the inflammatory response. The significance of the downregulation of negative APRs is not clear, but the liver might simply be shifting its synthetic capacity away from negative APRs to concentrate on producing the positive APRs required for modulation of inflammation [69]. C-reactive protein has long been used as a marker of inflammation. It is valuable in monitoring inflammation in rheumatologic diseases as well as in a wide variety of inflammatory disorders such as pancreatitis, myocardial infarction, pneumonia, osteomyelitis, and postoperative sepsis [69]. In more than 1000 randomly selected dialysis patients, Lowrie found an elevated serum concentration of C-reactive protein in approximately 35% of the patients [70]. Although he was able to correlate hypoalbuminemia with a high mortality rate, Kaysen noted no such correlation with C-reactive protein [71]. On the other hand, it was found that elevated C-reactive protein predicts early death in hemodialysis patients better than does serum albumin (abstract; Bergström et al, *J Am Soc Nephrol* 6:573, 1995).

Hypoalbuminemia is a powerful predictor of death in dialysis patients, but the reason is unknown [13]. Analbuminemic rats have a normal life span, so hypoalbuminemia per se likely is not the cause [71]. Because protein-calorie malnutrition can decrease albumin synthesis, it is assumed that hypoalbuminemia results mainly from malnourishment in these patients, but albumin synthesis also can be decreased as part of the acute-phase response [67]. Synthesis of APRs is impeded by protein malnutrition even following an appropriate inflammatory stimulus. Cytokine release, however, is unimpeded in protein-calorie

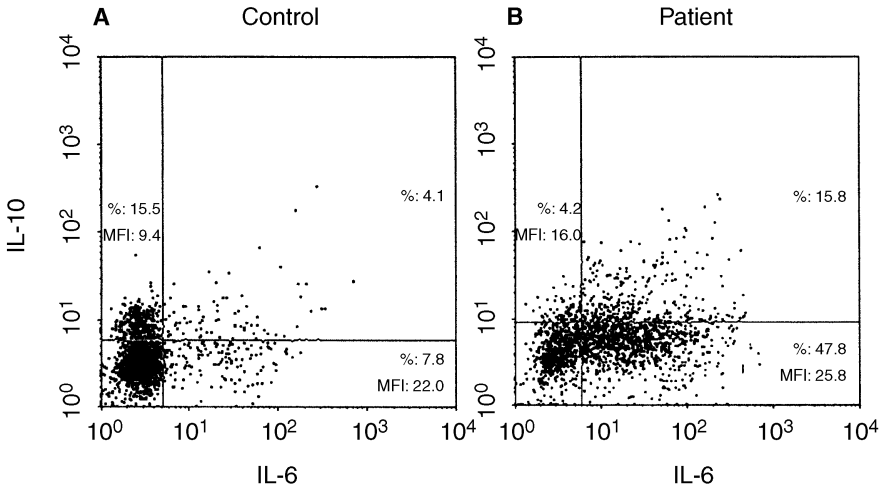

Fig. 3. Two-color flow cytometry detection of the production of interleukin-6 (IL-6) (x axis) and IL-10 (y axis) in monocytes of a healthy control subject and a hemodialysis patient after stimulation of cells in vitro with lipopolysaccharide (LPS). Percentages give the portion of cells above the cutoff for the respective cytokine or the portion of double-positive cells. The logarithmic axes of the panels give the fluorescence intensity (FI) values assigned to every single cell detected. The MFI is the mean fluorescence intensity of all cells above the cutoff. The MFI value is a relative indicator of cytokine production per cell. (Used with permission from *J Am Soc Nephrol* [72].)

malnourished states; this suggests that measurements of cytokine levels will provide greater insight into the existing inflammatory process [71].

Numerous studies have used circulating cytokine levels in patients with ESRD to evaluate the inflammatory response. However, the physiologic significance of circulating levels remains unclear. These proteins are commonly released locally by leukocytes at the site of inflammation and might act primarily by local effects, either autocrine (acting on the same cell) or paracrine (acting on a nearby cell). These local cytokine effects would not be detected by changes in circulating levels. When cytokines react with their cognate receptors, the receptors are shed into the serum and are more long lived, perhaps providing a more accurate measurement of cytokine activity [71]. Measurement of cytokine synthesis by peripheral blood mononuclear cells (PBMCs) probably offers a more consistent method of assessing cytokine production in dialysis patients. However, dialysis patients have profound alterations in the relative numbers of lymphocytes and monocytes in peripheral blood and with the current standard technique of measurement of cytokines in culture supernatant of mononuclear cells (by ELISA), the amount of cytokines is not given in relation to the absolute number of monocytes [72]. It appears that not even the use of PCR for detection of cytokines has enhanced sensitivity. Girndt et al determined cytokine production at a single-cell level by flow cytometry [72]. Since conventional techniques cannot differentiate the influence of the relative number of monocytes and lymphocytes in the production of inflammatory cytokines, the cytoflow technique gains precision because it measures only the products of monocytes (Fig. 3). Compared to ELISA, this method appears to have a higher discrimination power (Fig. 4). There are controversial findings in the literature regarding proinflammatory cytokines in hemodialysis patients. Several authors observed a significant increase in IL-1, IL-6, IL-8, TNF-α, and MCP-1 plasma levels [73, 74]; others found no difference or, surprisingly, a reduction [75].

Several studies have addressed the issue of nutritional parameters and cytokine production. Kaizu et al recently reported a correlation between pre-dialysis serum IL-6 levels and nutritional indices [41]. The authors showed that patients with high IL-6 levels had lost body weight by more than 4% over three years; serum albumin and serum creatinine also were lower in the patients with high IL-6 levels. Evidence also indicates that IL-6 promotes cancer cachexia [76]. Kehayias and colleagues also correlated the production of IL-1 receptor antagonist (IL-1Ra) by PBMCs and nutritional status in 16 hemodialysis patients over a three-month period. They found a direct correlation of cell content of IL-1Ra with several indices of nutritional status (body mass index, arm muscle area, serum cholesterol, and triglycerides) [77].

Relationship between malnutrition, inflammation, and cardiovascular mortality

Discussion has increased regarding the role of dialysis as a "chronic inflammatory process" contributing to the rapid progression of atherosclerosis in patients with ESRD. This hypothesis has been further stimulated by a report on the relation between inflammatory markers and cardiovascular risk [78]. According to the latest USRDS Registry report, cardiac causes (cardiac arrest, acute myocardial infarction, and other cardiac causes) account for almost 50% of the reported causes of dialysis patient deaths in all age groups (20 to 44, 45 to 64, and $\geq$65 years). Infection accounts for almost 25% of all deaths in the 20- to 44-year age group, but only 17% and 14% of deaths in the 45- to 64-year and $\geq$65-year age group, respectively [79]. Despite the high prevalence of malnutrition in chronic dialysis patients, malnutrition is generally not reported to be a prominent cause of

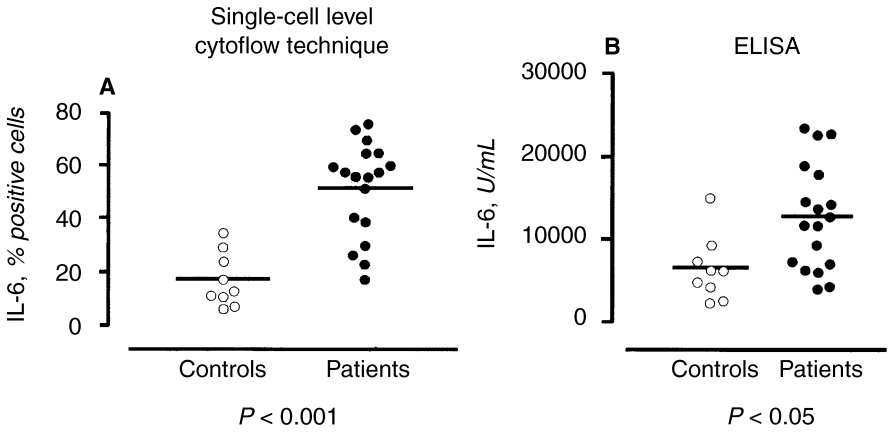

Fig. 4. (*A*) Cytoflow technique. Detection of IL-6 at the single-cell level after stimulation of cells by LPS for 20 hours in vitro. Percentage of cells positive for IL-6. Control vs. patients, $P < 0.001$. (*B*) ELISA of IL-6 secretion in supernatant of peripheral blood leukocytes (PBL) stimulated with LPS. Control vs. patients, $P < 0.05$. (Used with permission from [72].)

death, and it is not even listed on the categories for causes of death on the ESRD Death Notification Form (HCFA-2746) [79]. One can assume therefore that underreporting of death from cachexia is common in the registries and that patients who die from this condition are listed under other categories [80].

Nevertheless, one needs to explain why hypoalbuminemia and other nutritional indicators are strong risk factors for early death, considering that most dialysis patients die of atherosclerotic cardiovascular diseases. The link with infection is easy to understand, because malnourished, hypoalbuminemic ESRD patients have a high incidence of infection due to defects in cellular immunity, neutrophil function, and complement activation [79]. Additionally, dialysis patients have an elevated risk of infection associated with the vascular or peritoneal access. There is mounting evidence in the recent literature of an association between inflammatory mediators and atherosclerosis and death from myocardial infarction and cerebrovascular disease [78]. Accordingly, one might ascribe the excess cardiovascular mortality seen in dialysis patients with signs of malnutrition to these inflammatory cytokines, which also stimulate protein catabolism and reduce albumin synthesis. Foley et al prospectively studied, for an average of 41 months, 432 patients with ESRD (261 on hemodialysis and 171 on peritoneal dialysis). The authors found that among hemodialysis patients, a 1.0 g/dL fall in mean serum albumin was independently associated with the development of de novo and recurrent cardiac failure, de novo and recurrent ischemic heart disease, cardiac mortality, and overall mortality (Table 4) [81]. Their analyses strongly suggest that low serum albumin levels came before these adverse events and not after. The strong association between hypoalbuminemia and ischemic heart disease led the authors to speculate that low albumin results in a hypercoagulable state and is associated with other nutritional deficiencies, such as dietary deficiencies of folic acid, B_6, and B_{12}, and increased plasma levels of homocysteine that lead to ischemic heart disease. Also, evidence suggests increased cytokine generation in heart failure that is believed to result from tissue hypoxia or reduced tissue perfusion and liver congestion. Generated inflammatory cytokines could trigger the acute-phase response in the liver and result in decreased albumin synthesis and thus hypoalbuminemia [80].

Table 4. Association between mean serum albumin and clinical outcomes (expressed as the effect of a 1.0 g/dL fall) analyzed separately in hemodialysis ($N = 261$) and peritoneal dialysis ($N = 171$) patients[a]

	Hemodialysis		Peritoneal dialysis	
Outcome	Relative risk	*P*	Relative risk	*P*
Ischemic heart disease				
De novo	5.29	0.001	NA[b]	NA
Recurrent	4.24	0.005	NA	NA
Cardiac failure				
De novo	2.22	0.001	4.16	0.003
Recurrent	3.84	0.003	NA	NA
Mortality				
All cause	4.33	<0.001	2.06	<0.001
Cardiac	5.60	0.001	NA	NA
Non-cardiac	3.58	<0.001	3.52	<0.001

[a]From [81].
[b]NA, not associated

As I mentioned, recent evidence suggests that atherosclerosis is an inflammatory disease and that the first step in atherosclerosis is endothelial dysfunction [82]. Possible causes of endothelial dysfunction leading to atherosclerosis include elevated and modified LDL; free radicals caused by cigarette smoking, hypertension, and diabetes mellitus; genetic alterations; elevated plasma homocysteine concentrations; infectious micro-organisms such as Herpesvirus or *Chlamydia pneumoniae*; and combinations of these or other factors [82].

Hypertriglyceridemia, not an independent risk factor for atherogenesis, occurs in 33% to 70% of patients with chronic renal failure; hypercholesterolemia is found in

as many as 20% of patients. Levels of HDL cholesterol are decreased in 50% to 75%, and LDL tends to be in the normal range [83]. Lipoprotein a [Lp(a)] levels also are elevated [83]. Whether Lp(a) is an independent risk factor for cardiovascular death in hemodialysis patients is currently controversial [84]. In addition to abnormalities in serum total lipoprotein concentrations, uremic patients exhibit potentially atherogenic abnormalities in lipoprotein composition, most notably an elevated concentration of apo C-III [83].

The apolipoprotein (a) gene promoter region contains several hepatocyte-specific, IL-6-responsive elements [85], and this occurrence might explain why Lp(a) levels transiently increase during acute inflammatory states as part of the acute-phase response [86]. High plasma levels of Lp(a) in hemodialysis patients are closely related to the acute-phase reaction, as reflected by elevated levels of C-reactive protein, sialic acid, IL-6, serum amyloid A, and fibrinogen [87]. Stenvinkel et al reported that 47% of the malnourished uremic patients they studied had a higher prevalence of cardiovascular disease and higher C-reactive protein and Lp(a) levels than did those with normal nutritional status [88].

Homocysteine is a sulfur-containing amino acid formed during the metabolism of methionine. The rare syndrome of homocystinuria, an autosomal-recessive condition due to deficiency of cystathionine β-synthase, is associated with premature atherosclerotic and thromboembolic disease and with excessive quantities of circulating homocysteine in plasma [89]. Homocysteine is toxic to the endothelium and is prothrombotic, and it increases collagen production and decreases the availability of nitric oxide [82]. Plasma homocysteine concentrations are slightly elevated in many patients who have no enzymatic defects in homocysteine metabolism. These patients have an increased risk of symptomatic atherosclerosis of the coronary, peripheral, and cerebral arteries [82]. High plasma homocysteine concentrations are seen in chronic renal failure; deficiencies of folate, vitamin B_6, or vitamin B_{12}; and other conditions such as malignancies, psoriasis, and hypothyroidism [89]. High plasma concentrations of homocysteine-cysteine mixed disulfide in patients with chronic renal failure and in renal transplant patients were shown by Wilcken and Wilcken, who first recognized altered methionine metabolism as a risk factor for premature coronary disease [90]. Later, other studies confirmed the presence of hyperhomocysteinemia in renal failure as well as in hemodialysis and CAPD patients [89]. The causes of hyperhomocysteinemia in renal failure are unclear, but reduced excretion is not the principal cause. The major mechanism is thought to be reduced metabolism, although the exact metabolic derangement is unknown [89]. Patients with renal failure are at risk for vitamin deficiencies, particularly folate, B_6, and B_{12}, and lower serum levels of these compounds predict hyperhomocysteinemia [89].

Hypertension has inflammatory actions, increasing the formation of hydrogen peroxide and free radicals such as superoxide anion and hydroxyl radicals in plasma. These substances reduce the formation of nitric oxide by the endothelium, increase leukocyte adhesion, and increase peripheral resistance [82]. Angiotensin II, often elevated in hypertension, is a potent vasoconstrictor and can contribute to atherogenesis by stimulating the growth of smooth muscle [82].

Several reports have correlated the incidence of atherosclerosis with the presence of at least two types of infectious microorganisms: Herpesvirus and *Chlamydia pneumoniae.* Both organisms have been identified in atheromatous lesions, and increased titers of antibodies to these organisms have been detected, but no direct evidence has shown that these organisms can cause atherosclerotic lesions [82].

Several studies have reported the association of acute-phase-reactant proteins (indicators of inflammation) with ischemic heart disease and cerebrovascular disease. Associations were noted between elevated C-reactive protein and the severity of coronary artery atherosclerosis [91]; elevated levels of C-reactive protein and serum amyloid A protein in patients with unstable angina predicting more ischemic episodes and higher mortality rates [92]; inflammation/infection and increased risk of coronary disease [93]; and elevated C-reactive protein levels in the general population and various cardiovascular risk factors (increasing age, smoking, increased levels of serum fibrinogen, total cholesterol, triglycerides, and apolipoprotein B), as well as increased risk of myocardial infarction and stroke [94].

The serum concentration of C-reactive protein reflects the activity of cytokine-mediated acute-phase processes [95] and is roughly proportional to the extent of tissue injury [96]. Owen and Lowrie recently reported on the serum C-reactive protein levels in 845 hemodialysis patients; 35% of the values in this group exceeded the upper limit of the laboratory's reference range. The logistic regression analysis of the data described a strong, independent, inverse relationship between the serum albumin and creatinine concentrations and the odds risk of death, but no such relationship for C-reactive protein [96]. They also found that C-reactive protein had an inverse relationship with laboratory measures of protein stores (serum albumin, creatinine, and pre-albumin) [96]. Bergström's group reported that 53% of 128 hemodialysis patients had elevated serum levels of C-reactive protein and that over three years of follow-up, it was as strong a predictor of mortality as was hypoalbuminemia (abstract; Bergström et al, *J Am Soc Nephrol* 6:573, 1995). The difference in the two studies might be related to the number of patients, the use of a more extensive laboratory

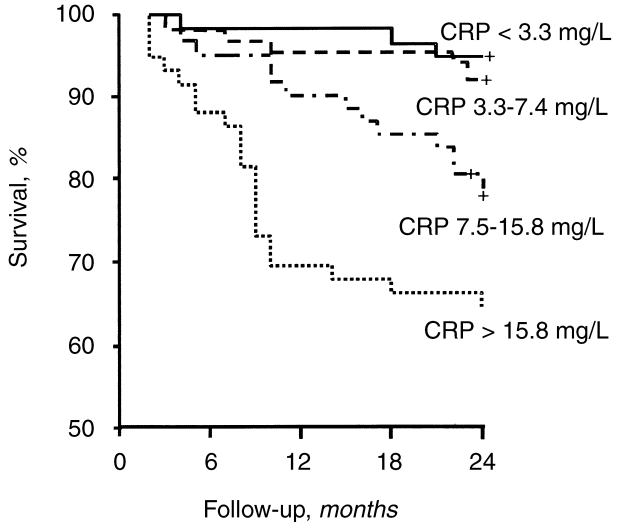

Fig. 5. Kaplan-Meier estimates of survival during follow-up with regard to cardiovascular mortality in relation to quartiles of serum concentration of C-reactive protein (CRP). (Used with permission from the International Society of Nephrology [98].)

profile, and the analysis of outcomes among ambulatory ESRD patients by Owen and Lowrie instead of hospitalized patients. In a cross-sectional study of 106 CAPD patients, those with serum albumin <3.5 g/dL had a serum C-reactive protein significantly greater than those with serum albumin ≥ 3.5 g/dL [97]. Kaysen et al also reported that among hypoalbuminemic patients with ESRD, the degree of hypoalbuminemia correlated with the elevation of serum levels of laboratory surrogates of inflammation, such as C-reactive protein, α_2-macroglobulin, ferritin, and serum amyloid A concentration [67, 68]. Zimmermann and colleagues recently examined 280 ambulatory patients on maintenance hemodialysis and found that C-reactive protein and serum amyloid A were elevated in almost 50% of the patients in the absence of clinically apparent infection, and that those patients had higher serum levels of lipoproteins and fibrinogen and lower levels of serum albumin, HDL cholesterol, and apo A_1. After two years, 26% of the patients had died, mostly because of cardiovascular events. As Figure 5 shows, C-reactive protein was a powerful independent predictor of total mortality and cardiovascular death [98].

Conclusion

The evidence that malnutrition is associated with increased morbidity and mortality rates in dialysis patients is not new. In 1983, Shapiro et al reported that patients on maintenance hemodialysis with low serum urea nitrogen levels, an indicator of low dietary protein intake, had increased morbidity rates [99]. The same year Acchiardo and colleagues reported an inverse correlation between PCR, also an indicator of dietary protein intake, and the frequency of hospitalizations and mortality rate in patients on maintenance hemodialysis [100]. Lowrie and Lew reported the relationship between serum albumin and mortality rate in 12,000 patients on hemodialysis [56]. The adjusted risk ratio for mortality increased progressively as the serum albumin level decreased. For serum albumin levels of 3.5 to 4.0 g/dL, 3.0 to 3.5 g/dL, 2.5 to 3.0 g/dL, and 2.5 g/dL or less, the adjusted risk ratios increased exponentially to approximately 2.2, 6.7, 15.3, and 18.5, respectively [56]. Lowrie and Lew also found that low serum levels of cholesterol, urea, creatinine, potassium, and phosphorus also were associated with an increased risk of mortality. Because these low values often reflect reduced nutrient intake, these data likely provide further evidence that decreased nutritional intake is associated with increased mortality rate. In a subsequent study of 17,185 patients on hemodialysis, Lowrie et al concluded that serum albumin was the strongest single predictor for mortality [101]. The clinical importance of these observations is that approximately 25% of patients on maintenance hemodialysis have low serum albumin levels (<3.7 g/dL) and serum cholesterol levels below 155 mg/dL [56], and that these low values are within the range associated with increased mortality rates in hemodialysis patients. Similar findings relating nutritional status to outcome have been observed in chronic peritoneal dialysis patients [102].

This evidence notwithstanding, the association between nutritional intake or status and clinical outcome does not indicate a causal relationship [103]. It is possible that a co-morbid condition independently impairs both nutritional intake or status and increases morbidity and mortality rates. Yet the finding that a low serum albumin, independent of Kt/V, the urea reduction ratio, or a co-morbid condition is a risk factor for early death suggests that poor nutrition results in increased mortality rates [28]. Moreover, interventions such as intradialytic parenteral nutrition in malnourished patients on maintenance hemodialysis have been shown to reduce mortality rates [104].

In short, poor nutrition in dialysis patients—due to malnourishment or to an inflammatory state—predisposes to increased cardiovascular morbidity and mortality. Recently, it was shown that urea might contribute to the development of atherosclerotic lesions associated with chronic renal failure and elevated blood urea nitrogen levels by reducing inducible nitric oxide synthesis with concomitant macrophage proliferation [105]. This phenomenon could help explain some of the cardiovascular events (Fig. 6). In the future, the establishment of "healthy start clinics" might avoid malnutrition at the start of dialysis, and the identification of patients with high levels of inflammatory mediators might provide an opportunity for a more rational intervention.

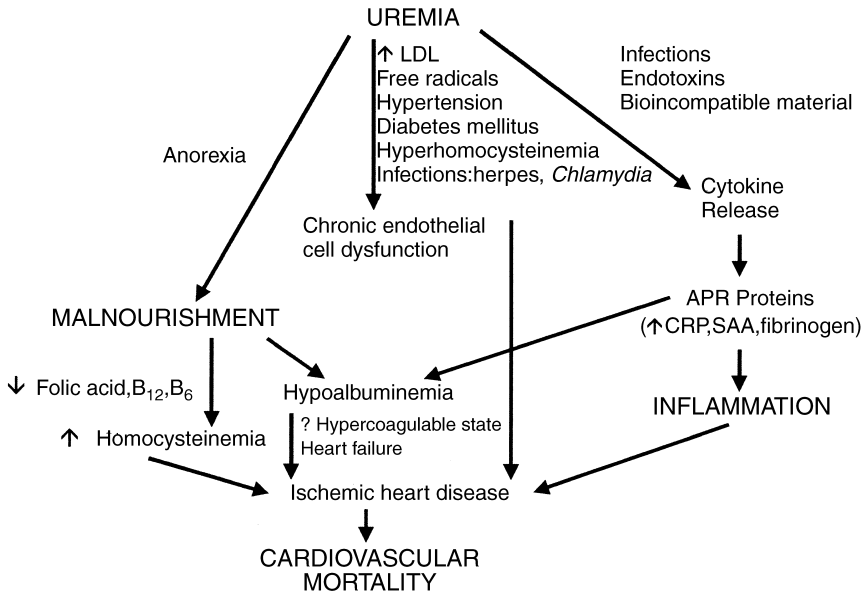

Fig. 6. Schematic outline of how uremia might lead to malnutrition, inflammation, and cardiovascular mortality.

QUESTIONS AND ANSWERS

Dr. Nicolas E. Madias (*Chief, Division of Nephrology, New England Medical Center, Boston, Massachusetts, USA*): Thank you very much, Dr. Riella, for your wonderful presentation. On the strength of your analysis of the available data on the relationship among inflammation, malnutrition, and cardiovascular disease, can you propose anti-inflammatory strategies aimed at improving nutritional and cardiovascular outcomes in ESRD?

Dr. Riella: I don't think we are prepared at this time to propose a single anti-inflammatory strategy. The finding of ongoing inflammation in patients with chronic renal failure prior to the start of dialysis treatment indicates that factors independent of hemodialysis treatment (endotoxins from dialysate, artificial vein grafts, membrane bioincompatibility) might play a role in activation of an acute-phase response in uremia.

Some progress has been made in non-renal disorders. For instance, weight loss in pancreatic cancer is associated with persistent activation of the acute-phase response. Oral administration of fish oil (eicosapentaenoic acid, EPA) to patients with pancreatic cancer cachexia resulted in a significant reduction in the serum concentration of the acute-phase reactant C-reactive protein. Production of interleukin-6 by peripheral blood mononuclear cells from patients receiving EPA was significantly reduced [106]. Giving a fish oil-enriched nutritional supplement to pancreatic cancer patients also has attenuated progression of the acute-phase response [107]. In addition, data from randomized clinical trials suggest that the efficacy of agents such as aspirin [108] and hydroxymethyglutaryl (HMG)CoA reductase inhibitors [109] derives in part from interactions with the inflammatory system. All this evidence raises the possibility that therapies targeting chronic low-grade inflammation might provide novel future strategies for cardiovascular disease prevention.

Dr. Brian Pereira (*Professor of Medicine, New England Medical Center, Tufts University, Boston, Massachusetts, USA*): I would like to make just two quick comments. One is in response to Dr. Madias' question about antiinflammatory strategies. In regard to anticytokine strategies, the problem is that you are attempting to control the response after it has already occurred. If you block IL-1, TNF replaces its action, so you need a number of inhibitors to block inflammatory responses. The ideal is to block the inflammation-inducing stimulus upstream: using ultrapure water for dialysate, more biocompatible membranes, and so on. Anticytokine strategies have been a complete failure in sepsis, and I think that controlling inflammatory responses downstream in our dialysis patients is likely to be a similar failure.

I would like to make just a small clarification. The fact is that plasma cytokine levels can be elevated in patients on hemodialysis or peritoneal dialysis, and in patients with advanced chronic renal failure who are not on dialysis. But the question we have to answer is, does this have biologic significance?

Dr. Riella: Numerous studies have used circulating cytokine levels in ESRD patients to evaluate the role of inflammatory mediators in the complications associated with dialysis. As you said, the physiologic significance of circulating levels remains unclear. Controversial results have been reported. While several authors observed a significant increase in IL-1, IL-6, TNF-α, IL-8, and

MCP-1 plasma levels, others have found no difference or, surprisingly, a reduction [110]. This discrepancy in results likely represents a combination of methodologic differences (earlier studies used bioassays with poor specificity), pulsatile release of cytokines, and other concurrent factors that might have affected IL-1 release (malnutrition, underlying inflammation). Another possible explanation is that the balance of the cytokine with its circulating inhibitor is more important than the cytokine level per se [69].

Pertosa et al showed that peripheral blood mononuclear cells of patients undergoing chronic hemodialysis presented an activated phenotype as demonstrated by the striking up-regulation of cytokine gene expression. However, the mononuclear cells were unable to synthesize and secrete these cytokines [110].

Dr. Richard Glassock (*Professor of Medicine; Head, Department of Medicine; University of Kentucky College of Medicine, Lexington, Kentucky, USA*): The thought occurred to me, as it perhaps occurred to you, that this descriptive analysis of inflammation and atherogenesis suggests the ingredients for a vicious Brenner-type cycle. In other words, atherogenesis begets inflammation, and inflammation begets atherosclerosis. If true, such a cycle probably would help explain why inflammation is present before dialysis is initiated. We know that most chronically uremic patients already have fairly extensive but sometimes subclinical atherosclerotic disease by the time they reach ESRD. Inhibitors of HMG-CoA reductase could interrupt this putative vicious cycle of atherogenesis and inflammation because they not only have potent effects on atherogenesis but they also exert anti-inflammatory effects. One might want to examine the possibility of a vicious cycle of atherogenesis and inflammation because of its powerful explanatory role.

Dr. Riella: In this same line of reasoning, extremely relevant is the recent finding that urea induces macrophage proliferation by inhibition of inducible nitric oxide synthesis [105]. Earlier dialysis might be associated with lesser atherosclerosis and explain the better survival observed.

Dr. Jirgen Ladefoged (*Rigshospital, Copenhagen, Denmark*): May I turn to another topic? Would you please comment on what sort of nutrition we should give our uremic patients. I personally think that sufficient caloric intake is far more important than protein intake. As far as I can see, there is some tendency in the literature to recommend high protein intakes for our uremic patients. I think this is wrong because protein is the main source of fixed acid. In this way we simply increase the severity of metabolic acidosis and thereby produce all the events you just described.

Dr. Riella: I agree with you. I'll try to make this clear by making two comments. One, when you correct metabolic acidosis, you decrease the oxidation of proteins [53]. The body then can adapt to a much lower protein intake. The other point was made through the data from Bergström; to maintain nitrogen balance, CAPD patients depend more on their caloric intake than on their protein intake [21]. Because we have evidence that many of our patients do take less than the required 35 Kcal/kg/day, you are correct that our emphasis should be on caloric intake.

Dr. Madias: Despite the decreased caloric and nutrient intake of hemodialysis patients, they have increased energy requirements compared to controls. What might be the explanation for this increased energy requirement?

Dr. Riella: There is no clear explanation. Several possible mechanisms have been postulated [15]: (1) increased myocardial workload, commonly seen in chronic hemodialysis patients because of interdialytic volume expansion, chronic anemia, coronary artery disease, and underlying cardiomyopathy; (2) increased sympathetic nervous system activity, a common finding in the uremic state, along with increased levels of cortisol, glucagon, and insulin; (3) increased total-body potassium, which has been associated with an increase in energy expenditure.

Dr. Roberto Garcia (*Professor of Medicine and Pharmacology, Faculty of Medicine, University of Valparaiso, Chile*): My question relates to the second case that you presented. In my view, this patient illustrates well the critical importance of residual renal function. In this patient initially, the total clearance probably was sufficient to maintain her in good condition, but later the decline of residual renal function put her into a more precarious condition. Moreover, the PET test showed a high transport pattern. Have you considered switching this patient to hemodialysis?

Dr. Riella: You are right by saying that the residual renal function was a contributory factor at the beginning. If you compare hemodialysis and peritoneal dialysis patients at the beginning of dialysis, hemodialysis patients have a much higher mortality rate [111]. As time goes by, the two lines come together; the favorable peritoneal dialysis results at the beginning are attributable to residual renal function.

As to transfer to hemodialysis, I would transfer her first to an automated therapy, such as nightly intermittent peritoneal dialysis (NIPD) or daily ambulatory peritoneal dialysis (DAPD) because she was a "rapid transporter." Rapid transporters require short dwell times to maximize solute clearances and net ultrafiltration. With the loss of residual renal function, rapid transporters on CAPD can retain fluid, develop hypertension, and require more hypertonic exchanges. These patients have a tendency to malnutrition and should be transferred to an automated therapy. I don't know whether transferring

such patients to hemodialysis will reduce their increased mortality rate.

Dr. Abelardo Aguilera (*Peritoneal Dialysis Unit, La Paz Hospital, Madrid, Spain*): I would like to comment on the results of our recent study [112]. We've investigated the association between plasma TNF-α levels and the presence of anorexia in peritoneal dialysis patients. We found that anorectic patients had high TNF-α plasma levels in relation to other peritoneal dialysis patients. TNF-α also showed a negative relationship with venous pH, serum albumin, pre-albumin, transferrin, cholesterol, and other proteins. Our results thus support the hypothesis of a linkage among malnutrition, inflammation, and anorexia. Did you say that Dr. Bergström's group didn't find this relation between TNF-α and anorexia?

Dr. Riella: No, I didn't say that. My comment was related to the possible association between a high-transport peritoneal membrane, as in the case presented, and inflammatory mediators. Bergström's group explored this possibility but found no association (Lindholm B, personal communication). But this does not mean much, because a high-transport membrane could result from a previous inflammatory process.

Dr. César San Martin (*Medical Director, RTS Cendyt Dialysis Unit, Buenos Aires, Argentina*): I have two questions. Is there any relationship between leptin levels and cytokines? What do you think of the use of bioimpedance for assessing lean and fat mass in patients on dialysis?

Dr. Riella: Cytokines such as TNF-α and IL-1 induce both an increase in leptin mRNA levels and anorexia, at least in experimental animals [39]. Elevated levels of cytokines have been reported in ESRD patients, so one might speculate that the inflammatory process itself contributes to the stimulation of *ob* gene expression and thereby increases the circulating leptin levels [39].

Although bioelectrical impedance analysis (BIA) has been validated in the estimation of total body water (TBW), only recently have efforts been made to investigate the role of BIA in nutritional assessment of ESRD patients. Chertow et al recently showed that BIA is a valid and reliable method of nutritional assessment in maintenance hemodialysis patients [113]. The group evaluated 33 patients on maintenance hemodialysis with BIA, DEXA, and deuterium oxide and sodium bromide isotope dilution studies. It appears that the estimation of body cell mass (BCM) is the most valuable aspect of BIA. Previous studies used fat-free or lean body mass (LBM) as the focus of body composition analysis, and LBM by definition includes extracellular water, a body compartment typically increased in patients with ESRD [113].

Dr. Madias: Do the levels of leptin differ between hemodialysis and peritoneal dialysis patients?

Dr. Riella: It seems that serum leptin levels are elevated both in hemodialysis and CAPD patients [39]. Some investigators have shown that high serum leptin levels occur only in those hemodialysis patients whose body fat exceeds 30%, while others showed no difference from controls [38]. Others have shown that in CAPD patients, serum leptin levels are high and correlate with body mass index, and that peritoneal and urinary losses of leptin have only a small or negligible effect on serum leptin concentration [114]. High-flux dialyzers appear to lower serum leptin levels by 30% [115]. Thus, differences in serum leptin levels in hemodialysis and CAPD patients must be interpreted in relation to the body mass fat.

Dr. Carlos Hernan Mejia Garcia (*Servicio de Terapia Renal Cruz Roja, Cali, Colombia*): I have two questions. Is there any role for L-carnitine in dialysis patients? Second, do we have any evidence for oxidative stress that might account for the high prevalence of cardiovascular disease in malnourished patients?

Dr. Riella: About five or six years ago, a Consensus Conference concluded that routine carnitine supplementation in dialysis patients is not justified. Notwithstanding, L-carnitine might be given in the following settings when standard therapy has not been effective: intradialytic muscle cramps and hypotension; lack of energy, skeletal muscle weakness, and/or myopathy; and cardiomyopathy and anemia of renal failure unresponsive to or requiring large doses of erythropoietin [116]. Oxidative stress, which occurs when there is excessive free-radical production or low antioxidant levels, has emerged as an important co-factor for the development of endothelial dysfunction and atherogenesis [117]. Free radicals accelerate the development of atherosclerosis by generating oxidized LDL, which damages the vascular wall and causes atherosclerotic lesions. Much recent evidence suggests that oxidative stress is present in pre-dialysis and dialysis patients [117]. The causes of increased oxidative stress are not known, but low levels of antioxidants such as selenium, vitamin C, and gluthathione peroxidase have been implicated.

Dr. Horacio Repetto (*Chief, Pediatric Service, Hospital Nacional, University of Buenos Aires, Argentina*): One of the first symptoms in any child who develops metabolic acidosis is decreased appetite. Are you aware of any study looking at the relationship of acid-base status and leptin production?

Dr. Riella: In animal models, both leptin administration and acidosis reduce food intake. In one recent study, acidotic uremic rats seemed to exhibit lower serum leptin levels than did their bicarbonate-supplemented counterparts [118].

Dr. Vipul Chitalia (*Nephrology Fellow, Christchurch Hospital, Christchurch, New Zealand*): Most patients with chronic renal failure are faced with continuous inflammatory stimuli, and there are spells of superimposed inflammatory stresses with dialysis. The inflammation in turn seems to be associated with a rapid decline in residual renal function. My question is: are there studies com-

paring residual renal function in patients with malnutrition versus those who are not malnourished? This knowledge might have a great implication on the dose of dialysis in the future.

Dr. Riella: Several papers have correlated residual renal function and nutritional status. This relationship was clearly shown in the CANUSA study [119]. Among 680 patients on peritoneal dialysis, there was a clinically important and statistically significant decrease in several estimates of nutritional status with decreased renal function. The estimates of nutritional status were serum albumin concentration, SGA, percentage of LBM, and nPCR [119].

Dr. Madias: Does malnutrition affect the ability of monocytes to produce cytokines?

Dr. Riella: A direct correlation exists between nutrition and cytokine production, and there is evidence that malnutrition depresses cytokine production and potentially contributes to reduced immune responsiveness in patients on chronic dialysis [120].

Dr. Pereira: This is a response to a query you've raised, Nick. About three years ago, we published data from a study in which we isolated mononuclear cells from dialysis patients and stimulated those cells with endotoxins. The albumin levels of the patients were directly correlated with the endotoxin-stimulated IL-1 and TNF production. This finding suggested to us that well-nourished patients' monocytes seem to be healthier based on that one single index [120].

Dr. Tom Parker III (*Clinical Professor, University of Texas, Southwestern Medical School, Dallas, Texas, USA*): It seems as though we are talking about perhaps two separate phenomena, or at least a spectrum. We have patients who are malnourished and in whom there is evidence of inflammation. On the other hand, we have quite a few patients who are not malnourished by conventional markers, and yet these patients die of cardiovascular disease and have evidence of inflammation. Is there a spectrum? Getting to Brian's point, are there things we currently are doing under the auspices of making our patients better but that actually are accelerating their demise? Should all dialysis patients be on a biocompatible membrane? Should everyone be on an endotoxin-free dialysate? Should everyone be on high doses of folate? Should the acidosis be corrected in every patient to decrease the inflammatory response and thereby decrease the cardiovascular disease in patients who do not have markers of malnutrition?

Dr. Riella: You are probably right. Given our current ignorance in this area, perhaps we should take the available evidence and implement many of the actions you are suggesting.

Dr. Mahmoud M. Salem (*Assistant Professor of Medicine, Division of Nephrology, The University of Mississippi Medical Center, Jackson, Mississippi, USA*): I want to change the subject to another aspect of malnutrition, which is obesity. Two months ago, a Jackson group reported that a large percentage of dialysis patients were obese. Surprisingly, the authors claim that the one-year mortality rate was lower in these patients than in their non-obese patients [121]. What do you think about this? Should we be worried about obesity in our dialysis patients? Is BMI a good parameter to be used in our dialysis units?

Dr. Riella: You've brought up a good point. In the general population, there is evidence that a higher BMI is associated with a lower survival rate and more cardiovascular complications. I am aware of two papers regarding obesity in dialysis patients, one from the USRDS in which a BMI below 23.9 was associated with an increased mortality rate. In that same study, a higher BMI in fact was associated with a lower mortality rate [8].

The second paper is the one you are quoting [121]. The authors measured BMI and biochemical markers of nutrition in a large hemodialysis population and found that 40% were overweight, mainly black females. The authors found that for every one unit increase in BMI over 27.5, the relative risk of dying was reduced by 30%. Because this was predominantly an Afro-American group, and because it is known that within this group females have the highest BMI, this finding simply might reflect a statistical artifact. But I don't have a clear answer for you. At present, I would not suggest obesity as the cure for malnutrition!

Dr. Madias: Could you please comment on the efficacy of interventions to treat malnutrition in ESRD, such as administration of rhGH, rhIGF-1, and intradialytic parenteral nutrition? Under what circumstances, if any, would you recommend these maneuvers?

Dr. Riella: Anabolic hormones such as growth hormone and its major mediator, insulin-like growth factor type 1 (IGF-1), have been used in several catabolic states. The use of growth hormone in uremia is based on a presumed GH resistance in patients with chronic renal failure. Preliminary studies in dialysis patients have suggested that rhGH administration reduces urea generation, improves the efficacy of dietary protein utilization, and diminishes body protein catabolism. A double-blind, placebo-controlled study of rhGH for six months in elderly patients undergoing chronic hemodialysis showed an increase in serum albumin concentration and increased muscle area and free-fatty mass [122]. However, due to the high cost of the therapy, larger and more prolonged studies will be required to assess the ultimate effects on quality of life, morbidity, and mortality.

Recombinant human growth hormone also promotes growth in children with chronic renal failure; it is approved by the US Food and Drug Administration (FDA) for this purpose, and changes in body composition can be expected during growth hormone treatment [123]. The agent responsible for the most of the anabolic effects

of growth hormone, IGF-1 is not approved by the FDA for use as an anabolic agent. Due to the twice-daily dosing schedule and toxic effects (jaw pain, nausea, hypoglycemia, occasional altered mentation, cardiac arrhythmias), it is less desirable than growth hormone.

Intradialytic hormone nutrition (IDPN) is provided during the hemodialysis procedure, and because it is given only for four hours thrice weekly, it is a method of nutritional supplementation rather than total nutritional support. The potential benefits and indications for IDPN have not been investigated adequately in large-scale, randomized, prospective clinical trials. Such trials should include comparisons between IDPN and other methods of nutritional management, such as dietary counseling, food supplements, and enteral tube feeding, to determine the relative benefits and risks and the therapeutic indications for each of these treatment modalities. Several studies have suggested a limited benefit of IDPN on nutritional parameters in non-uniform samples of patients. Chertow et al, in a retrospective cohort study, showed a survival advantage among hypoalbuminemic IDPN recipients [104]. Given its expense and the absence of more definitive data, its use probably should be limited to patients who are unable to tolerate oral or enteral nutrients or formulas designed to meet protein-energy requirements. Except for the patient with a permanently and totally diseased gastrointestinal tract, IDPN should be a short-term resuscitative therapy [124].

Dr. Paul Kimmel (*Division of Renal Disease and Hypertension, Department of Medicine, George Washington University Medical Center, Washington, DC, USA*): Again, I would like to compliment you on your approach to this difficult topic. To illustrate how difficult it is, there are outcome data on circulating cytokines and survival on dialysis patients. We recently reported data showing that circulating levels of IL-1 and other inflammatory cytokines predict death [125]. But the more interesting finding was that IL-2 and IL-12 (cytokines critical for T-cell growth and function), IL-4, IL-5, T-cell number and functional status, and CH50 were independently associated with survival. The levels of particular cytokines, while predictive of mortality, might not be causally linked to effectors of outcome. For example, IL-1, a mortality factor in our study, increases synthesis of IL-2 (a correlate of survival) by lymphocytes, suggesting that its association with mortality must be mediated through other pathways. The cytokine network is so difficult to manipulate, and it is so interrelated, that it probably makes intervention very difficult.

Dr. Riella: Thank you. To further illustrate the complexity of the cytokine network, one is reminded that in healthy people, monocytes differentiate into populations that mutually exclusively express IL-6 (an inflammatory cytokine) or IL-10 (a regulator of monocyte activation that downregulates inflammatory cytokines). One might postulate a dichotomous differentiation of monocytes in analogy to that seen in T-lymphocytes (Th_1 and Th_2). Possibly monocytes also differentiate into populations with different functions [72].

Dr. Madias: Regarding your point on correcting the metabolic acidosis of hemodialysis patients by raising the bicarbonate concentration of the dialysate, experience suggests that this is not an easily accomplished task [57]. This difficulty is analogous to the fact that introduction of high-flux dialysis, increases in dialysis time, and higher blood flow rates have not produced a higher pre-dialysis plasma bicarbonate concentration [126]. The most reasonable explanation for the major discrepancy between the amount of bicarbonate delivered to the patient during hemodialysis and the attained plasma bicarbonate concentration is marked stimulation of organic acid production by the rapid alkalinization of body fluids. The resultant outpouring of protons titrates bicarbonate ions, whereas the loss of the organic anions in the dialysate prevents bicarbonate regeneration. Thus, rather than increasing plasma bicarbonate concentration substantially, raising the bicarbonate concentration of the bath appears to induce a catabolic process. I believe that the acid-base and metabolic responses to increasing the bicarbonate concentration in the dialysate require careful study before we recommend that increase as a measure of correcting metabolic acidosis. A more effective means for this purpose might be oral bicarbonate supplementation.

Dr. Riella: If I may add, high-concentration bicarbonate dialysis (36 mmol/L) has been associated with hypoxemia during dialysis. A lower concentration of bicarbonate in dialysate prevented hypoxemia [127].

Dr. Madias: As you know, Dr. Mitch's work has shown that glucocorticoids are necessary to mediate the catabolic effects of NH_4Cl-induced metabolic acidosis, such as increased protein degradation and amino acid oxidation. Is it known whether glucocorticoids also are necessary to mediate the catabolic effects of uremic acidosis in animals or humans?

Dr. Riella: The studies by Mitch were done in the intact rat, but Garibotto et al found that the rate of protein degradation measured in the forearm of patients with chronic renal failure was inversely related to the serum bicarbonate concentration but linearly related to the plasma cortisol concentration [128].

Dr. John Donohoe (*Consultant Nephrologist, Beaumont Hospital, Dublin, Ireland*): It seems to me that the total quantity of clearance appears to be a dominant feature. Patients can tolerate very low levels of renal function before finally becoming uremic and needing dialysis. I wonder whether what we are doing at the moment is attempting to make the best of a poor substitute for renal function. For example, when patients who are extremely ill receive a renal transplant, their malnutrition disappears immediately and often is replaced by

obesity just a few months later. So I wonder, on a quantum basis, where would you place the role of clearance among the inflammatory problems, metabolic acidosis, cytokines, etc., that you described? If we were able to easily improve the number of mL of clearance per minute from a miserable 10 or 18 mL/min that we achieve with CAPD, to clearances of 20 to 30 mL/min, might this be at least part of the answer?

Dr. Riella: You bring up a good point. First, when one looks at the survival of peritoneal dialysis versus hemodialysis patients, how important is the residual renal function in accounting for the better results of peritoneal dialysis in the early time on dialysis? Some series show benefit of as long as 18 months; others like the Canadian Registry show benefit as long as 30 months [111]. Thus, I do indeed think that residual renal function is beneficial and has to be preserved at all cost. The second is a comment I've just made related to renal clearance versus dialysis clearance, which brings up the question, can you equate renal Kt/V with dialysis Kt/V? I don't think we know the answer. Using the available evidence, I would predict that renal clearance is more physiologic and better than the same level of dialysis clearance.

Dr. Nathan Levine (*Division of Nephrology-Hypertension, Beth Israel Medical Center, New York, New York, USA*): In the absence of renal clearance, in the absence of transplantation, it seems that the future is hardly in the direction of increasing the clearance of small molecules, as Dr. Donohoe implies. The future surely must include technology that goes further than high-flux dialysis and deals with the larger protein substances, which the kidney normally metabolizes and then breaks down to smaller components. The only one we talk about frequently is β_2-microglobulin. A number of proteins that have substantial effects on neutrophil function, and leptin as well, might be the substances which, if removed by polymers, could benefit our patients. Such an approach might be a more effective way of dealing with uremia than increasing the clearance of small molecules alone. With urea clearance one can only go so far; the USRDS data suggest that once you get to an eKt/V of 1.1 or 1.2, there is hardly any point to going further. Our clearance of the larger molecules, relatively speaking, is nowhere in that range, and that's where we should aim for in the future.

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